ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 May 6; 11(13): 2855-3113

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 11 Number 13 May 6, 2023

OPINION REVIEW

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Case Control Study

Retrospective Study

Observational Study

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 13 May 6, 2023

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 13 May 6, 2023

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 13 May 6, 2023

Contents

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
May 6, 2023

COPYRIGHT
© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 2855-2863

DOI: 10.12998/wjcc.v11.i13.2855

ISSN 2307-8960 (online)

OPINION REVIEW

Long-term implications of fetal growth restriction

Martina D'Agostin, Chiara Di Sipio Morgia, Giovanni Vento, Stefano Nobile

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kumar S, India; Tolunay HE, Turkey

Received: January 27, 2023
Peer-review started: January 27, 2023
First decision: February 17, 2023
Revised: March 8, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 6, 2023

Martina D'Agostin, Department of Pediatrics, University of Trieste, Trieste 34100, Italy

Chiara Di Sipio Morgia, Department of Woman and Child Health and Public Health, Università Cattolica del Sacro Cuore, Rome 00168, Italy

Giovanni Vento, Stefano Nobile, Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome 000168, Italy

Corresponding author: Stefano Nobile, MD, MSc, PhD, Instructor, Staff Physician, Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, Rome 00168, Italy. stefano.nobile@policlinicogemelli.it

Abstract

Fetal growth restriction (FGR), or intrauterine growth restriction (IUGR), is a complication of pregnancy where the fetus does not achieve its genetic growth potential. FGR is characterized by a pathological retardation of intrauterine growth velocity in the curve of intrauterine growth. However, the FGR definition is still debated, and there is a lack of a uniform definition in the literature. True IUGR, compared to constitutional smallness, is a pathological condition in which the placenta fails to deliver an adequate supply of oxygen and nutrients to the developing fetus. Infants with IUGR, compared to appropriately grown gestational age infants, have a significantly higher risk of mortality and neonatal complications with long-term consequences. Several studies have demonstrated how suboptimal fetal growth leads to long-lasting physiological alterations for the developing fetus as well as for the newborn and adult in the future. The long-term effects of fetal growth retardation may be adaptations to poor oxygen and nutrient supply that are effective in the fetal period but deleterious in the long term through structural or functional alterations. Epidemiologic studies showed that FGR could be a contributing factor for adult chronic diseases including cardiovascular disease, metabolic syndrome, diabetes, respiratory diseases and impaired lung function, and chronic kidney disease. In this review we discussed pathophysiologic mechanisms of FGR-related complications and potential preventive measures for FGR.

Key Words: Fetal growth restriction; Intrauterine chronic hypoxia; Long-lasting physiological alterations; Cardiovascular disease; Metabolic syndrome; Obstructive pulmonary disease

Core Tip: Fetal growth restriction (FGR) is a common complication of pregnancy where the fetus does not achieve its genetic growth potential. It is well known that FGR appears to be a contributing factor for adult chronic diseases including cardiovascular disease, metabolic syndrome, diabetes, dyslipidemia, and hypertension. Several studies demonstrated how suboptimal fetal growth leads to long-lasting physiological alterations for the developing fetus as well as for the newborn and adult in the future. Preventive measures and treatments should be assessed and adopted to prevent chronic diseases in FGR patients.

Citation: D'Agostin M, Di Sipio Morgia C, Vento G, Nobile S. Long-term implications of fetal growth restriction. *World J Clin Cases* 2023; 11(13): 2855-2863
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/2855.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.2855

INTRODUCTION

Fetal growth restriction (FGR), or intrauterine growth restriction (IUGR), is a complication of pregnancy where the fetus does not achieve its genetic growth potential[1]. In FGR, intrauterine growth velocity is delayed, expressed by a characteristic kink in intrauterine curve of growth. Several definitions have been proposed and used in clinical practice. FGR has been defined as fetus with an estimated fetal weight or abdominal circumference of less than the 10th percentile for the specific gestational age[1]. There is variation among international society guidelines, with some including abdominal circumference thresholds < 10th or ≤ 5th percentile alone as a diagnostic criteria[2-4]. Based on a survey of expert opinion, FGR is defined by a birth weight < 3rd percentile or the combination of three criteria: (1) Birth weight < 10th percentile; (2) Head circumference < 10th percentile; (3) Birth length < 10th percentile (4) Antenatal FGR diagnosis; and (5) Prenatal risk factors associated with FGR[5]. Frequently, FGR results in the birth of a small for gestational age (SGA) infant. However, an infant can be SGA without having FGR, and some growth restricted infants can have a birth weight above the 10th percentile. In the literature, IUGR and SGA were often used as interchangeable terms even though often used improperly.

Several factors are involved in the development of FGR, such as genetic abnormalities, intrauterine infections, fetal structural anomalies, multiple gestations, and ischemic placental diseases[6]. According to the various definition of FGR, almost 9% pregnancies in wealthy countries and almost 30% in poor countries are prone developing FGR[7,8].

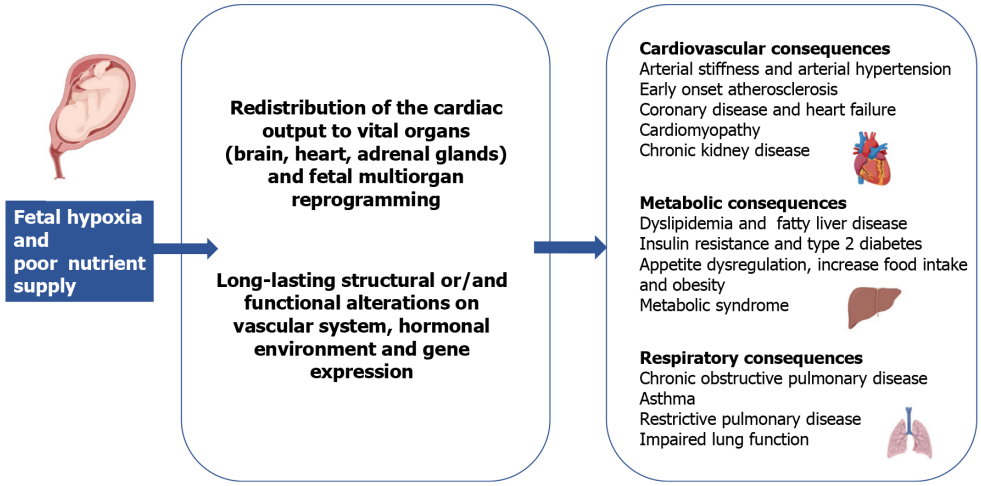
FGR is well known to contribute to adult chronic diseases including cardiovascular disease (CVD), metabolic syndrome, diabetes and chronic kidney disease[9]. Several studies have demonstrated how suboptimal fetal growth leads to long-lasting physiological alterations for the developing fetus as well as for the newborn and adult in the future. The primary cause of fetus growth restriction is a decreased oxygen and nutrient supply, which causes chronic hypoxia. As a response, the fetus redistributes the cardiac output to the brain, the heart, and the adrenals in order to preserve function in these vital organs [10] (Figure 1). Potentially, all the organs may be affected by growth restriction.

This review focuses on the long-term impacts of FGR on the cardiovascular, metabolic, and respiratory systems and discusses pathophysiologic mechanisms and preventive measures for FGR.

LONG-TERM METABOLIC IMPLICATIONS OF FGR

Several studies have reported the association between FGR and subsequent development of disease, like obesity, metabolic syndrome, CVD and cancer. A possible explanation has been proposed by developmental origin of health and disease concept[9]. According to this hypothesis, fetuses developing in an adverse intrauterine environment adapt through changing their endocrine-metabolic status to save energy and redirect nutrients to essential organs. The reprogramming at hepatic level predisposes to future dyslipidemia, vascular modifications induce endothelial damage and future hypertension, and insulin resistance contributes to the development of metabolic syndrome (dyslipidemia, fatty liver, arterial hypertension, and type 2 diabetes mellitus)[11].

The proposed pathophysiologic factors underlying these changes include epigenetic modifications of the expression of genes[12]. These modifications could induce appetite dysregulation and increase food intake and adipogenesis, resulting in future obesity and cardiovascular risk. The increased risk of metabolic syndrome and CVD may also be found during childhood, particularly in cases of rapid weight gain during infancy[13,14]. In a recent study from Singapore, a rapid weight gain from 0 to 2



DOI: 10.12998/wjcc.v11.i13.2855

Figure 1 Long-term implications of fetal growth retardation.

years, with or without prior fetal growth deceleration, was associated with unfavorable cardiometabolic markers at 3 years of life[15]. Similarly, Norris *et al*[16] reported that the adverse consequences of rapid infant weight gain in the first 2 years of life may occur regardless of FGR occurrence.

Other important determinants of adult anthropometric and inflammatory alterations are fetal growth trajectories, as reported in a relatively small Australian cohort[17]. A relationship between small fetal head and abdominal circumference and higher adult blood pressure was described, independent of confounding variables, such as adult adiposity[17]. In a later report, a significant association between fetal growth patterns and markers of adiposity [body mass index (BMI), waist circumference] and inflammation [C-reactive protein (CRP)] was found in 27-year-old subjects. Good growth in early gestation had a protective effect on adiposity in later life, whereas reduced early growth was associated to adiposity. For example, a very-low-to-rising femoral length trajectory was associated with higher adult BMI, as confirmed by other studies in different populations[18].

Average or above-average abdominal growth from early-mid pregnancy with later deceleration was associated with lower adult BMI and abdominal circumference. Decreased waist circumference during gestation was related to higher CRP level in adulthood, while increased abdominal and head circumference was associated with lower CRP, even after adjustments for several factors, including postnatal lifestyle factors and maternal and pregnancy covariates. These effects were more pronounced in females than in males. However, it should be noted that obesity is a complex phenomenon involving multiple genetic and environmental factors, and the reported observations do not clarify the pathophysiology of adult obesity in former FGR individuals.

Potential preventive measures and treatments for the onset of metabolic complications include breastfeeding, adequate nutrition and physical exercise starting from early childhood, growth hormone, and metformin[10]. However, the studies have included small numbers of patients and need to be replicated in larger cohorts. Moreover, in the follow-up of FGR children, pediatricians should perform routine blood pressure monitoring, advice on healthy diet, and encourage physical activity.

LONG-TERM CARDIOVASCULAR IMPLICATIONS OF FGR

FGR compared to normal growth is associated with a significantly higher incidence of CVD later in life [19]. FGR is also associated with metabolic syndrome and the effect of IUGR on cardiovascular system may be mediated by diabetes, dyslipidemia, or hypertension. An increased risk of high systolic blood pressure, arterial stiffness, and reduced renal functional reserve have been described in young adults born after FGR[20]. Hypertension, coronary disease, cardiomyopathy, and heart failure have been found extensively in adulthood and older age[21]. However, growing evidence suggests that FGR is the direct cause of cardiovascular alterations independently from pre-existing metabolic disease[22], which can increase the level of mortality and morbidity among IUGR patients.

Several studies have examined the relationship between FGR and the development of CVD later in life[9,19]. Leon *et al*[23] were the first to conduct a large epidemiological study of about 15000 births in Sweden and reported a statistically significant relationship between low birth weight and mortality from CVD in male individuals aged > 65 years. Moreover, another cohort study showed an inverse correlation between birth weight and systolic pressure in 50-year-old patients in the United Kingdom [24].

Cardiovascular impairment may already exist in growth restricted children preclinically in childhood, before the clinical development of CVD in adulthood. Long-term exposure to hypoxemia may be associated with permanent alterations in the structure and function of the cardiovascular system. To date, available evidence suggests that chronic hypoxemia *in utero* induces physiological modifications of autonomic nervous system function, oxidative stress, impaired secretion of hormones, and functional and structural modifications of the blood vessels[25]. A more spherical shape is typically evident in the heart of a restricted fetus, which can evolve into hypertrophy in the most severe cases [26]. Furthermore, prenatal echocardiography shows reduced longitudinal myocardial motion, abnormal transmitral E/A ratios (a marker of left ventricular function and late diastolic filling), prolonged isovolumic relaxation time, and decreased diastolic annular peak velocities. These modifications are functional to ensure an efficient stroke volume output and tolerance to pressure overload[27].

Interestingly, biomarkers of cardiac dysfunction and damage, such as B-type natriuretic peptide and troponin[27,28], have been found to be increased in the cord blood of FGR fetuses, potentially explaining the cardiac impairment caused by a suboptimal intrauterine environment. The altered prenatal echocardiographic findings were also confirmed in the 1st days after birth[29]. In fact, decreased absolute "E" and "A2 wave velocities", higher "E/A" ratio, a prolonged isovolumic relaxation time, and reduced contractility and cardiac output have been described in these neonates, leading to increased blood pressure and both diastolic and systolic dysfunction[30].

The same findings were also identified by other studies including infants from FGR pregnancies aged 3-4 months[31]. Interestingly, a prospective study of 150 infants conducted by Crispi *et al*[32] compared cardiovascular morphology of 3-year-old to 6-year-old FGR infants with a control group. The authors showed that FGR children were more likely to present globular-shaped hearts, increased cardiac output, and left ventricular thickening. Similar findings were found by Rodríguez-López *et al*[33] in children aged 8-12 years. Altered vascular elastin and collagen content, extracellular matrix remodeling, and endothelial dysfunction are some of the prenatal circulatory modifications found in growth restricted offspring[25]. Multiple molecular mechanisms are involved in the pathogenesis of endothelial dysfunction in FGR patients such as the disruption in placental-mTORC and transforming growth factor beta signaling cascades, and changes in expression of endothelial nitric oxide synthase, as clearly explained in a recent review by Amruta *et al*[34]. Vascular changes may persist after birth and cause early onset preclinical atherosclerosis in children. For example, carotid artery thickness was found by Martin *et al*[35] in 3-year-old to 6-year-old children, and this evidence was confirmed by autopsy studies [36].

It is important to underline that other factors may influence the development of CVD in FGR patients. For example, pre-eclampsia, obesity, maternal diabetes, and prematurity are independent risk factors of hypertension during childhood.

To summarize, even if epidemiologic studies showed an association between FGR and late complications, the underlying mechanisms may be numerous. Some of these have recently been described and may coexist. Finally, there is an urgent need for studies for the evaluation of preventive measures in the FGR population.

LONG-TERM RESPIRATORY IMPLICATIONS OF FGR

Lung development occurs through several stages, namely embryonic, pseudoglandular, canalicular, saccular, and alveolar[37]. In many growth restricted infants, placental insufficiency occurs in late pregnancy in parallel with distal lung development (acinar and alveolar structures), suggesting that FGR may especially impact distal lung development[38]. Clinical observations in newborns show that SGA infants have a more severe early respiratory course and increased risk of developing bronchopulmonary dysplasia[39,40].

The long-term effects of FGR may be due to adaptations to poor oxygen exposure and nutrient supply that might result in structural or functional alterations[41]. FGR impacts lung function through molecular and cellular events, involving parenchyma, airway, and vasculature[38]. In fact, evidence showed that perinatal undernutrition changed the hormonal environment, which has an important impact on lung development and function, conditioning a higher risk for lung pathology in adulthood. Particularly, a deficit of retinol, cholecalciferol, leptin, ghrelin, and GLP-1 could be present in undernutrition in pregnancy and play a role in lung development, suggesting a correction of these deficiencies with diet supplementation during gestation[42,43].

Epidemiological studies showed that changes in lung development impacted both lung function and respiratory disease in early life, as well as in adulthood, particularly reduced forced expiratory volume in 1 s (FEV1) and chronic obstructive lung disease[38,44].

Much of our understanding of the relationship between FGR and lung development comes from animal studies. Maritz *et al*[45] showed that structural alterations induced by growth restriction during fetal lung development were still evident in adult sheep and were similar both qualitatively and quantitatively to those observed at 8 weeks, suggesting that restricted growth may induce permanent alterations in the morphology of the offspring's lungs as well as faster lung aging[46]. Adult FGR

animals have fewer alveoli (larger than in controls), thickening of the interalveolar septa and basement membrane due to the accumulation of extracellular matrix[46], and inhibition of surfactant maturation [47]. FGR rats experienced significant pulmonary arterial hypertension and pulmonary vascular remodeling secondary to epigenetic mechanisms and pulmonary artery endothelial cell dysfunction [48]. Another study in sheep demonstrated that chronic placental insufficiency and subsequent FGR during late gestation resulted in alveolar simplification after birth, without concomitant alteration in lung weight and reduced septation[49]. This observation was in contrast to a previous study from the same group[50] in which lungs were inspected for a short time after the onset of placental insufficiency and FGR, supporting the concept that prolonged exposure to chronic hypoxia negatively influences lung growth, whereas exposure for short time did not.

Other studies have evaluated the relationship of FGR and functional respiratory values. A recent study showed a lower FEV1 Z-score in subjects aged 8-15 years who were born preterm and with a diagnosis of FGR, suggesting a worse conducting airway function. In this study, confounding factors, potentially contributing themselves to the lung function impairment, were prematurity and bronchodysplasia[51]. The study of Nikolajev *et al*[52] showed that FGR has its most pronounced effect on airway dynamics. Particularly, no differences were found in FEV1 or peak expiratory flow between FGR children and controls, but mid-expiratory flow measurements were significantly lower, suggesting that FGR has a more pronounced effect on airway development than on lung volumes. FGR has an impact on lung function not fully understood, as current evidence is mainly based on studies in children born SGA or low birth weight but not necessarily with FGR.

In a recent systematic review, different lung function trajectories were described, and low birth weight was associated with subnormal lung function trajectories[53]. Karmaus *et al*[54] described a relationship between 'low' FEV1 trajectories in both genders and 'low' FEV1/forced vital capacity (FVC) trajectories in females between ages 10 years and 26 years, whereas other authors reported 'low' FEV1, FVC, and FEV1/FVC trajectories in FGR individuals aged 15 to 22[55]. However, other studies found only modest associations for low birth weight[56]. Stein *et al*[57] studied the potential association between fetal growth and adult lung function in South India. They found an association between low birth weight/small head circumference at birth and reduced FEV1, independent from age and current stature; FVC was similarly associated with low birth weight. Canoy *et al*[58] followed a large population from fetal period until adulthood showing that adult FEV1 and FVC increased linearly with birth weight, and that the reduction in lung function was more pronounced in adults with lower birth weight.

Several studies showed that low birth weight is an important determinant for later development of chronic obstructive pulmonary disease[59,60]. On the other hand, a meta-analysis reported a significant association between birth weight and adult FVC, indicative of restrictive pattern, and weaker evidence for airflow obstruction[61].

A crucial point to investigate is the relationship between FGR and the subsequent risk of asthma. Käll én *et al*[62] found that FGR is associated with an increased risk of asthma, even if a stronger predisposing factor is prematurity. A study evaluated the association between fetal growth and childhood asthma, showing that it is independent of gestational age, familial context, and genetic factors[63]. In fact, a cohort study of twins described the association between lower birth weight and increased risk of asthma, suggesting that this association is not influenced by shared environmental or genetic factors as twins are theoretically exposed to the same factors[64].

Further studies are required to evaluate the impact of FGR, based on a consensus-defined definition, and long-term pulmonary outcomes. In fact, the confusion between IUGR, SGA, and low birth weight confound the interpretation of the literature, and there is the risk of over/underestimating the relationship between the two entities. Several animal studies demonstrated the impact of FGR on both short-term and long-term structure and function of the lung. The association between FGR and impaired functional respiratory values is controversial, and it is still not clear whether the impairment, if any, is mainly due to a restrictive or obstructive pattern.

PREVENTIVE MEASURES

Several preventive measures have been identified and considered to promote long-term health in former FGR individuals (Table 1). A useful antenatal measure is an improved identification of subjects with increased risk of complications (*i.e.* earlier/more frequent ecographic growth assessment). Other strategies could include the promotion of dietary modifications during gestation to facilitate normalization of body weight, micronutrient levels, glycemia and blood pressure, lifestyle measures (*i.e.* avoidance of alcohol and smoke, enhancement of maternal education, reduction of stress and exposure to pollution), and control of chronic diseases. Some of these are currently being evaluated by clinical studies[65-68].

Postnatal early-life interventions include: Breastfeeding promotion, provision of adequate nutrition and growth, follow-up of high risk patients, and appropriate resource distribution[41]. Maternal and offspring microbiota modifications (*i.e.* dietary supplementation with docosahexaenoic acid and arachidonic acid to improve neurodevelopmental outcomes)[65], pre-probiotics are a potential

Table 1 Potential preventive measures to avoid chronic diseases in fetal growth restriction patients

Prenatal interventions	Postnatal interventions
Early detection of fetal growth restriction	Breastfeeding
Dietary modifications/supplementations during pregnancy	Adequate nutrition in childhood
Normalization of body weight, glycemia and blood pressure control during pregnancy	Growth follow-ups and blood pressure monitoring
Lifestyle measures (*i.e.* avoidance of alcohol and tobacco, maximization of maternal education, reduced stress)	Lifestyle measures (*i.e.* avoidance of alcohol and tobacco, reduced stress, avoid overweight)
Management of maternal chronic diseases	Pharmacological interventions: Growth hormone, metformin

interventions needing further studies. Lactoferrin and stem cell administration are under investigation.

CONCLUSION

In this review, we reported the most important complications of FGR with their proposed pathophysiology, according to the most recent literature. FGR is not only a complication of pregnancy but a condition with relevant short- and long-term unfavorable outcomes for children and adults. Potential benefits from the research in this area could include reduced stillbirths and neonatal deaths and improved outcomes in pregnancies affected by FGR. Moreover, the prevention, detection, and treatment of FGR might have important positive reflections on public health worldwide, and it is expected that these themes will be on the next research agenda. Indeed, in recent years a number of government agencies extensively funded research studies in this area (*i.e.* European Commission's 7th Framework Programme, United States National Institutes of Health, among others).

Moreover, the interplay between FGR and other environmental exposures (*i.e.* microbiome, smoking, pollution, malnutrition, *etc.*) will be another interesting area of research likely to be covered by future studies.

FOOTNOTES

Author contributions: Nobile S conceived the idea for the manuscript; Di Sipio Morgia C, D'Agostin M, and Nobile S reviewed the literature and drafted the manuscript; Di Sipio Morgia C and D'Agostin M contributed equally; Vento G supervised and edited the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Italy

ORCID number: Stefano Nobile 0000-0002-5304-1485.

S-Editor: Liu XF
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Society for Maternal-Fetal Medicine (SMFM)**, Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction: (Replaces Clinical Guideline Number 3, April 2012). *Am J Obstet Gynecol* 2020; **223**: B2-B17 [PMID: 32407785 DOI: 10.1016/j.ajog.2020.05.010]

2 **Lees CC**, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, Hecher K, Kingdom J, Poon LC, Salomon LJ, Unterscheider J. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol* 2020; **56**: 298-312 [PMID: 32738107 DOI: 10.1002/uog.22134]

3 **Molina LCG**, Odibo L, Zientara S, Običan SG, Rodriguez A, Stout M, Odibo AO. Validation of Delphi procedure consensus criteria for defining fetal growth restriction. *Ultrasound Obstet Gynecol* 2020; **56**: 61-66 [PMID: 31520557 DOI: 10.1002/uog.20854]

4 **Resnik R**. Intrauterine growth restriction. *Obstet Gynecol* 2002; **99**: 490-496 [PMID: 11864679 DOI: 10.1016/s0029-7844(01)01780-x]

5 **Beune IM**, Bloomfield FH, Ganzevoort W, Embleton ND, Rozance PJ, van Wassenaer-Leemhuis AG, Wynia K, Gordijn SJ. Consensus Based Definition of Growth Restriction in the Newborn. *J Pediatr* 2018; **196**: 71-76.e1 [PMID: 29499988 DOI: 10.1016/j.jpeds.2017.12.059]

6 **Nardozza LM**, Caetano AC, Zamarian AC, Mazzola JB, Silva CP, Marçal VM, Lobo TF, Peixoto AB, Araujo Júnior E. Fetal growth restriction: current knowledge. *Arch Gynecol Obstet* 2017; **295**: 1061-1077 [PMID: 28285426 DOI: 10.1007/s00404-017-4341-9]

7 **Lee AC**, Kozuki N, Cousens S, Stevens GA, Blencowe H, Silveira MF, Sania A, Rosen HE, Schmiegelow C, Adair LS, Baqui AH, Barros FC, Bhutta ZA, Caulfield LE, Christian P, Clarke SE, Fawzi W, Gonzalez R, Humphrey J, Huybregts L, Kariuki S, Kolsteren P, Lusingu J, Manandhar D, Mongkolchati A, Mullany LC, Ndyomugyenyi R, Nien JK, Roberfroid D, Saville N, Terlouw DJ, Tielsch JM, Victora CG, Velaphi SC, Watson-Jones D, Willey BA, Ezzati M, Lawn JE, Black RE, Katz J; CHERG Small-for-Gestational-Age-Preterm Birth Working Group. Estimates of burden and consequences of infants born small for gestational age in low and middle income countries with INTERGROWTH-21(st) standard: analysis of CHERG datasets. *BMJ* 2017; **358**: j3677 [PMID: 28819030 DOI: 10.1136/bmj.j3677]

8 **Miller SL**, Huppi PS, Mallard C. The consequences of fetal growth restriction on brain structure and neurodevelopmental outcome. *J Physiol* 2016; **594**: 807-823 [PMID: 26607046 DOI: 10.1113/JP271402]

9 **Barker DJ**. The fetal and infant origins of adult disease. *BMJ* 1990; **301**: 1111 [PMID: 2252919 DOI: 10.1136/bmj.301.6761.1111]

10 **Rock CR**, White TA, Piscopo BR, Sutherland AE, Miller SL, Camm EJ, Allison BJ. Cardiovascular and Cerebrovascular Implications of Growth Restriction: Mechanisms and Potential Treatments. *Int J Mol Sci* 2021; **22** [PMID: 34299174 DOI: 10.3390/ijms22147555]

11 **Hales CN**, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull* 2001; **60**: 5-20 [PMID: 11809615 DOI: 10.1093/bmb/60.1.5]

12 **Gluckman PD**, Hanson MA, Buklijas T, Low FM, Beedle AS. Epigenetic mechanisms that underpin metabolic and cardiovascular diseases. *Nat Rev Endocrinol* 2009; **5**: 401-408 [PMID: 19488075 DOI: 10.1038/nrendo.2009.102]

13 **Eriksson J**, Forsén T, Tuomilehto J, Osmond C, Barker D. Fetal and childhood growth and hypertension in adult life. *Hypertension* 2000; **36**: 790-794 [PMID: 11082144 DOI: 10.1161/01.hyp.36.5.790]

14 **Stettler N**, Stallings VA, Troxel AB, Zhao J, Schinnar R, Nelson SE, Ziegler EE, Strom BL. Weight gain in the first week of life and overweight in adulthood: a cohort study of European American subjects fed infant formula. *Circulation* 2005; **111**: 1897-1903 [PMID: 15837942 DOI: 10.1161/01.CIR.0000161797.67671.A7]

15 **Ong YY**, Sadananthan SA, Aris IM, Tint MT, Yuan WL, Huang JY, Chan YH, Ng S, Loy SL, Velan SS, Fortier MV, Godfrey KM, Shek L, Tan KH, Gluckman PD, Yap F, Choo JTL, Ling LH, Tan K, Chen L, Karnani N, Chong YS, Eriksson JG, Wlodek ME, Chan SY, Lee YS, Michael N. Mismatch between poor fetal growth and rapid postnatal weight gain in the first 2 years of life is associated with higher blood pressure and insulin resistance without increased adiposity in childhood: the GUSTO cohort study. *Int J Epidemiol* 2020; **49**: 1591-1603 [PMID: 32851407 DOI: 10.1093/ije/dyaa143]

16 **Norris T**, Crozier SR, Cameron N, Godfrey KM, Inskip H, Johnson W. Fetal growth does not modify the relationship of infant weight gain with childhood adiposity and blood pressure in the Southampton women's survey. *Ann Hum Biol* 2020; **47**: 150-158 [PMID: 32429761 DOI: 10.1080/03014460.2020.1717616]

17 **Yadav A**, Beilin LJ, Huang RC, Vlaskovsky P, Newnham JP, White SW, Mori TA. The relationship between intrauterine foetal growth trajectories and blood pressure in young adults. *J Hypertens* 2022; **40**: 478-489 [PMID: 34751171 DOI: 10.1097/HJH.0000000000003035]

18 **Rytter D**, Bech BH, Frydenberg M, Henriksen TB, Olsen SF. Fetal growth and cardio-metabolic risk factors in the 20-year-old offspring. *Acta Obstet Gynecol Scand* 2014; **93**: 1150-1159 [PMID: 25053259 DOI: 10.1111/aogs.12463]

19 **Barker DJ**. Fetal origins of cardiovascular disease. *Ann Med* 1999; **31** Suppl 1: 3-6

20 **Chan PY**, Morris JM, Leslie GI, Kelly PJ, Gallery ED. The long-term effects of prematurity and intrauterine growth restriction on cardiovascular, renal, and metabolic function. *Int J Pediatr* 2010; **2010**: 280402 [PMID: 21197428 DOI: 10.1155/2010/280402]

21 **Demicheva E**, Crispi F. Long-term follow-up of intrauterine growth restriction: cardiovascular disorders. *Fetal Diagn Ther* 2014; **36**: 143-153 [PMID: 23948759 DOI: 10.1159/000353633]

22 **Menendez-Castro C**, Rascher W, Hartner A. Intrauterine growth restriction - impact on cardiovascular diseases later in life. *Mol Cell Pediatr* 2018; **5**: 4 [PMID: 29560535 DOI: 10.1186/s40348-018-0082-5]

23 **Leon DA**, Lithell HO, Vâgerö D, Koupilová I, Mohsen R, Berglund L, Lithell UB, McKeigue PM. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915-29. *BMJ* 1998; **317**: 241-245 [PMID: 9677213 DOI: 10.1136/bmj.317.7153.241]

24 **Martyn CN**, Barker DJ, Jespersen S, Greenwald S, Osmond C, Berry C. Growth in utero, adult blood pressure, and arterial compliance. *Br Heart J* 1995; **73**: 116-121 [PMID: 7696018 DOI: 10.1136/hrt.73.2.116]

25 **Visentin S**, Londero AP, Calanducci M, Grisan E, Bongiorno MC, Marin L, Cosmi E. Fetal Abdominal Aorta: Doppler and Structural Evaluation of Endothelial Function in Intrauterine Growth Restriction and Controls. *Ultraschall Med* 2019; **40**: 55-63 [PMID: 30253430 DOI: 10.1055/s-0043-122230]

26 **Crispi F**, Miranda J, Gratacós E. Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease. *Am J Obstet Gynecol* 2018; **218**: S869-S879 [PMID: 29422215 DOI: 10.1016/j.ajog.2017.12.012]

27 **Mäkikallio K**, Vuolteenaho O, Jouppila P, Räsänen J. Ultrasonographic and biochemical markers of human fetal cardiac dysfunction in placental insufficiency. *Circulation* 2002; **105**: 2058-2063 [PMID: 11980685 DOI: 10.1161/01.cir.0000015505.24187.fa]

28 **Girsen A**, Ala-Kopsala M, Mäkikallio K, Vuolteenaho O, Räsänen J. Cardiovascular hemodynamics and umbilical artery N-terminal peptide of proB-type natriuretic peptide in human fetuses with growth restriction. *Ultrasound Obstet Gynecol* 2007; **29**: 296-303 [PMID: 17323307 DOI: 10.1002/uog.3934]

29 **Larsen LU**, Petersen OB, Sloth E, Uldbjerg N. Color Doppler myocardial imaging demonstrates reduced diastolic tissue velocity in growth retarded fetuses with flow redistribution. *Eur J Obstet Gynecol Reprod Biol* 2011; **155**: 140-145 [PMID: 21256662 DOI: 10.1016/j.ejogrb.2010.12.020]

30 **Sehgal A**, Doctor T, Menahem S. Cardiac function and arterial indices in infants born small for gestational age: analysis by speckle tracking. *Acta Paediatr* 2014; **103**: e49-e54 [PMID: 24127769 DOI: 10.1111/apa.12465]

31 **Änghagen O**, Engvall J, Gottvall T, Nelson N, Nylander E, Bang P. Developmental Differences in Left Ventricular Strain in IUGR vs. Control Children the First Three Months of Life. *Pediatr Cardiol* 2022; **43**: 1286-1297 [PMID: 35333947 DOI: 10.1007/s00246-022-02850-y]

32 **Crispi F**, Hernandez-Andrade E, Pelsers MM, Plasencia W, Benavides-Serralde JA, Eixarch E, Le Noble F, Ahmed A, Glatz JF, Nicolaides KH, Gratacos E. Cardiac dysfunction and cell damage across clinical stages of severity in growth-restricted fetuses. *Am J Obstet Gynecol* 2008; **199**: 254.e1-254.e8 [PMID: 18771973 DOI: 10.1016/j.ajog.2008.06.056]

33 **Rodríguez-López M**, Cruz-Lemini M, Valenzuela-Alcaraz B, Garcia-Otero L, Sitges M, Bijnens B, Gratacós E, Crispi F. Descriptive analysis of different phenotypes of cardiac remodeling in fetal growth restriction. *Ultrasound Obstet Gynecol* 2017; **50**: 207-214 [PMID: 27859818 DOI: 10.1002/uog.17365]

34 **Amruta N**, Kandikattu HK, Intapad S. Cardiovascular Dysfunction in Intrauterine Growth Restriction. *Curr Hypertens Rep* 2022; **24**: 693-708 [PMID: 36322299 DOI: 10.1007/s11906-022-01228-y]

35 **Martin H**, Hu J, Gennser G, Norman M. Impaired endothelial function and increased carotid stiffness in 9-year-old children with low birthweight. *Circulation* 2000; **102**: 2739-2744 [PMID: 11094041 DOI: 10.1161/01.cir.102.22.2739]

36 **Napoli C**, Glass CK, Witztum JL, Deutsch R, D'Armiento FP, Palinski W. Influence of maternal hypercholesterolaemia during pregnancy on progression of early atherosclerotic lesions in childhood: Fate of Early Lesions in Children (FELIC) study. *Lancet* 1999; **354**: 1234-1241 [PMID: 10520631 DOI: 10.1016/S0140-6736(99)02131-5]

37 **Herriges M**, Morrisey EE. Lung development: orchestrating the generation and regeneration of a complex organ. *Development* 2014; **141**: 502-513 [PMID: 24449833 DOI: 10.1242/dev.098186]

38 **Pike K**, Jane Pillow J, Lucas JS. Long term respiratory consequences of intrauterine growth restriction. *Semin Fetal Neonatal Med* 2012; **17**: 92-98 [PMID: 22277109 DOI: 10.1016/j.siny.2012.01.003]

39 **Nobile S**, Marchionni P, Gidiucci C, Correani A, Palazzi ML, Spagnoli C, Rondina C; Marche Neonatal Network, Carnielli VP. Oxygen saturation/FIO2 ratio at 36 wk' PMA in 1005 preterm infants: Effect of gestational age and early respiratory disease patterns. *Pediatr Pulmonol* 2019; **54**: 637-643 [PMID: 30688034 DOI: 10.1002/ppul.24265]

40 **Nobile S**, Marchionni P, Carnielli VP. Neonatal outcome of small for gestational age preterm infants. *Eur J Pediatr* 2017; **176**: 1083-1088 [PMID: 28660312 DOI: 10.1007/s00431-017-2957-1]

41 **Pike KC**, Hanson MA, Godfrey KM. Developmental mismatch: consequences for later cardiorespiratory health. *BJOG* 2008; **115**: 149-157 [PMID: 18081597 DOI: 10.1111/j.1471-0528.2007.01603.x]

42 **Briana DD**, Malamitsi-Puchner A. Small for gestational age birth weight: impact on lung structure and function. *Paediatr Respir Rev* 2013; **14**: 256-262 [PMID: 23249620 DOI: 10.1016/j.prrv.2012.10.001]

43 **Fandiño J**, Toba L, González-Matías LC, Diz-Chaves Y, Mallo F. Perinatal Undernutrition, Metabolic Hormones, and Lung Development. *Nutrients* 2019; **11** [PMID: 31771174 DOI: 10.3390/nu11122870]

44 **Arigliani M**, Spinelli AM, Liguoro I, Cogo P. Nutrition and Lung Growth. *Nutrients* 2018; **10** [PMID: 30021997 DOI: 10.3390/nu10070919]

45 **Maritz GS**, Cock ML, Louey S, Joyce BJ, Albuquerque CA, Harding R. Effects of fetal growth restriction on lung development before and after birth: a morphometric analysis. *Pediatr Pulmonol* 2001; **32**: 201-210 [PMID: 11536449 DOI: 10.1002/ppul.1109]

46 **Maritz GS**, Cock ML, Louey S, Suzuki K, Harding R. Fetal growth restriction has long-term effects on postnatal lung structure in sheep. *Pediatr Res* 2004; **55**: 287-295 [PMID: 14630984 DOI: 10.1203/01.PDR.0000106314.99930.65]

47 **Orgeig S**, Crittenden TA, Marchant C, McMillen IC, Morrison JL. Intrauterine growth restriction delays surfactant protein maturation in the sheep fetus. *Am J Physiol Lung Cell Mol Physiol* 2010; **298**: L575-L583 [PMID: 20097737 DOI: 10.1152/ajplung.00226.2009]

48 **Xu XF**, Lv Y, Gu WZ, Tang LL, Wei JK, Zhang LY, Du LZ. Epigenetics of hypoxic pulmonary arterial hypertension following intrauterine growth retardation rat: epigenetics in PAH following IUGR. *Respir Res* 2013; **14**: 20 [PMID: 23406533 DOI: 10.1186/1465-9921-14-20]

49 **Polglase GR**, Barbuto J, Allison BJ, Yawno T, Sutherland AE, Malhotra A, Schulze KE, Wallace EM, Jenkin G, Ricardo SD, Miller SL. Effects of antenatal melatonin therapy on lung structure in growth-restricted newborn lambs. *J Appl Physiol (1985)* 2017; **123**: 1195-1203 [PMID: 28819007 DOI: 10.1152/japplphysiol.00783.2016]

50 **Sutherland AE**, Crossley KJ, Allison BJ, Jenkin G, Wallace EM, Miller SL. The effects of intrauterine growth restriction and antenatal glucocorticoids on ovine fetal lung development. *Pediatr Res* 2012; **71**: 689-696 [PMID: 22337223 DOI: 10.1038/pr.2012.19]

51 **Arigliani M**, Stocco C, Valentini E, De Pieri C, Castriotta L, Ferrari ME, Canciani C, Driul L, Orsaria M, Cattarossi L, Cogo P. Lung function between 8 and 15 years of age in very preterm infants with fetal growth restriction. *Pediatr Res* 2021; **90**: 657-663 [PMID: 33469172 DOI: 10.1038/s41390-020-01299-0]

52 **Nikolajev K**, Heinonen K, Hakulinen A, Länsimies E. Effects of intrauterine growth retardation and prematurity on spirometric flow values and lung volumes at school age in twin pairs. *Pediatr Pulmonol* 1998; **25**: 367-370 [PMID: 9671162 DOI: 10.1002/(sici)1099-0496(199806)25:6<367::aid-ppul2>3.0.co;2-e]

53 **Okyere DO**, Bui DS, Washko GR, Lodge CJ, Lowe AJ, Cassim R, Perret JL, Abramson MJ, Walters EH, Waidyatillake NT, Dharmage SC. Predictors of lung function trajectories in population-based studies: A systematic review. *Respirology* 2021; **26**: 938-959 [PMID: 34490723 DOI: 10.1111/resp.14142]

54 **Karmaus W**, Mukherjee N, Janjanam VD, Chen S, Zhang H, Roberts G, Kurukulaaratchy RJ, Arshad H. Distinctive lung

function trajectories from age 10 to 26 years in men and women and associated early life risk factors - a birth cohort study. *Respir Res* 2019; **20**: 98 [PMID: 31118050 DOI: 10.1186/s12931-019-1068-0]

55 **Weber P**, Menezes AMB, Gonçalves H, Perez-Padilla R, Jarvis D, de Oliveira PD, Wehrmeister FC. Characterisation of pulmonary function trajectories: results from a Brazilian cohort. *ERJ Open Res* 2020; **6** [PMID: 32864380 DOI: 10.1183/23120541.00065-2020]

56 **Belgrave DCM**, Granell R, Turner SW, Curtin JA, Buchan IE, Le Souëf PN, Simpson A, Henderson AJ, Custovic A. Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. *Lancet Respir Med* 2018; **6**: 526-534 [PMID: 29628377 DOI: 10.1016/S2213-2600(18)30099-7]

57 **Stein CE**, Kumaran K, Fall CH, Shaheen SO, Osmond C, Barker DJ. Relation of fetal growth to adult lung function in south India. *Thorax* 1997; **52**: 895-899 [PMID: 9404378 DOI: 10.1136/thx.52.10.895]

58 **Canoy D**, Pekkanen J, Elliott P, Pouta A, Laitinen J, Hartikainen AL, Zitting P, Patel S, Little MP, Järvelin MR. Early growth and adult respiratory function in men and women followed from the fetal period to adulthood. *Thorax* 2007; **62**: 396-402 [PMID: 17105780 DOI: 10.1136/thx.2006.066241]

59 **Savran O**, Ulrik CS. Early life insults as determinants of chronic obstructive pulmonary disease in adult life. *Int J Chron Obstruct Pulmon Dis* 2018; **13**: 683-693 [PMID: 29520136 DOI: 10.2147/COPD.S153555]

60 **Duan P**, Wang Y, Lin R, Zeng Y, Chen C, Yang L, Yue M, Zhong S, Zhang Q. Impact of early life exposures on COPD in adulthood: A systematic review and meta-analysis. *Respirology* 2021; **26**: 1131-1151 [PMID: 34541740 DOI: 10.1111/resp.14144]

61 **Saad NJ**, Patel J, Burney P, Minelli C. Birth Weight and Lung Function in Adulthood: A Systematic Review and Meta-analysis. *Ann Am Thorac Soc* 2017; **14**: 994-1004 [PMID: 28362513 DOI: 10.1513/AnnalsATS.201609-746SR]

62 **Källén B**, Finnström O, Nygren KG, Otterblad Olausson P. Association between preterm birth and intrauterine growth retardation and child asthma. *Eur Respir J* 2013; **41**: 671-676 [PMID: 22700840 DOI: 10.1183/09031936.00041912]

63 **Ortqvist AK**, Lundholm C, Carlström E, Lichtenstein P, Cnattingius S, Almqvist C. Familial factors do not confound the association between birth weight and childhood asthma. *Pediatrics* 2009; **124**: e737-e743 [PMID: 19786434 DOI: 10.1542/peds.2009-0305]

64 **Villamor E**, Iliadou A, Cnattingius S. Is the association between low birth weight and asthma independent of genetic and shared environmental factors? *Am J Epidemiol* 2009; **169**: 1337-1343 [PMID: 19357326 DOI: 10.1093/aje/kwp054]

65 **Heath RJ**, Klevebro S, Wood TR. Maternal and Neonatal Polyunsaturated Fatty Acid Intake and Risk of Neurodevelopmental Impairment in Premature Infants. *Int J Mol Sci* 2022; **23** [PMID: 35054885 DOI: 10.3390/ijms23020700]

66 **Petersen AB**, Ogunrinu T, Wallace S, Yun J, Belliard JC, Singh PN. Implementation and Outcomes of a Maternal Smoking Cessation Program for a Multi-ethnic Cohort in California, USA, 2012-2019. *J Community Health* 2022; **47**: 257-265 [PMID: 34739686 DOI: 10.1007/s10900-021-01042-8]

67 **van Hoorn F**, de Wit L, van Rossem L, Jambroes M, Groenendaal F, Kwee A, Lamain-de Ruiter M, Franx A, van Rijn BB, Koster MPH, Bekker MN. A prospective population-based multicentre study on the impact of maternal body mass index on adverse pregnancy outcomes: Focus on normal weight. *PLoS One* 2021; **16**: e0257722 [PMID: 34555090 DOI: 10.1371/journal.pone.0257722]

68 **McCarthy EK**, Murray DM, Kiely ME. Iron deficiency during the first 1000 days of life: are we doing enough to protect the developing brain? *Proc Nutr Soc* 2022; **81**: 108-118 [PMID: 34548120 DOI: 10.1017/S0029665121002858]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 2864-2873

DOI: 10.12998/wjcc.v11.i13.2864

ISSN 2307-8960 (online)

REVIEW

Appraisal of gastric stump carcinoma and current state of affairs

Ankit Shukla, Raja Kalayarasan, Senthil Gnanasekaran, Biju Pottakkat

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Jia J, China; Kotelevets SM, Russia

Received: December 28, 2022
Peer-review started: December 28, 2022
First decision: March 9, 2023
Revised: March 21, 2023
Accepted: March 30, 2023
Article in press: March 30, 2023
Published online: May 6, 2023

Ankit Shukla, Raja Kalayarasan, Senthil Gnanasekaran, Biju Pottakkat, Department of Surgical Gastroenterology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry 605006, India

Corresponding author: Ankit Shukla, DNB, Senior Resident, Department of Surgical Gastroenterology, Jawaharlal Institute of Postgraduate Medical Education and Research, JIPMER Campus Rd, Gorimedu, Puducherry 605006, India.
nkitshukla@hotmail.com

Abstract

Gastric stump carcinoma, also known as remnant gastric carcinoma, is a malignancy arising in the remnant stomach following gastrectomy for a benign or malignant condition. Enterogastric reflux and preexisting risk factors in a patient with gastric cancer are the major contributors to the development of gastric stump carcinoma. The occurrence of gastric stump carcinoma is time-dependent and seen earlier in patients operated on for malignant rather than benign diseases. The tumor location is predominantly at the anastomotic site towards the stomach. However, it can occur anywhere in the remnant stomach. The pattern of lymph node involvement and the type of surgery required is distinctly different compared to primary gastric cancer. Gastric stump carcinoma is traditionally considered a malignancy with a dismal outcome. However, recent advances in diagnostic and therapeutic strategies have improved outcomes. Recent advances in molecular profiling of gastric stump carcinoma have identified distinct molecular subtypes, thereby providing novel therapeutic targets. Also, reports of gastric stump carcinoma following pancreatoduodenectomy and bariatric surgery highlight the need for more research to standardize the diagnosis, staging, and treatment of these tumors. The present review aims to provide an overview of gastric stump carcinoma highlighting the differences in clinicopathological profile and management compared to primary gastric carcinoma.

Key Words: Gastric cancer; Gastritis; Carcinoma; Endoscopic surveillance; Gastric stump cancer; Remnant gastric carcinoma

Core Tip: Gastric stump carcinoma is a rare malignancy with many unanswered questions regarding precise staging, molecular subtyping, and surgical management. The spectrum of its incidence is changing due to better medical management of peptic ulcer disease, increased survival of patients with malignancies, and malignancy in gastric stump following various other surgeries. The altered pattern of lymphatic spread deems further research to develop a newer staging system. Endoscopic surveillance with early gastric stump carcinoma detection made endoscopic resection and minimally invasive surgery feasible in selected patients with improved quality of life.

Citation: Shukla A, Kalayarasan R, Gnanasekaran S, Pottakkat B. Appraisal of gastric stump carcinoma and current state of affairs. *World J Clin Cases* 2023; 11(13): 2864-2873
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/2864.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.2864

INTRODUCTION

Gastric carcinoma, with an incidence of 5.6% and mortality of 7.7%, ranks fifth in incidence and fourth in mortality among all cancers, making it a worldwide health problem[1]. On the other hand, gastric stump or remnant gastric carcinoma is a less common entity and accounts for 2% to 6% of all gastric carcinoma and a pooled prevalence of 2.6%[2,3]. In 1922, Donald Church Balfour, a Canadian surgeon, first observed that patients undergoing gastric surgery for peptic ulcer disease had decreased survival due to the development of malignancy in the remnant stomach[4]. There has been a steady rise in gastric stump carcinoma from 1970 to the late twentieth century[5]. However, with a paradigm shift in the management of peptic ulcers to medical therapy, there is a decrease in the incidence of gastric stump carcinoma following benign disease. Surgical and systemic treatment advances have improved the postoperative survival of gastric carcinoma patients and those with pancreatic cancer who share similar risk factors due to changes in gastrointestinal continuity[5-7]. Also, screening programs for gastric cancer in high-incidence areas allowed early detection and better management of early gastric carcinoma. These factors could potentially increase the incidence of gastric stump carcinoma. Also, reports of gastric stump carcinoma in patients undergoing bariatric surgery could further increase the incidence of gastric stump carcinoma[8,9]. Compared to primary gastric carcinoma, gastric stump carcinoma is usually described as a malignancy with a dismal outcome with low resectability rates. The present review aims to highlight etiopathogenesis, the differences in the clinicopathological features, and the management of gastric stump carcinoma compared to primary gastric carcinoma. Also, recent advances in molecular typing of gastric stump carcinoma might open newer therapeutic options in the future[10].

Definition

Various definitions and nomenclature have been used for defining gastric stump carcinoma concerning the type of previous gastric surgery and the interval between the index gastric surgery and the development of malignancy. Some authors describe it as gastric cancer detected more than five years following gastric cancer surgery, while others recommend using a ten-year interval[11,12]. A few included all carcinoma arising in the remnant stomach regardless of the initial disease or duration following previous surgery as gastric stump carcinoma[13]. In Chinese literature, gastric stump carcinoma is defined as new cancer occurring in the residual stomach more than five or ten years after gastrectomy for benign diseases or gastric cancer, respectively[14]. The Japanese literature defines it as cancer in the remnant stomach following gastrectomy for benign disease or gastric cancer at least five years after the primary surgery[15]. As there is no consensus on the definition it is imperative to have uniform definition to address various issues related to gastric stump carcinoma.

Etiopathogenesis

Pathogenesis of gastric stump carcinoma is multifactorial and influenced by the indication for index gastric surgery and type of reconstruction[16-20]. Stump carcinoma tends to develop in a shorter period following index gastric surgery for a malignant etiology than benign causes. On average, it takes approximately 300 mo for benign gastroduodenal diseases and 100 mo for gastric cancer to turn into gastric stump carcinoma following primary gastric surgery[5,21]. However, irrespective of the initial gastric pathology, the shorter duration between index gastric surgery and the onset of stump carcinoma worsens the outcome[22-24]. In gastric carcinoma patients with a single lesion during index surgery, the transformation rate to gastric stump carcinoma has been reported to be 1.9% in 4 years[22]. A few studies have shown that Billroth II reconstruction has more preponderance for gastric stump carcinoma than Billroth I reconstruction[18-20]. While gastric stump carcinoma is commonly reported at the anastomotic site, it can occur anywhere in the remnant stomach[25]. Anastomotic site gastric stump

carcinoma is common following Billroth II reconstruction, whereas it can occur anywhere in the gastric stump after Billroth I reconstruction[23,25]. However, a meta-analysis and a study from Sweden have documented that reconstruction type does not affect the risk of gastric stump cancer development, highlighting the multifactorial pathways in the genesis of gastric stump carcinoma[26,27].

Various physiological and anatomical alterations after partial gastric resection account for the occurrence of gastric stump carcinoma. Increased enterogastric reflux, and bacterial overgrowth secondary to vagotomy-induced achlorhydria are two dominant factors implicated in the pathogenesis. Bacterial overgrowth reduces dietary nitrates to nitrites resulting in overexposure of gastric mucosa to nitrosamines leading to metaplasia and dysplasia[28,29]. Hypochlorhydria also increases epithelial cell proliferation rendering the mucosa more susceptible to DNA damage[30,31]. Kaminishi *et al*[32] showed that the denervation of gastric mucosa encourages carcinogenesis in a rat model. Miwa *et al*[31], documented that enterogastric reflux has carcinogenic potential in rats. It has been suggested that the hydrophobic nature of bile acids causes stress-induced oxidative DNA damage and reduces DNA repair in epithelial cells[33-35]. Enterogastric reflux changes the physiological environment and pH of the remnant stomach, making it susceptible to Epstein-Barr virus infection and facilitating entry into epithelial cells, which is associated with the development of gastric stump carcinoma[36]. A few studies have documented Epstein-Barr virus infection rate of 22.2% to 41.2% in all patients following distal gastrectomy, with higher incidence following Billroth II compared to Billroth I reconstruction[23,37,38]. Higher frequency of Epstein–Barr virus infection that occurs in gastric stump carcinoma compared to primary gastric cancer is an area of intense research.

The role of *Helicobacter pylori* in gastric stump carcinoma is questionable because gastroduodenal reflux hampers the growth of bacteria in the gastric stump[11,30]. However, some studies suggest that *Helicobacter pylori*-induced gastritis, in combination with bile reflux, stimulates cellular proliferation in the remnant stomach[39,40]. Hence, the role of *Helicobacter pylori* as a risk factor for gastric stump carcinoma remains an area of debate[41]. Attempts have been made to reduce the risk of gastric stump carcinoma by connecting the afferent and efferent limbs of the Billroth II reconstruction distal to gastro-jejunostomy (Braun's anastomosis) to reduce the reflux. However, nuclear studies have revealed that Braun's anastomosis is inadequate in suppressing the biliopancreatic reflux in the fasting state as well as following fatty meals[42]. Also, the use of Roux-en-Y reconstruction, or placing a jejunal interposition graft, to reduce reflux have reduced but does not entirely eliminate the risk, as cases of gastric stump carcinoma have been reported even after these reconstructions[43-45]. In addition to the aforementioned risk factors, patients who underwent gastrectomy for malignancy have a gastric microenvironment that is already conducive to the development of remnant gastric carcinomas like atrophic gastritis and intestinal metaplasia[2]. Also, patients undergoing proximal gastrectomy for gastric cancer have more risk of gastric stump carcinoma compared to those undergoing distal gastrectomy[22,23].

Molecular biology

Detailed molecular characteristics of gastric stump carcinoma remain to be clarified because of its rarity. Studies have shown that Programmed death ligand 1 (PD-L1) expression in gastric stump carcinoma tumor cells is lesser than in primary gastric cancer. However, PDL-1 expression in tumor-infiltrating immune cells is higher in gastric stump carcinoma than in primary gastric cancer[33,46]. In patients with gastro-enteric reconstruction, PD-L1 overexpression in inflammatory cells is aimed at suppressing inflammation. However, it also contributes to the immune escape of tumor cells in patients with gastric stump carcinoma. As the expression of epidermal growth factor and human epidermal growth factor receptor 2 (HER2) is less, HER2-targeted therapy may not frequently be applicable for treating gastric stump carcinoma[46]. Some authors reported that microsatellite instability was more common in gastric stump carcinoma compared to sporadic carcinoma stomach[33]. Also, the inactivation of hMLH1 and hMSH2 is more in Billroth II compared to Billroth I reconstruction[33,34]. Microsatellite instability and high PD-L1 expression suggest immunotherapy's role in managing gastric stump carcinoma. Also, C promoter polymorphism (IL-1B-31T) is associated with gastric stump carcinoma, with the T allele offering protection against gastric stump carcinoma[47]. A comprehensive understanding of molecular characteristics of gastric stump carcinoma may enable the selection of effective treatment options and the development of novel therapeutic strategies.

Histological transformation

According to the Lauren classification, two histological types of gastric carcinoma have been identified using hematoxylin and eosin staining, namely diffuse and intestinal type[48]. In gastric stump carcinoma, the histology of the tumor depends upon the location. Patients with tumors at the anastomotic site often have diffuse-type gastric cancer. Biliopancreatic reflux results in adenocystic proliferation of the gastric glands at the anastomotic site leading to a diffuse type of carcinoma[11]. Intestinal type is common in patients with gastric stump carcinoma located other than the anastomotic site. In the body of the remnant stomach, dysplasia ensues, leading to loss of gastric phenotype and resulting in intestinal type of carcinoma, which is attributed to the denervation of the gastric stump[32]. Another salient feature noticed on histology is that adjacent gastric mucosa in gastric stump carcinoma is less atrophic compared to proximal gastric carcinoma patients signifying a difference in the pathogenesis of gastric stump carcinoma[49]. Also, serosal tumor involvement seen in 37% to 48% of

patients with remnant gastric carcinoma is significantly higher compared to 19% in proximal gastric carcinoma[50].

Pattern of lymph node involvement

The involvement of lymph nodes in gastric stump carcinoma is peculiar due to anatomical changes occurring after the type of primary surgery. Also, the pattern of lymph node spread is influenced by the indication of index gastric surgery. The lymphatic trunks are transected during the primary surgery, altering the lymphatic drainage pathways. Proximal gastric carcinoma normally drains along the celiac artery *via* lesser curvature, left gastric artery, and right cardiac lymph nodes. However, post-primary surgery, the draining pathway is through greater curvature, posterior gastric, and splenic artery lymph nodes[11,16,51]. Tumors in the gastrojejunal anastomotic site tend to have higher jejunal mesentery lymph nodal involvement, which ranges between 7% and 46.8%. Also, they tend to have a higher stage at presentation and poor outcomes[15,52-54]. Overall proportion of patients with splenic hilar node involvement is significantly higher in gastric stump carcinoma compared to primary gastric cancer. Jejunal mesentery lymph node involvement is primarily encountered after Billroth II reconstruction[15,51]. Though mediastinal and paraaortic lymph nodal spread is reported, the exact incidence is not known, as clearance of these nodes is not routine for gastric stump carcinoma[51,55-57].

The total number of lymph nodes harvested following surgery for remnant gastric carcinoma is significantly less than primary gastric carcinoma, especially if the prior surgery was for gastric malignancy, as the nodes would have already been removed. Hence, the lymph node grouping used in the TNM classification for primary gastric carcinoma may not be appropriate for staging remnant gastric carcinoma[58]. Some authors have advocated the use of the lymph node ratio as a better prognostic marker and for selecting adjuvant therapy[58,59]. However, the lymph node ratio determined by dividing the number of positive lymph nodes by the total harvested nodes has different cut-off values in different studies[60-62]. Lack of standardization, primarily due to the limited sample size in the reported studies, limits the widespread use of lymph node ratio in gastric stump carcinoma. Hence, a novel staging system is required for gastric stump carcinoma, which considers the alterations of primary surgery and the type of reconstruction to accurately predict outcomes in these patients.

Management principles

The primary treatment of gastric stump carcinoma is radical surgical resection with lymphadenectomy and en bloc resection of involved adjacent organs[63-65]. As it is difficult to differentiate between tumor infiltration and inflammatory adhesions, en bloc resection of the involved adjacent organ is recommended. Most commonly resected adjacent organs are the spleen, transverse colon, jejunum, and distal pancreas[66]. In patients with gastric stump carcinoma following Billroth II reconstruction, a minimum of 10 cm of the jejunum distal to anastomosis is resected along with the ligament of Treitz and jejunal mesentery for better oncological outcomes[66-69]. Stump carcinoma infiltrating the esophagus requires cardiac, infradiaphragmatic, supradiaphragmatic, esophageal hiatal and lower thoracic lymphadenectomy. A few authors recommend splenic and paraaortic lymph node dissection for advanced gastric stump carcinoma when they are involved[51,54,69,70]. However, the standard lymph node dissection in gastric stump carcinoma is yet to be defined. Major factors influencing overall survival in gastric stump carcinoma are T stage, R0 resection and the time interval between primary gastrectomy and remnant gastrectomy[24].

Conventionally, gastric stump carcinoma is managed with open surgical approach. However, recently minimally invasive approaches have been used to resect these tumors. Compared to open surgery, minimally invasive surgery is associated with less blood loss, decreased morbidity, and similar 5 year survival rates[67,68]. Also the feasibility and comparable long term outcomes with endoscopic resection of early gastric stump carcinoma has been recently reported[71]. The overall survival and disease specific survival rates of 87.3% and 100% respectively was reported with endoscopic resection [71].

Current status of diagnosis

The poor outcome in patients with gastric stump carcinoma is primarily due to late diagnosis resulting in a presentation at an advanced stage with a poor resectability rate. As symptoms of gastric stump carcinoma are non-specific and often resemble the postgastrectomy symptoms, active endoscopic surveillance is an option for early diagnosis[72-74]. A few authors have suggested annual endoscopic surveillance from one-year post gastric cancer surgery to at least ten years. While surveillance endoscopy has been suggested following gastrectomy for the benign disease, it should be kept in mind that the primary diagnosis of a benign disease makes patients less compliant for future endoscopies[5,75]. Early detection of gastric stump carcinoma does not always require macroscopic lesions. Recent advances in endoscopic diagnostic techniques for diagnosis have resulted in the detection of early gastric carcinoma at an earlier stage, thereby facilitating endoscopic resection[76-80].

Appraisal of future perspectives

Several studies have documented en bloc resection and complete resection rates of 91% to 100% and

Table 1 Summary of endoscopic submucosal dissection for early gastric stump carcinoma, *n* (%)

Ref.	Number of patients (number of lesion)	*En bloc* resection	Complete resection	Perforation	Bleeding
Takenaka *et al*[91], 2008	31	30 (97)	23 (74)	4 (13)	0
Hirasaki *et al*[92], 2008	17	17 (100)	14 (82)	0	3 (18)
Hoteya *et al*[93], 2010	40	-	38 (95)	1 (2.5)	2 (5)
Lee *et al*[94], 2010	13	13 (100)	12 (92.3)	0	0
Nonaka *et al*[78], 2013	139	131 (94)	118 (85)	2 (14)	2 (14)
Tanaka *et al*[95], 2013	33	33 (100)	31 (94)	3 (9)	1(3)
Nishide *et al*[87], 2012	58 (62)	59 (95)	53 (85)	11 (18)	5 (8)

74% to 94%, respectively, for endoscopic submucosal dissection (Table 1)[71,80-84]. Some authors have tried endoscopic submucosal dissection with insulated tipped diathermic knife with good results, however operative time was more[85]. Comparing endoscopic mucosal dissection to endoscopic mucosal resection the former has significantly higher resection rates[86]. Though endoscopic mucosal dissection is difficult in the upper part of stomach, it have been found to be safe and feasible[87]. Perforation is relatively common after endoscopic gastric stump carcinoma resection and usually occurs at the anastomotic site[84,88]. As previously mentioned minimally invasive approach is increasingly used for gastric stump carcinoma. Studies comparing laparoscopic and open total gastrectomy for stump carcinoma have shown that laparoscopic surgery has less blood loss, more lymph node harvest, early post-operative recovery and lower complication rates[67,68,89-93]. However, all studies reported prolonged operative time compared to open surgery (Table 2). Although 5 year survival rates were equivalent between both groups, most studies had short follow up[67,91,93].

Recently more studies are showing the association of gastric stump carcinoma with various other surgeries like pancreatoduodenectomy, bariatric surgery, and following gastric pull-up, though the numbers are not alarming[7,94-96]. Enterogastric reflux is the primary mechanism. Gastric stump carcinoma post pancreatoduodenectomy usually occurs at the gastrojejunostomy site and is frequently poorly differentiated[96]. Some authors have reported cases of remnant gastric carcinoma even after pylorus preserving pancreatoduodenectomy at the pancreaticogastrostomy site[97]. A few researchers consider pancreatoduodenectomy an emerging risk factor for gastric stump carcinoma as the survival post pancreatic cancer surgery is increasing[7,98]. Sleeve gastrectomy is one of the most common procedures performed for managing morbid obesity. A few studies have reported remnant gastric carcinoma 15 to 25 years after bariatric surgery[8,99]. Gastric stump carcinoma after Roux-en-Y gastric bypass is often reported in the excluded antrum followed by body, pylorus and fundus[45]. As the reported number of gastric stump carcinoma cases post-bariatric surgery is less, more studies are needed to document whether bariatric surgery represents a true risk factor for gastric stump carcinoma. However, it is reasonable to suggest post-bariatric surgery endoscopic surveillance in gastric cancer endemic regions. Well-designed epidemiologic studies are needed to investigate these new associations with gastric stump carcinoma thoroughly.

With the rise of targeted therapy in gastric carcinoma, the interest of researchers has grown in gastric stump carcinoma, too. High incidence of microsatellite instability and PD-L1 expression in gastric stump carcinoma suggests a possible role of immunotherapy in these patients[100,101]. Prevalence of PTEN and SMAD 4 mutations in gastric stump carcinoma could also provide therapeutic targets[101]. The widespread availability of next-generation sequencing could facilitate molecular profiling of gastric stump cancer and the development of novel therapeutic strategies in the future.

CONCLUSION

Gastric stump carcinoma will not remain a rare clinical problem and may be more frequently encountered in the future. This entity still needs introspection and research concerning precise definition, appropriate staging and management. Owing to recent advances in diagnostic and therapeutic options, gastric stump carcinoma can be detected early and have survival equivalent to primary gastric carcinoma. Endoscopic management and minimally invasive surgery feasible in selected patients may offer a better quality of life. Recent advances in the molecular biology of gastric stump carcinoma may help to develop novel therapeutic strategies.

Table 2 Overview of minimally invasive and open surgery for gastric stump carcinoma

Ref.	Country	No of patients (Lap/open/robotic)	Operative time (Lap/open)	Blood loss (Lap/open)	Postoperative hospital stay (Lap/open)	Conversion to open	Number of lymph nodes retrieved (Lap/open)
Son *et al* [100], 2013	Korea	17/17/0	234.4/170 minutes	227.6/184.1 mL	9.3/9.3 days	8	18.8/22.3
Nagai *et al* [98], 2014	Japan	12/10/0	362.3/270.5 minutes	65.8/746.3 mL	11.3/24.9 days	NA	23.7/15.9
Kwon *et al* [74], 2014	Korea	10/58/8	266.2/203.3 minutes	182.2/193.1 mL	6/9 days	1	8/7
Kim *et al* [97], 2014	Korea	17/50/0	197.2/149.3 minutes	NA	11.1/13.8 days	0	12.9/NA
Tsunoda *et al*[99], 2014	Japan	10/6/0	325/289 minutes	55/893 mL	13/24 days	0	22/7
Otsuka *et al* [96], 2018	Japan	7/20/0	364/309 minutes	70/1066 mL	13/27 days	0	22/12
Booka *et al* [75], 2019	Japan	23/8/0	307.5/295.8 minutes	135.5/568.3 mL	10.6/21.3 days	2	8.8/6

Lap: Laparoscopic; ml: Milliliter; NA: Not applicable.

FOOTNOTES

Author contributions: All the authors did the literature search. Shukla A wrote the first draft of the review; Kalayarasan R conceptualized the work, supervised the writing, gave intellectual inputs; all the authors critically revised the manuscript.

Conflict-of-interest statement: All authors have no conflicts of interest to report.

Country/Territory of origin: India

ORCID number: Ankit Shukla 0000-0002-5037-8525; Raja Kalayarasan 0000-0003-4056-8672; Senthil Gnanasekaran 0000-0002-8639-5423; Biju Pottakkat 0000-0002-8474-0270.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]
2 **Hanyu T**, Wakai A, Ishikawa T, Ichikawa H, Kameyama H, Wakai T. Carcinoma in the Remnant Stomach During Long-Term Follow-up After Distal Gastrectomy for Gastric Cancer: Analysis of Cumulative Incidence and Associated Risk Factors. *World J Surg* 2018; **42**: 782-787 [PMID: 28924721 DOI: 10.1007/s00268-017-4227-9]
3 **Mak TK**, Guan B, Peng J, Chong TH, Wang C, Huang S, Yang J. Prevalence and characteristics of gastric remnant cancer: A systematic review and meta-analysis. *Asian J Surg* 2021; **44**: 11-17 [PMID: 32253109 DOI: 10.1016/j.asjsur.2020.03.012]
4 **Balfour DC**. FACTORS INFLUENCING THE LIFE EXPECTANCY OF PATIENTS OPERATED ON FOR GASTRIC ULCER. *Ann Surg* 1922; **76**: 405-408 [PMID: 17864703 DOI: 10.1097/00000658-192209000-00014]
5 **Ohashi M**, Katai H, Fukagawa T, Gotoda T, Sano T, Sasako M. Cancer of the gastric stump following distal gastrectomy for cancer. *Br J Surg* 2007; **94**: 92-95 [PMID: 17054314 DOI: 10.1002/bjs.5538]
6 **Fujita T**, Gotohda N, Takahashi S, Nakagohri T, Konishi M, Kinoshita T. Relationship between the histological type of initial lesions and the risk for the development of remnant gastric cancers after gastrectomy for synchronous multiple

gastric cancers. *World J Surg* 2010; **34**: 296-302 [PMID: 20012285 DOI: 10.1007/s00268-009-0325-7]
7 **Bouquot M**, Dokmak S, Barbier L, Cros J, Levy P, Sauvanet A. Gastric stump carcinoma as a long-term complication of pancreaticoduodenectomy: report of two cases and review of the English literature. *BMC Gastroenterol* 2017; **17**: 117 [PMID: 29166862 DOI: 10.1186/s12876-017-0682-x]
8 **De Roover A**, Detry O, Desaive C, Maweja S, Coimbra C, Honoré P, Meurisse M. Risk of upper gastrointestinal cancer after bariatric operations. *Obes Surg* 2006; **16**: 1656-1661 [PMID: 17217643 DOI: 10.1381/096089206779319419]
9 **Nakayoshi T**, Tajiri H, Matsuda K, Kaise M, Ikegami M, Sasaki H. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology (including video). *Endoscopy* 2004; **36**: 1080-1084 [PMID: 15578298 DOI: 10.1055/s-2004-825961]
10 **Ramos MFKP**, Pereira MA, de Castria TB, Ribeiro RRE, Cardili L, de Mello ES, Zilberstein B, Ribeiro-Júnior U, Cecconello I. Remnant gastric cancer: a neglected group with high potential for immunotherapy. *J Cancer Res Clin Oncol* 2020; **146**: 3373-3383 [PMID: 32671505 DOI: 10.1007/s00432-020-03322-7]
11 **Sinning C**, Schaefer N, Standop J, Hirner A, Wolff M. Gastric stump carcinoma - epidemiology and current concepts in pathogenesis and treatment. *Eur J Surg Oncol* 2007; **33**: 133-139 [PMID: 17071041 DOI: 10.1016/j.ejso.2006.09.006]
12 **Ahn HS**, Kim JW, Yoo MW, Park DJ, Lee HJ, Lee KU, Yang HK. Clinicopathological features and surgical outcomes of patients with remnant gastric cancer after a distal gastrectomy. *Ann Surg Oncol* 2008; **15**: 1632-1639 [PMID: 18379851 DOI: 10.1245/s10434-008-9871-8]
13 **Lu J**, Huang CM, Zheng CH, Li P, Xie JW, Wang JB, Lin JX, Chen QY, Cao LL, Lin M. Prognostic value of tumor size in patients with remnant gastric cancer: is the seventh UICC stage sufficient for predicting prognosis? *PLoS One* 2014; **9**: e115776 [PMID: 25549339 DOI: 10.1371/journal.pone.0115776]
14 **Gao Z**, Jiang K, Ye Y, Wang S. [Interpretation on Chinese surgeons' consensus opinion for the definition of gastric stump cancer (version 2018)]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2018; **21**: 486-490 [PMID: 29774927]
15 **Shimada H**, Fukagawa T, Haga Y, Oba K. Does remnant gastric cancer really differ from primary gastric cancer? *Gastric Cancer* 2016; **19**: 339-349 [PMID: 26667370 DOI: 10.1007/s10120-015-0582-0]
16 **Sasako M**, Maruyama K, Kinoshita T, Okabayashi K. Surgical treatment of carcinoma of the gastric stump. *Br J Surg* 1991; **78**: 822-824 [PMID: 1873711 DOI: 10.1002/bjs.1800780718]
17 **Newman E**, Brennan MF, Hochwald SN, Harrison LE, Karpeh MS Jr. Gastric remnant carcinoma: just another proximal gastric cancer or a unique entity? *Am J Surg* 1997; **173**: 292-297 [PMID: 9136783 DOI: 10.1016/S0002-9610(96)00403-5]
18 **Yamamoto M**, Yamanaka T, Baba H, Kakeji Y, Maehara Y. The postoperative recurrence and the occurrence of second primary carcinomas in patients with early gastric carcinoma. *J Surg Oncol* 2008; **97**: 231-235 [PMID: 18095298 DOI: 10.1002/jso.20946]
19 **Caygill CP**, Hill MJ, Kirkham JS, Northfield TC. Mortality from gastric cancer following gastric surgery for peptic ulcer. *Lancet* 1986; **1**: 929-931 [PMID: 2871238 DOI: 10.1016/s0140-6736(86)91041-x]
20 **Toftgaard C**. Gastric cancer after peptic ulcer surgery. A historic prospective cohort investigation. *Ann Surg* 1989; **210**: 159-164 [PMID: 2757419 DOI: 10.1097/00000658-198908000-00004]
21 **Komatsu S**, Ichikawa D, Okamoto K, Ikoma D, Tsujiura M, Nishimura Y, Murayama Y, Shiozaki A, Ikoma H, Kuriu Y, Nakanishi M, Fujiwara H, Ochiai T, Kokuba Y, Otsuji E. Progression of remnant gastric cancer is associated with duration of follow-up following distal gastrectomy. *World J Gastroenterol* 2012; **18**: 2832-2836 [PMID: 22719193 DOI: 10.3748/wjg.v18.i22.2832]
22 **Nozaki I**, Hato S, Kobatake T, Ohta K, Kubo Y, Nishimura R, Kurita A. Incidence of metachronous gastric cancer in the remnant stomach after synchronous multiple cancer surgery. *Gastric Cancer* 2014; **17**: 61-66 [PMID: 23624766 DOI: 10.1007/s10120-013-0261-y]
23 **Tanigawa N**, Nomura E, Lee SW, Kaminishi M, Sugiyama M, Aikou T, Kitajima M; Society for the Study of Postoperative Morbidity after Gastrectomy. Current state of gastric stump carcinoma in Japan: based on the results of a nationwide survey. *World J Surg* 2010; **34**: 1540-1547 [PMID: 20182716 DOI: 10.1007/s00268-010-0505-5]
24 **Ozgun YM**, Oter V, Piskin E, Colakoglu MK, Aydin O, Surel AA, Aksoy E, Bostanci EB. Is complete resection has a better survival in remnant gastric cancer and what are the prognositic factors affecting these results? *Indian J Surg* 2022; **84**: 55-62 [DOI: 10.1007/s12262-021-02801-6]
25 **Takeno S**, Noguchi T, Kimura Y, Fujiwara S, Kubo N, Kawahara K. Early and late gastric cancer arising in the remnant stomach after distal gastrectomy. *Eur J Surg Oncol* 2006; **32**: 1191-1194 [PMID: 16797159 DOI: 10.1016/j.ejso.2006.04.018]
26 **Tersmette AC**, Offerhaus GJ, Tersmette KW, Giardiello FM, Moore GW, Tytgat GN, Vandenbroucke JP. Meta-analysis of the risk of gastric stump cancer: detection of high risk patient subsets for stomach cancer after remote partial gastrectomy for benign conditions. *Cancer Res* 1990; **50**: 6486-6489 [PMID: 2145061]
27 **Lagergren J**, Lindam A, Mason RM. Gastric stump cancer after distal gastrectomy for benign gastric ulcer in a population-based study. *Int J Cancer* 2012; **131**: E1048-E1052 [PMID: 22532306 DOI: 10.1002/ijc.27614]
28 **Safatle-Ribeiro AV**, Ribeiro Júnior U, Sakai P, Iriya K, Ishioka S, Gama-Rodrigues J. Gastric stump mucosa: is there a risk for carcinoma? *Arq Gastroenterol* 2001; **38**: 227-231 [PMID: 12068532 DOI: 10.1590/s0004-28032001000400004]
29 **Sitarz R**, Maciejewski R, Polkowski WP, Offerhaus GJ. Gastroenterostoma after Billroth antrectomy as a premalignant condition. *World J Gastroenterol* 2012; **18**: 3201-3206 [PMID: 22783043 DOI: 10.3748/wjg.v18.i25.3201]
30 **Păduraru DN**, Nica A, Ion D, Handaric M, Andronic O. Considerations on risk factors correlated to the occurrence of gastric stump cancer. *J Med Life* 2016; **9**: 130-136 [PMID: 27453741]
31 **Miwa K**, Hasegawa H, Fujimura T, Matsumoto H, Miyata R, Kosaka T, Miyazaki I, Hattori T. Duodenal reflux through the pylorus induces gastric adenocarcinoma in the rat. *Carcinogenesis* 1992; **13**: 2313-2316 [PMID: 1473239 DOI: 10.1093/carcin/13.12.2313]
32 **Kaminishi M**, Shimizu N, Shiomoyama S, Yamaguchi H, Ogawa T, Sakai S, Kuramoto S, Oohara T. Etiology of gastric remnant cancer with special reference to the effects of denervation of the gastric mucosa. *Cancer* 1995; **75**: 1490-1496 [PMID: 7889480 DOI: 10.1002/1097-0142(19950315)75:6+<1490::aid-cncr2820751518>3.0.co;2-3]
33 **Aya M**, Yashiro M, Nishioka N, Onoda N, Hirakawa K. Carcinogenesis in the remnant stomach following distal

gastrectomy with billroth II reconstruction is associated with high-level microsatellite instability. *Anticancer Res* 2006; **26**: 1403-1411 [PMID: 16619551]

34 **Nakachi A**, Miyazato H, Shimoji H, Hiroyasu S, Isa T, Shiraishi M, Muto Y. Microsatellite instability in patients with gastric remnant cancer. *Gastric Cancer* 1999; **2**: 210-214 [PMID: 11957100 DOI: 10.1007/s101200050065]

35 **Payne CM**, Bernstein C, Dvorak K, Bernstein H. Hydrophobic bile acids, genomic instability, Darwinian selection, and colon carcinogenesis. *Clin Exp Gastroenterol* 2008; **1**: 19-47 [PMID: 21677822 DOI: 10.2147/ceg.s4343]

36 **Lu C**, Zhang H, Zhou W, Wan X, Li L, Yu C. Epstein-Barr virus infection and genome polymorphisms on gastric remnant carcinoma: a meta-analysis. *Cancer Cell Int* 2020; **20**: 401 [PMID: 32843851 DOI: 10.1186/s12935-020-01498-z]

37 **Nishikawa J**, Yanai H, Hirano A, Okamoto T, Nakamura H, Matsusaki K, Kawano T, Miura O, Okita K. High prevalence of Epstein-Barr virus in gastric remnant carcinoma after Billroth-II reconstruction. *Scand J Gastroenterol* 2002; **37**: 825-829 [PMID: 12190097 DOI: 10.1080/gas.37.7.825.829]

38 **Kaizaki Y**, Hosokawa O, Sakurai S, Fukayama M. Epstein-Barr virus-associated gastric carcinoma in the remnant stomach: de novo and metachronous gastric remnant carcinoma. *J Gastroenterol* 2005; **40**: 570-577 [PMID: 16007390 DOI: 10.1007/s00535-005-1590-3]

39 **Seoane A**, Bessa X, Alameda F, Munné A, Gallen M, Navarro S, O'Callaghan E, Panadès A, Andreu M, Bory F. Role of Helicobacter pylori in stomach cancer after partial gastrectomy for benign ulcer disease. *Rev Esp Enferm Dig* 2005; **97**: 778-785 [PMID: 16438621 DOI: 10.4321/s1130-01082005001100002]

40 **Leivonen M**, Nordling S, Haglund C. Does Helicobacter pylori in the gastric stump increase the cancer risk after certain reconstruction types? *Anticancer Res* 1997; **17**: 3893-3896 [PMID: 9427799]

41 **Lynch DA**, Mapstone NP, Clarke AM, Jackson P, Dixon MF, Quirke P, Axon AT. Cell proliferation in the gastric corpus in Helicobacter pylori associated gastritis and after gastric resection. *Gut* 1995; **36**: 351-353 [PMID: 7698691 DOI: 10.1136/gut.36.3.351]

42 **Vogel SB**, Drane WE, Woodward ER. Clinical and radionuclide evaluation of bile diversion by Braun enteroenterostomy: prevention and treatment of alkaline reflux gastritis. An alternative to Roux-en-Y diversion. *Ann Surg* 1994; **219**: 458-65; discussion 465 [PMID: 8185396 DOI: 10.1097/00000658-199405000-00003]

43 **Chan DC**, Fan YM, Lin CK, Chen CJ, Chen CY, Chao YC. Roux-en-Y reconstruction after distal gastrectomy to reduce enterogastric reflux and Helicobacter pylori infection. *J Gastrointest Surg* 2007; **11**: 1732-1740 [PMID: 17876675 DOI: 10.1007/s11605-007-0302-0]

44 **Hollands MJ**, Filipe I, Edwards S, Brame K, Maisey M, Owen WJ. Clinical and histological sequelae of Roux-en-Y diversion. *Br J Surg* 1989; **76**: 481-484 [PMID: 2736362 DOI: 10.1002/bjs.1800760518]

45 **Tornese S**, Aiolfi A, Bonitta G, Rausa E, Guerrazzi G, Bruni PG, Micheletto G, Bona D. Remnant Gastric Cancer After Roux-en-Y Gastric Bypass: Narrative Review of the Literature. *Obes Surg* 2019; **29**: 2609-2613 [PMID: 31001760 DOI: 10.1007/s11695-019-03892-7]

46 **Tanigawa H**, Uesugi H, Mitomi H, Saigenji K, Okayasu I. Possible association of active gastritis, featuring accelerated cell turnover and p53 overexpression, with cancer development at anastomoses after gastrojejunostomy. Comparison with gastroduodenostomy. *Am J Clin Pathol* 2000; **114**: 354-363 [PMID: 10989635 DOI: 10.1093/ajcp/114.3.354]

47 **Sitarz R**, de Leng WW, Polak M, Morsink FH, Bakker O, Polkowski WP, Maciejewski R, Offerhaus GJ, Milne AN. IL-1B -31T>C promoter polymorphism is associated with gastric stump cancer but not with early onset or conventional gastric cancers. *Virchows Arch* 2008; **453**: 249-255 [PMID: 18688641 DOI: 10.1007/s00428-008-0642-5]

48 **Lauren P**. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. An attempt at a HISTO-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49 [PMID: 14320675 DOI: 10.1111/apm.1965.64.1.31]

49 **Sasaki K**, Fujiwara Y, Kishi K, Motoori M, Yano M, Ohigashi H, Ohue M, Noura S, Maruhashi S, Takahashi H, Gotoh K, Shingai T, Yamamoto T, Tomita Y, Ishikawa O. Pathological findings of gastric mucosa in patients with gastric remnant cancer. *Hepatogastroenterology* 2014; **61**: 251-254 [PMID: 24895831]

50 **Tokunaga M**, Sano T, Ohyama S, Hiki N, Fukunaga T, Yamada K, Yamaguchi T. Clinicopathological characteristics and survival difference between gastric stump carcinoma and primary upper third gastric cancer. *J Gastrointest Surg* 2013; **17**: 313-318 [PMID: 23233273 DOI: 10.1007/s11605-012-2114-0]

51 **Han SL**, Hua YW, Wang CH, Ji SQ, Zhuang J. Metastatic pattern of lymph node and surgery for gastric stump cancer. *J Surg Oncol* 2003; **82**: 241-246 [PMID: 12672008 DOI: 10.1002/jso.10228]

52 **Chowdappa R**, Tiwari AR, Ranganath N, Kumar RV. Is there difference between anastomotic site and remnant stump carcinoma in gastric stump cancers? *J Gastrointest Oncol* 2019; **10**: 307-313 [PMID: 31032099 DOI: 10.21037/jgo.2018.12.03]

53 **Di Leo A**, Pedrazzani C, Bencivenga M, Coniglio A, Rosa F, Morgani P, Marrelli D, Marchet A, Cozzaglio L, Giacopuzzi S, Tiberio GA, Doglietto GB, Vittimberga G, Roviello F, Ricci F. Gastric stump cancer after distal gastrectomy for benign disease: clinicopathological features and surgical outcomes. *Ann Surg Oncol* 2014; **21**: 2594-2600 [PMID: 24639193 DOI: 10.1245/s10434-014-3633-6]

54 **Komatsu S**, Ichikawa D, Okamoto K, Ikoma D, Tsujiura M, Shiozaki A, Fujiwara H, Murayama Y, Kuriu Y, Ikoma H, Nakanishi M, Ochiai T, Kokuba Y, Otsuji E. Differences of the lymphatic distribution and surgical outcomes between remnant gastric cancers and primary proximal gastric cancers. *J Gastrointest Surg* 2012; **16**: 503-508 [PMID: 22215245 DOI: 10.1007/s11605-011-1804-3]

55 **Ohashi M**, Morita S, Fukagawa T, Kushima R, Katai H. Surgical treatment of non-early gastric remnant carcinoma developing after distal gastrectomy for gastric cancer. *J Surg Oncol* 2015; **111**: 208-212 [PMID: 25175816 DOI: 10.1002/jso.23774]

56 **Li F**, Zhang R, Liang H, Liu H, Quan J, Zhao J. The pattern of lymph node metastasis and the suitability of 7th UICC N stage in predicting prognosis of remnant gastric cancer. *J Cancer Res Clin Oncol* 2012; **138**: 111-117 [PMID: 22048654 DOI: 10.1007/s00432-011-1034-9]

57 **Yonemura Y**, Ninomiya I, Tsugawa K, Masumoto H, Takamura H, Fushida S, Yamaguchi A, Miwa K, Miyazaki I. Lymph node metastases from carcinoma of the gastric stump. *Hepatogastroenterology* 1994; **41**: 248-252 [PMID:

7959547]
58 **Wang H**, Qi H, Liu X, Gao Z, Hidasa I, Aikebaier A, Li K. Positive lymph node ratio is an index in predicting prognosis for remnant gastric cancer with insufficient retrieved lymph node in R0 resection. *Sci Rep* 2021; **11**: 2022 [PMID: 33479327 DOI: 10.1038/s41598-021-81663-0]
59 **Costa-Pinho A**, Pinto-de-Sousa J, Barbosa J, Costa-Maia J. Gastric stump cancer: more than just another proximal gastric cancer and demanding a more suitable TNM staging system. *Biomed Res Int* 2013; **2013**: 781896 [PMID: 24151622 DOI: 10.1155/2013/781896]
60 **Deng J**, Liang H, Wang D, Sun D, Ding X, Pan Y, Liu X. Enhancement the prediction of postoperative survival in gastric cancer by combining the negative lymph node count with ratio between positive and examined lymph nodes. *Ann Surg Oncol* 2010; **17**: 1043-1051 [PMID: 20039218 DOI: 10.1245/s10434-009-0863-0]
61 **Son SY**, Kong SH, Ahn HS, Park YS, Ahn SH, Suh YS, Park DJ, Lee HJ, Kim HH, Yang HK. The value of N staging with the positive lymph node ratio, and splenectomy, for remnant gastric cancer: A multicenter retrospective study. *J Surg Oncol* 2017; **116**: 884-893 [PMID: 28650587 DOI: 10.1002/jso.24737]
62 **Nakagawa M**, Choi YY, An JY, Hong JH, Kim JW, Kim HI, Cheong JH, Hyung WJ, Choi SH, Noh SH. Staging for Remnant Gastric Cancer: The Metastatic Lymph Node Ratio vs. the UICC 7th Edition System. *Ann Surg Oncol* 2016; **23**: 4322-4331 [PMID: 27370654 DOI: 10.1245/s10434-016-5390-1]
63 **Thorban S**, Böttcher K, Etter M, Roder JD, Busch R, Siewert JR. Prognostic factors in gastric stump carcinoma. *Ann Surg* 2000; **231**: 188-194 [PMID: 10674609 DOI: 10.1097/00000658-200002000-00006]
64 **Mezhir JJ**, Gonen M, Ammori JB, Strong VE, Brennan MF, Coit DG. Treatment and outcome of patients with gastric remnant cancer after resection for peptic ulcer disease. *Ann Surg Oncol* 2011; **18**: 670-676 [PMID: 21063791 DOI: 10.1245/s10434-010-1425-1]
65 **Li F**, Zhang R, Liang H, Zhao J, Liu H, Quan J, Wang X, Xue Q. A retrospective clinicopathologic study of remnant gastric cancer after distal gastrectomy. *Am J Clin Oncol* 2013; **36**: 244-249 [PMID: 22495457 DOI: 10.1097/COC.0b013e3182467ebd]
66 **Nakafusa Y**, Tanaka T, Tanaka M, Kitajima Y, Sato S, Miyazaki K. Comparison of multivisceral resection and standard operation for locally advanced colorectal cancer: analysis of prognostic factors for short-term and long-term outcome. *Dis Colon Rectum* 2004; **47**: 2055-2063 [PMID: 15657654 DOI: 10.1007/s10350-004-0716-7]
67 **Kwon IG**, Cho I, Guner A, Choi YY, Shin HB, Kim HI, An JY, Cheong JH, Noh SH, Hyung WJ. Minimally invasive surgery for remnant gastric cancer: a comparison with open surgery. *Surg Endosc* 2014; **28**: 2452-2458 [PMID: 24622766 DOI: 10.1007/s00464-014-3496-8]
68 **Booka E**, Kaihara M, Mihara K, Nishiya S, Handa K, Ito Y, Shibutani S, Egawa T, Nagashima A. Laparoscopic total gastrectomy for remnant gastric cancer: A single-institution experience. *Asian J Endosc Surg* 2019; **12**: 58-63 [PMID: 29745474 DOI: 10.1111/ases.12495]
69 **Kunisaki C**, Shimada H, Nomura M, Hosaka N, Akiyama H, Ookubo K, Moriwaki Y, Yamaoka H. Lymph node dissection in surgical treatment for remnant stomach cancer. *Hepatogastroenterology* 2002; **49**: 580-584 [PMID: 11995502]
70 **Watanabe M**, Kinoshita T, Morita S, Yura M, Tokunaga M, Otsuki S, Yamagata Y, Kaito A, Yoshikawa T, Katai H. Clinical impact of splenic hilar dissection with splenectomy for gastric stump cancer. *Eur J Surg Oncol* 2019; **45**: 1505-1510 [PMID: 30940422 DOI: 10.1016/j.ejso.2019.03.030]
71 **Nonaka S**, Oda I, Makazu M, Haruyama S, Abe S, Suzuki H, Yoshinaga S, Nakajima T, Kushima R, Saito Y. Endoscopic submucosal dissection for early gastric cancer in the remnant stomach after gastrectomy. *Gastrointest Endosc* 2013; **78**: 63-72 [PMID: 23566640 DOI: 10.1016/j.gie.2013.02.006]
72 **Orlando R 3rd**, Welch JP. Carcinoma of the stomach after gastric operation. *Am J Surg* 1981; **141**: 487-491 [PMID: 6164300 DOI: 10.1016/0002-9610(81)90145-8]
73 **Ovaska JT**, Havia TV, Kujari HP. Retrospective analysis of gastric stump carcinoma patients treated during 1946-1981. *Acta Chir Scand* 1986; **152**: 199-204 [PMID: 3716739]
74 **Kodera Y**, Yamamura Y, Torii A, Uesaka K, Hirai T, Yasui K, Morimoto T, Kato T, Kito T. Gastric stump carcinoma after partial gastrectomy for benign gastric lesion: what is feasible as standard surgical treatment? *J Surg Oncol* 1996; **63**: 119-124 [PMID: 8888805 DOI: 10.1002/(SICI)1096-9098(199610)63:2<119::AID-JSO9>3.0.CO;2-H]
75 **Ojima T**, Iwahashi M, Nakamori M, Nakamura M, Naka T, Katsuda M, Iida T, Tsuji T, Hayata K, Takifuji K, Yamaue H. Clinicopathological characteristics of remnant gastric cancer after a distal gastrectomy. *J Gastrointest Surg* 2010; **14**: 277-281 [PMID: 19911236 DOI: 10.1007/s11605-009-1090-5]
76 **Hosokawa O**, Kaizaki Y, Watanabe K, Hattori M, Douden K, Hayashi H, Maeda S. Endoscopic surveillance for gastric remnant cancer after early cancer surgery. *Endoscopy* 2002; **34**: 469-473 [PMID: 12048630 DOI: 10.1055/s-2002-32007]
77 **Pointner R**, Schwab G, Königsrainer A, Bodner E, Schmid KW. Early cancer of the gastric remnant. *Gut* 1988; **29**: 298-301 [PMID: 3356360 DOI: 10.1136/gut.29.3.298]
78 **Sowa M**, Onoda N, Nakanishi I, Maeda K, Yoshikawa K, Kato Y, Chung YS. Early stage carcinoma of the gastric remnant in Japan. *Anticancer Res* 1993; **13**: 1835-1838 [PMID: 8267389]
79 **Podzimek A**, Valenta J, Novák V, Fessl V, Klecka J, Opatrný K, Karlícek V, Topolcan O, Petrácková E. [Experience with renal transplantation (author's transl)]. *Cas Lek Cesk* 1975; **114**: 1115-1121 [PMID: 1102091]
80 **Nishide N**, Ono H, Kakushima N, Takizawa K, Tanaka M, Matsubayashi H, Yamaguchi Y. Clinical outcomes of endoscopic submucosal dissection for early gastric cancer in remnant stomach or gastric tube. *Endoscopy* 2012; **44**: 577-583 [PMID: 22402983 DOI: 10.1055/s-0031-1291712]
81 **Tanigawa N**, Nomura E, Niki M, Shinohara H, Nishiguchi K, Okuzawa M, Toyoda M, Morita S. Clinical study to identify specific characteristics of cancer newly developed in the remnant stomach. *Gastric Cancer* 2002; **5**: 23-28 [PMID: 12021856 DOI: 10.1007/s101200200003]
82 **An JY**, Choi MG, Noh JH, Sohn TS, Kim S. The outcome of patients with remnant primary gastric cancer compared with those having upper one-third gastric cancer. *Am J Surg* 2007; **194**: 143-147 [PMID: 17618792 DOI: 10.1016/j.amjsurg.2006.10.034]

83 **Schaefer N**, Sinning C, Standop J, Overhaus M, Hirner A, Wolff M. Treatment and prognosis of gastric stump carcinoma in comparison with primary proximal gastric cancer. *Am J Surg* 2007; **194**: 63-67 [PMID: 17560911 DOI: 10.1016/j.amjsurg.2006.12.037]

84 **Takenaka R**, Kawahara Y, Okada H, Tsuzuki T, Yagi S, Kato J, Ohara N, Yoshino T, Imagawa A, Fujiki S, Takata R, Nakagawa M, Mizuno M, Inaba T, Toyokawa T, Sakaguchi K. Endoscopic submucosal dissection for cancers of the remnant stomach after distal gastrectomy. *Gastrointest Endosc* 2008; **67**: 359-363 [PMID: 18226704 DOI: 10.1016/j.gie.2007.10.021]

85 **Hirasaki S**, Kanzaki H, Matsubara M, Fujita K, Matsumura S, Suzuki S. Treatment of gastric remnant cancer post distal gastrectomy by endoscopic submucosal dissection using an insulation-tipped diathermic knife. *World J Gastroenterol* 2008; **14**: 2550-2555 [PMID: 18442204 DOI: 10.3748/wjg.14.2550]

86 **Hoteya S**, Iizuka T, Kikuchi D, Yahagi N. Clinical advantages of endoscopic submucosal dissection for gastric cancers in remnant stomach surpass conventional endoscopic mucosal resection. *Dig Endosc* 2010; **22**: 17-20 [PMID: 20078659 DOI: 10.1111/j.1443-1661.2009.00912.x]

87 **Lee JY**, Choi IJ, Cho SJ, Kim CG, Kook MC, Lee JH, Ryu KW, Kim YW. Endoscopic submucosal dissection for metachronous tumor in the remnant stomach after distal gastrectomy. *Surg Endosc* 2010; **24**: 1360-1366 [PMID: 19997930 DOI: 10.1007/s00464-009-0779-6]

88 **Tanaka S**, Toyonaga T, Morita Y, Fujita T, Yoshizaki T, Kawara F, Wakahara C, Obata D, Sakai A, Ishida T, Ikehara N, Azuma T. Endoscopic submucosal dissection for early gastric cancer in anastomosis site after distal gastrectomy. *Gastric Cancer* 2014; **17**: 371-376 [PMID: 23868403 DOI: 10.1007/s10120-013-0283-5]

89 **Otsuka R**, Hayashi H, Sakata H, Uesato M, Hayano K, Murakami K, Kano M, Fujishiro T, Toyozumi T, Semba Y, Matsubara H. Short-term clinical outcomes of laparoscopic gastrectomy for remnant gastric cancer: A single-institution experience and systematic review of the literature. *Ann Gastroenterol Surg* 2019; **3**: 181-186 [PMID: 30923787 DOI: 10.1002/ags3.12221]

90 **Kim HS**, Kim BS, Lee IS, Lee S, Yook JH. Laparoscopic gastrectomy in patients with previous gastrectomy for gastric cancer: a report of 17 cases. *Surg Laparosc Endosc Percutan Tech* 2014; **24**: 177-182 [PMID: 24686356 DOI: 10.1097/SLE.0b013e31828f6bfb]

91 **Nagai E**, Nakata K, Ohuchida K, Miyasaka Y, Shimizu S, Tanaka M. Laparoscopic total gastrectomy for remnant gastric cancer: feasibility study. *Surg Endosc* 2014; **28**: 289-296 [PMID: 24013469 DOI: 10.1007/s00464-013-3186-y]

92 **Tsunoda S**, Okabe H, Tanaka E, Hisamori S, Harigai M, Murakami K, Sakai Y. Laparoscopic gastrectomy for remnant gastric cancer: a comprehensive review and case series. *Gastric Cancer* 2016; **19**: 287-292 [PMID: 25503677 DOI: 10.1007/s10120-014-0451-2]

93 **Son SY**, Lee CM, Jung DH, Lee JH, Ahn SH, Park DJ, Kim HH. Laparoscopic completion total gastrectomy for remnant gastric cancer: a single-institution experience. *Gastric Cancer* 2015; **18**: 177-182 [PMID: 24477417 DOI: 10.1007/s10120-014-0339-1]

94 **Orlando G**, Pilone V, Vitiello A, Gervasi R, Lerose MA, Silecchia G, Puzziello A. Gastric cancer following bariatric surgery: a review. *Surg Laparosc Endosc Percutan Tech* 2014; **24**: 400-405 [PMID: 25238176 DOI: 10.1097/SLE.0000000000000050]

95 **Dunn LJ**, Shenfine J, Griffin SM. Columnar metaplasia in the esophageal remnant after esophagectomy: a systematic review. *Dis Esophagus* 2015; **28**: 32-41 [PMID: 24224923 DOI: 10.1111/dote.12129]

96 **Kassahun WT**, Lamesch P, Wittekind C, Neid M, Schneider JP, Mössner J, Hauss J. Signet-ring cell carcinoma arising in the gastric stump after duodenopancreatectomy for ductal adenocarcinoma of the pancreas: a case report. *Clin Med Oncol* 2008; **2**: 109-112 [PMID: 21892272 DOI: 10.4137/cmo.s384]

97 **Mihara Y**, Kubota K, Nemoto T, Rokkaku K, Yamamoto S, Tachibana M, Sakuma A, Ohkura Y, Fujimori T. Gastric cancer developing in the stomach after pylorus-preserving pancreaticoduodenectomy with pancreaticogastrostomy: case report and review of the literature. *J Gastrointest Surg* 2005; **9**: 498-502 [PMID: 15797230 DOI: 10.1016/j.gassur.2004.10.007]

98 **Pflüger MJ**, Felsenstein M, Schmocker R, Wood LD, Hruban R, Fujikura K, Rozich N, van Oosten F, Weiss M, Burns W, Yu J, Cameron J, Pratschke J, Wolfgang CL, He J, Burkhart RA. Gastric cancer following pancreaticoduodenectomy: Experience from a high-volume center and review of existing literature. *Surg Open Sci* 2020; **2**: 32-40 [PMID: 32954246 DOI: 10.1016/j.sopen.2020.06.003]

99 **Angrisani L**, Santonicola A, Iovino P, Vitiello A, Zundel N, Buchwald H, Scopinaro N. Bariatric Surgery and Endoluminal Procedures: IFSO Worldwide Survey 2014. *Obes Surg* 2017; **27**: 2279-2289 [PMID: 28405878 DOI: 10.1007/s11695-017-2666-x]

100 **Kuboki Y**, Yamashita S, Niwa T, Ushijima T, Nagatsuma A, Kuwata T, Yoshino T, Doi T, Ochiai A, Ohtsu A. Comprehensive analyses using next-generation sequencing and immunohistochemistry enable precise treatment in advanced gastric cancer. *Ann Oncol* 2016; **27**: 127-133 [PMID: 26489445 DOI: 10.1093/annonc/mdv508]

101 **Watanabe M**, Kuwata T, Setsuda A, Tokunaga M, Kaito A, Sugita S, Tonouchi A, Kinoshita T, Nagino M. Molecular and pathological analyses of gastric stump cancer by next-generation sequencing and immunohistochemistry. *Sci Rep* 2021; **11**: 4165 [PMID: 33603111 DOI: 10.1038/s41598-021-83711-1]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 2874-2889

DOI: 10.12998/wjcc.v11.i13.2874

ISSN 2307-8960 (online)

REVIEW

Burden of severe infections due to carbapenem-resistant pathogens in intensive care unit

Maria Caterina Pace, Antonio Corrente, Maria Beatrice Passavanti, Pasquale Sansone, Stephen Petrou, Sebastiano Leone, Marco Fiore

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Hu H, China; Jain N

Received: December 29, 2022
Peer-review started: December 29, 2022
First decision: January 17, 2023
Revised: February 17, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 6, 2023

Maria Caterina Pace, Antonio Corrente, Maria Beatrice Passavanti, Pasquale Sansone, Marco Fiore, Department of Women, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Naples 80138, Italy

Stephen Petrou, Department of Emergency Medicine, University of California San Francisco, San Francisco, CA 94143, United States

Sebastiano Leone, Division of Infectious Diseases, "San Giuseppe Moscati" Hospital, Avellino 83100, Italy

Corresponding author: Marco Fiore, MD, Doctor, Department of Women, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Piazza Luigi Miraglia, 2, Naples 80138, Italy. marco.fiore@unicampania.it

Abstract

Intensive care units (ICU) for various reasons, including the increasing age of admitted patients, comorbidities, and increasingly complex surgical procedures (*e.g.*, transplants), have become "the epicenter" of nosocomial infections, these are characterized by the presence of multidrug-resistant organisms (MDROs) as the cause of infection. Therefore, the perfect match of fragile patients and MDROs, as the cause of infection, makes ICU mortality very high. Furthermore, carbapenems were considered for years as last-resort antibiotics for the treatment of infections caused by MDROs; unfortunately, nowadays carbapenem resistance, mainly among Gram-negative pathogens, is a matter of the highest concern for world-wide public health. This comprehensive review aims to outline the problem from the intensivist's perspective, focusing on the new definition and epidemiology of the most common carbapenem-resistant MDROs (*Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacterales*) to emphasize the importance of the problem that must be permeating clinicians dealing with these diseases.

Key Words: Antimicrobial resistance; Multidrug-resistant; PDR; Carbapenem-resistance; Multidisciplinary critical care; Intensive care unit

Core Tip: Intensive care units for various reasons have become "the epicenter" of nosocomial infections due to multidrug-resistant organisms: a perfect combination of critically ill patients and multidrug-resistant organisms, as the cause of infection, makes these patients' mortality very high. This comprehensive review aims to outline the problem from the clinician's perspective, focusing on the new definition and epidemiology of the most common multidrug-resistant organisms that are *Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacterales* to emphasize the importance of the problem.

Citation: Pace MC, Corrente A, Passavanti MB, Sansone P, Petrou S, Leone S, Fiore M. Burden of severe infections due to carbapenem-resistant pathogens in intensive care unit. *World J Clin Cases* 2023; 11(13): 2874-2889
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/2874.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.2874

INTRODUCTION

Carbapenem resistance is such an important public health issue worldwide[1,2] that the 2017 World Health Organization (WHO) global priority list of pathogens ranks carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant *Acinetobacter baumannii* (CRAB) in the highest priority category (*i.e.,* Critical)[3]. Infections sustained by these bacteria lead to longer lengths of stay, increased healthcare costs, and higher mortality[4-6], especially in patients admitted to the intensive care unit (ICU)[7]. Many studies demonstrated the link between carbapenem use and carbapenem resistance[8-10]. This has even greater clinical relevance when we consider that the rise in the consumption rate of carbapenems was 45% worldwide[11]. Carbapenems are the third most widely used class of antibiotics worldwide for community-acquired infections in ICU (10.7%) and the first class for hospital-acquired infections (HAI) (21.5%)[12]. This comprehensive review aims to analyze from the perspective of worldwide epidemiology the global burden of severe infections supported by carbapenems-resistant germs in the ICU setting.

LITERATURE SEARCH

To review the published clinical data on the epidemiology of carbapenem resistance in the ICU setting, a systematic search of the biomedical literature was conducted. Medline (*via* PubMed) was searched, limited from 2012 to 2022, for articles using the following terms: [(carbapenem or imipenem or meropenem or doripenem or ertapenem) and (resistance or resistant or susceptible or susceptibility)] or (carbapenemase). The result of this search was combined with three separate searches for ''*Pseudomonas aeruginosa*'', ''*Acinetobacter baumannii*'' and "*Enterobacteriales* or *Enterobacteriaceae*". The retrieved studies were scheduled from the geographical area of origin in the five continents: ''Africa'', ''America'', ''Asia", "Europe", "and Australia".

DEFINITIONS

Carbapenem-resistant Gram-negative bacteria (GNBs), namely, CRE (*e.g., Klebsiella pneumoniae, Escherichia coli*), CRAB and CRPA, are a matter of national and international concern as they are an emerging cause of HAI that pose a significant threat to public health. The term 'CROS' is used as a generic term that refers to all of these GNBs[13]. Centers for disease control and prevention (CDC) define CRE as multidrug-resistant organisms that are resistant to at least one of the carbapenem antibiotics (ertapenem, meropenem, doripenem, or imipenem) or produce a carbapenemase. CRE is a phenotypic definition (*i.e.*, based on the organism susceptibility pattern). A lot of different mechanisms (*i.e.*, genotypes) can result in carbapenem resistance, for example, the production of enzymes that break down carbapenems and related antimicrobials making them ineffective: CRE that produce carbapenemases are called carbapenemase-producing CRE (CP-CRE); therefore, CP-CRE are a subset of all CRE (approximately 30% of CRE carry a carbapenemase), carbapenemase genes are often on mobile genetic elements, which can be easily shared between bacteria, leading to the rapid spread of resistance. Carbapenemases are classified by ambler into three classes - A, B and D (class C includes enzymes that hydrolyze primarily cephalosporins[14]) based on their central catalytic domain and substrate preference[15]. Class A [*e.g., Klebsiella pneumoniae* carbapenemase (KPC), imipenem-hydrolyzing β-lactamase and *Serratia marcescens* enzyme] and D [oxacillin carbapenemase/oxacillinase (OXA)] carbapenemases have serine residues in their active sites and hence are called serine-proteases, while

Class B [New Delhi metallo-β-lactamase (NDM), Verona integron-encoded metallo-β-lactamase (VIM) and imipenemase metallo-β-lactamase (IMP)] enzymes are metallo-β-lactamases with zinc in the active site[16]. The five carbapenemases most frequently identified in CRE are KPC, which was the first carbapenemase identified in the United States (US) in 2001, the NDM, VIM, oxacillinase-48 (OXA-48-type), and IMP[17]. The European committee on antimicrobial susceptibility testing defined the meropenem breakpoints for *Escherichia coli* and *Klebsiella pneumoniae* as $S \leq 2$ mg/L and $R > 8$ mg/L; the corresponding breakpoints for ertapenem are $S \leq 0.5$ mg/L and $R > 0.5$ mg/L. Isolates with meropenem minimum inhibitory concentration (MIC) > 2 mg/L and/or ertapenem MIC > 0.5 mg/L are considered resistant and should be investigated for carbapenem resistance mechanisms. This approach will not identify all *Escherichia coli* and *klebsiella pneumoniae* isolates but will detect most isolates with clinically significant carbapenem non-susceptibility. As the CDC also the European CDC encourages proceeding with the detection of carbapenemase production in carbapenem non-susceptible isolates with MIC values above the susceptible breakpoint[18].

EPIDEMIOLOGY

To monitor antibiotic resistance and plan contrast strategies, the different continents established epidemiological surveillance networks: European antimicrobial resistance surveillance network and central Asian and eastern European surveillance of antimicrobial resistance in Europe and Asia while the national healthcare safety network at the CDC in the US. They documented that multidrug-resistant organisms (MDROs) have become much more prevalent during the last decade[19-21]. CDC estimates that each year in the US, at least 2.8 million people get an antibiotic-resistant infection, and more than 35000 people die. The estimated national cost to treat infections caused by six MDROs identified in the last CDC report and frequently found in healthcare can be substantial—more than $4.6 billion annually [22]. In a report conducted for "the review on antimicrobial resistance (AMR)", commissioned in July 2014 by the United Kingdom prime minister, it is predicted that the toll of global antimicrobial resistance will be 10 million deaths per year and up to $100 trillion lost to the global economy by 2050 [23]. In a survey promoted by the European society of intensive care medicine, 12.4% of ICU physicians reported that they had, during the preceding six months, at least one patient with an infection caused by a bacterium resistant to all or almost all antibiotics available in their ICU[24]. An international multicenter study concluded that 19% of patients admitted to the ICU for more than 24 hours acquired an infection, with rates ranging between 2.3% and 49.2% depending on the hospital unit[25]. The most common ICU-acquired infections are pneumonia, surgical site infection, gastrointestinal infection, urinary tract infection (UTI) and bloodstream infection (BSI)[26]. In a large surveillance report from 183 US hospitals, 84% of BSI were related to the use of a central line catheter, 39% of pneumonia cases were ventilator-associated pneumonia and 68% of UTIs were related to urinary catheters[27]. According to the Gram staining results, bacteria can be classified into 2 categories: GNBs and Gram-positive bacteria (GPBs). Infections caused by multidrug-resistant GNBs are more frequent than multidrug-resistant GPBs, compared to the past. in a large prevalence study on infected ICU patients with isolates from 75 countries, 62% were GNBs, 47% were GPBs and 19% were fungal[28]. Many acronyms help clinicians remember the most prevalent germs: ESKAPE organisms identify a group of highly resistant germs that 'escape' to β-lactam antibiotics and consist of *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter spp.*, *Pseudomonas aeruginosa*, and *Enterobacter spp.*[29,30]. ESKAPE organisms represent the 6 most common MDROs of HAI[31]. However, since it was pointed out that this acronym excluded other enteric GNBs including *Escherichia coli*, it was modified into ESKAPE+C where "c" refers to *Clostridium difficile*, an important nosocomial pathogen that may easily acquire an MDROs phenotype and "e" refers *Enterobacteriaceae* covering all enteric GNBs including *Escherichia coli, Klebsiella pneumoniae, Proteus spp.* and *Enterobacter spp.*[32]. In Europe and other areas, of particular concern is the rapid spread of resistance mediated by extended-spectrum β-lactamases (ESBLs), especially in *Klebsiella pneumoniae*. ESBLs organisms are usually resistant to multiple antimicrobials, including third-generation and fourth-generation cephalosporins and aztreonam[33]. Sader and colleagues in their large cross-national research study reported that among *Escherichia coli* isolates from the ICUs, 13.7% were ESBLs producers while ESBLs-*klebsiella spp.* were 17.2%[34]. Another antibiotic class that over time increased the resistance of *Escherichia coli* is that of fluoroquinolones, usually considered active in this species[35, 36]. Resistance of *Pseudomonas aeruginosa* to fluoroquinolones and imipenem has increased rapidly; above 10% of *Pseudomonas aeruginosa* are now resistant to multiple antibiotics classes such as cephalosporins, carbapenems, aminoglycosides and fluoroquinolones[33]. The increased use of carbapenems, which are among the most effective classes of antibiotics active against MDROs contributed to the emergence of CRE or CRAB[37,38]: Up to 25% of *Acinetobacter baumannii* isolates are CRAB[33]. The CRAB prevalence in Europe seems to be higher in south-eastern Europe, with the highest prevalence in Romania (86.5% meropenem 94.6% imipenem resistance)[39]. In the American continent, there seems to be a north-south gradient with all isolated *Acinetobacter baumannii* resistant to carbapenems in Uruguay[40], and practically absent in Canada[41]. More contained data come from Asia with China which seems to have the greatest number of CRAB. As for the African continent, there

are few studies on the prevalence of carbapenem resistance[42,43]; in a study conducted in Uganda, the prevalence of CRAB is 81.25%[44]. Table 1 and Figure 1 report the worldwide prevalence of meropenem-resistant *Acinetobacter baumannii*; we decided to use meropenem as a benchmark to determine the occurrence of carbapenem resistance, to make tables and figures easier to read because *in vitro* studies involving isolates from ICU patients indicate that meropenem is more active against most GNBs than other comparators (including imipenem)[45]. More contained data concern the CRPA: In Europe, the data are more varied with very variable resistance, also between homogeneous nations in terms of geography, economy, and social progress; for example, in the Netherlands, the prevalence is 8.3%-17%[46] while in Germany it is 66.7%[47]. In North America the prevalence does not seem to exceed the two-fifths of the isolates, on the contrary, in a study conducted in Costa Rica, these exceeded four-fifths[48]. In Asia, the highest prevalence is in Korea with 92.9% of the BSI isolated from a burn ICU[49]. In Africa, the prevalence varies from about half of the isolates to almost all, as in Uganda with 88.8% of the CRPA[44] (Table 2). Figure 2 reports the worldwide prevalence of meropenem-resistant *Pseudomonas aeruginosa.*

CRE account for approximately 20%-70% of *Enterobacterales* isolated in Europe[50,51], in North America, they remain almost non-existent in Canada[41], with a prevalence similar to the European one in the US[52-55]. In Asia data are very varied with a prevalence in China of 56.6%-76.7% of carbapenem-resistant *Klebsiella pneumoniae* (CRKP)[56,57]. From studies conducted in the African continent, Tunisia seems to be the country with the highest prevalence with a percentage of 85.2% of CRKP[58]. In Table 3 we reported the worldwide prevalence of meropenem-resistant *Enterobacteriales*, and in Figure 3 is shown the worldwide prevalence of CRKP which is the most common CRE.

RISK FACTORS

Many risk factors can contribute to the genesis of antimicrobial resistance. They can be categorized as host, environmental, human, and protective barrier integrity factors[109]. Host risk factors include advanced age, organ and bone marrow transplant, end-stage renal disease in dialysis, intra-abdominal surgical procedures, cancer chemotherapy, immunosuppressive disease or therapy[26,110-112]. Prior use of antibiotics (90 days), prolonged antimicrobial usage and hospitalization (more than 5 days), use of indwelling catheters, long mechanical ventilation and residence in nursing homes and long-term care facilities are other important risk factors[110,112,113]. Numerous drugs used in ICU can be a risk factor predisposing patients to infections such as pneumonia (*e.g.*, sedatives and muscle relaxants because they can reduce the cough and swallow reflexes) or gastrointestinal infections (*e.g.*, proton pump inhibitors for stress ulcer prophylaxis because they disrupt the normal non-pathogenic bacterial flora)[110]. In this category, an important independent risk factor is previous MDROs infection or MDROs colonization. If the latter case occurs the probability of developing an infection is high[113]. Considering that some microorganisms can survive on surfaces, environmental is a category of risk factors, very dangerous for the genesis of antimicrobial resistance. It includes poor cleaning and disinfection of environmental surfaces as well as medical devices used for patient care (*e.g.*, stethoscopes, thermometers, suction apparatus) that so became a source or reservoir to disseminate germs to other patients[114]. Among environmental risk factors, colonization pressure is of great importance. First described by Bonten for vancomycin-resistant *Enterococci*[115], and later for other bacteria as well[116-118], it is a critical parameter in the epidemiology of MDROs defined as the proportion of patients colonized with a microorganism in a given geographic area for a specified period[119]. It can be used to estimate the probability of cross-contamination[118], which is in turn an important indicator of poor hygiene especially when there is a clonal relationship of isolates[120]. In their study, Arvaniti *et al*[121] found that out of the total number of patients admitted to their ICU, 5.7% were already colonized at the hospitalization and of these 15.7% acquired *Acinetobacter spp.* during their ICU stay.

The main physical barriers of our body are the skin and mucosa membranes. They represent the first defensive bulwark against infections in general and therefore also for those supported by MDROs. Damage or interruption of their integrity using invasive devices in the ICU increases the risk of infections. In a recent meta-analysis by Hui Ang and Xuan, it was found that male gender (OR 1.40, 95%CI: 1.09, 1.80), having an operative procedure (OR 1.31, 95%CI: 1.10, 1.56), a central venous catheter (OR 1.22, 95%CI: 1.01, 1.48), mechanical ventilation (OR 1.25, 95%CI: 1.07, 1.46), previous antibiotic therapy (OR 1.66, 95%CI: 1.41, 1.96), length of ICU stay (weighted mean difference 8.18, 95%CI: 0.27, 16.10) were the identified risk factors associated with MDROs infections in ICU[122].

CURRENT AND FUTURE STRATEGIES AGAINST ANTIMICROBIAL RESISTANCE IN ICU

Infection prevention strategies can be divided into vertical or horizontal approaches[123,125]. Both go to integrate themselves into complex and various strategies to prevent MDROs infections. Vertical approaches involve the reduction of the risk of colonization, infection and transmission from high-risk pathogens or a specific group of them (*e.g.*, *Clostridium difficile*, multidrug-resistant GNBs, and others)

Table 1 Worldwide prevalence of Meropenem-resistant *Acinetobacter Baumannii*, n %

Continent	Country	Prevalence	Site of infection	Ref.
Africa	Uganda	81.25	Mix	[44]
America	Brazil	22.8-94.2	Mix	[42,59]
	Canada	4.4	Mix	[41]
	French Guiana	16.2	Mix	[60]
	Mexico	56.6	Mix	[61]
	Uruguay	100	Mix	[40]
	United States	61.2-74.2	Mix	[26]
Asia	China	76.7-91.8	Mix	[42,43]
	India	65.2	VAP	[62]
	Indonesia	16.7-68	Mix	[50,63]
	Iran	53.8-94.5	Mix	[64,65]
	Jordan	88.2	Mix	[66]
	Kazakhstan	44.4	Mix	[67]
	Korea	55.8-91.8	Mix	[52,53]
	Saudi Arabia	6.2-52.6	Mix	[68,69]
	Taiwan	50.7	Mix	[70]
	Thailand	40.5-69	Mix	[71,72]
	Vietnam	84	VAP	[73]
Europe	Germany	43[1]	Mix	[74,75]
	Greece	58.9	Mix	[76]
	Italy	70	VAP	[77]
	Lithuania	30	VAP	[78]
	Poland	74.9-92.3	Mix	[54,55]
	Romania	86.5	Mix	[39]
	Russia	38-67.5	Mix	[79,80]
	Serbia	82	HAC	[81]
		85.3	VAP	
	Spain	86.05	Mix	[82]
	Switzerland	37	Mix	[51]

[1]Authors used carbapenems other than Meropenem or do not specify the carbapenem tested.

VAP: Ventilator-associated pneumonia; HAC: Hospital-acquired condition; Mix: More than one infection site or aggregated data about them.

[124]. For this reason, they are valuable tools in controlling and managing an outbreak[123,124]. Vertical approaches are centered on the use of active surveillance testing to detect patients who are MDROs carriers (*i.e.*, asymptomatic colonizers) and separate them from patients who are not colonized with that specific pathogen. This is because asymptomatic colonizers can spread the microorganism contaminating the environment and devices and favoring transmission through direct and indirect contact [124]. Examples of active surveillance testing are a rectal culture for CRE. Vertical strategies include also contact precaution and targeted decolonization (TD) for specific pathogens. TD has some limitations: the different decolonization strategies reduce the diffusion of a single specific target organism and not all-important organisms, such as multidrug-resistant GNBs and VRE, have options for decolonization[126]. Horizontal infection prevention strategies aim to reduce the risk of infections sustained by a broad spectrum of pathogens[124]. They include standard precautions (such as hand hygiene and use of personal protective equipment) and antimicrobial stewardship (AS). It should be noted that some interventions falling within the vertical approach, such as the use of gloves with or without gowns or the decolonization of the skin, can be applied to all patients (*i.e.*, in a horizontal approach), not just those

Table 2 Worldwide prevalence of Meropenem-resistant *Pseudomonas Aeruginosa*, n %

Continent	Country	Prevalence	Site of infection	Ref.
Africa	Egypt	41.82-78	Mix	[83,84]
	Lebanon	42.9	Mix	[83]
	Libya	46	Mix	[83]
	Tunisia	53.7[1]	Mix	[83]
	Uganda	88.8	Mix	[83]
America	Brazil	22.9-51.8	Mix	[85,86]
	Canada	18.3	Mix	[41]
	Costa Rica	91.3	Ns	[48]
	United States	12.9-43.3	Mix	[87,88]
Asia	Indonesia	12.4-38.1	Mix	[89,90]
	Indonesia	12.4-38.1	Mix	[89,90]
	Iran	25	BSI	[91]
	Korea	50-92.9	BSI	[49,92]
	Qatar	85.7	Mix	[93]
	Saudi Arabia	52.5	Mix	[83]
	Taiwan	22.5	Mix	[94]
	United Arab Emirates	7.7	Mix	[83]
	Turkey	46.7	Mix	[95]
Europe	Germany	61-66.7	Mix	[47,75]
	Netherlands	8.3-17	Mix	[46]
	Serbia	65.1	HAC	[81]
		70.2	VAP	
	Switzerland	27	Mix	[51]

[1]Authors used carbapenems other than Meropenem or do not specify the carbapenem tested.

BSI: Bloodstream infections; VAP: Ventilator-associated pneumonia; HAC: Hospital-acquired condition; NS: Not specified; Mix: More than one infection site or aggregated data about them.

with a specific pathogen. According to the CDC and the WHO, hand hygiene remains the simplest and most important practice in infection control. In May 2009 the WHO drew up a simple and precise infographic (called "The 5 moments of hand hygiene") for hand hygiene or the transition from one patient to the next, to prevent cross-transmission[127]. Despite the evidence showing the effectiveness of hand hygiene in preventing infections and efforts to increase compliance rate, it remains low at between 40% and 60%[128,129]. AS is a set of strategies used to improve the use of antibiotics and limit the onset of resistance. It is centred on a systematic approach in multidisciplinary teams[130,131].

An AS programme should provide for: (1) The systematic search for causal agents by carrying out targeted crop surveys; the use of molecular biology tests can also enable important data to be obtained quickly; (2) Limiting the use of broad-spectrum drugs and reducing the duration of empirical therapy through de-escalation strategies[132], with timely replacement of these drugs with other narrow-spectrum drugs; (3) Base therapies on pharmacokinetic and pharmacodynamic criteria adapted to the conditions of critical patients and any changes in the volume of distribution, metabolism, and elimination of drugs; and (4) Optimization of therapy (*i.e.*, adequate dosage, optimal mode of administration for the shortest possible time).

About AS it is important to note that data suggest that 30% to 60% of antibiotics prescribed in ICU are unnecessary, inappropriate, or suboptimal[133]. One of the possible reasons for this is the widespread belief that once the diagnosis of infection is made it is necessary to immediately start the antibiotic therapy with broad-spectrum drugs as each delay is associated with a worsening of the patient's outcome. This is true in infections with a rapid evolution (*e.g.*, Meningitis) or for patients hemodynamically unstable. However, data suggest that in patients with infection but stable, a limited delay in the start of antibiotic therapy allowing the execution of targeted cultures would allow a more appropriate

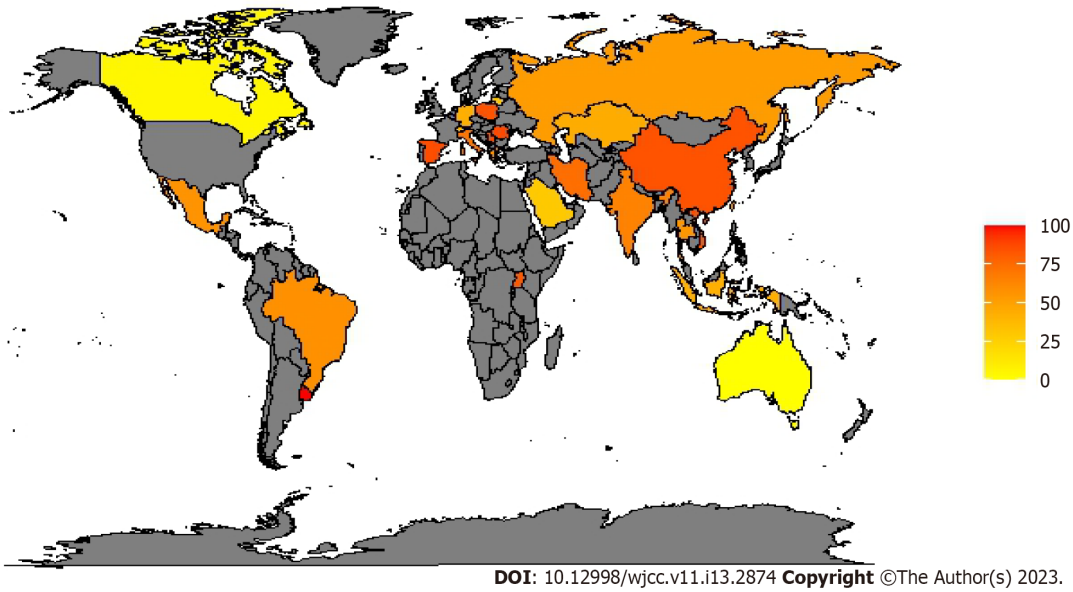
Table 3 Worldwide prevalence of Meropenem-resistant *Enterobacteriales*, n %

Continent	Country	Pathogen	Prevalence	Site of infection	Ref.
Africa	Egypt	*Enterobacter cloacae; Escherichia coli; Klebsiella pneumoniae*	43.5; 27.1; 53.7	Mix	[96]
	Morocco	*Enterobacteriales*	2.6	Mix	[97]
	South Africa	*Enterobacter spp.* Other; *Klebsiella spp.*	18; 6; 18	Mix	[98]
	Tunisia	*Enterobacter aerogenes; Enterobacter cloacae; Escherichia coli; K. Pneumonia; Providencia Stuartii*	0.9; 9.8; 2.9; 85.2; 0.9	Mix	[58]
America	Argentina	*Enterobacteriales*	2.8	BSI	[99]
	Canada	*Enterobacter cloacae; Escherichia coli; K. pmeumoniae; S marcescens*	0.8; 0.1; 0.2;0.5	Mix	[41]
	United States	*Citrobacter spp.; Enterobacter aerogenes; Enterobacter cloacae; Escherichia coli; Klebsiella oxytoca; Klebsiella pneumonia*	4; 6; 42; 14; 4; 30	Mix	[87,88,100,101]
Asia	China	*Escherichia coli; Klebsiella Pneumoniae*	11.9; 57-76.7	Mix	[56,57,102]
	India	*Klebsiella spp.*	54	Mix	[103]
	Iran	*Klebsiella Pneumoniae*	25.3	Mix	[104]
	Korea	*Enterobacteriales*	31.1	BSI	[49]
	Pakistan	*Klebsiella Pneumoniae*	72	Mix	[97]
	Turkey	*Klebsiella Pneumoniae*	44.7-67.47	Mix	[105]
Europe	France	*Enterobacteriales*	72.8	Mix	[106]
	Germany	*Escherichia coli; Klebsiella Pneumoniae*	3; 13	Mix	[75]
	Greece	*Klebsiella pneumoniae*	74	NS	[107]
	Russia	*Escherichia coli; Klebsiella spp.; Proteus spp.*	3; 16; 29	NS	[108]
	Serbia	*Enterobacter spp.*	36.4/35.9	HAC/VAP	[81]
		Klebsiella pneumoniae	50/56.8		
		Proteus mirabilis	40/39.5		
	Spain	*Enterobacteriales*	30.3	NS	[84]
	Switzerland	*Enterobacter spp.; Escherichia coli; Klebsiella pneumoniae*	77; 8; 11	Mix	[50]

BSI: Bloodstream infections; VAP: Ventilator-associated pneumonia; HAC: Hospital-acquired condition; NS: Not specified; Mix: More than one infection site or aggregated data about them.

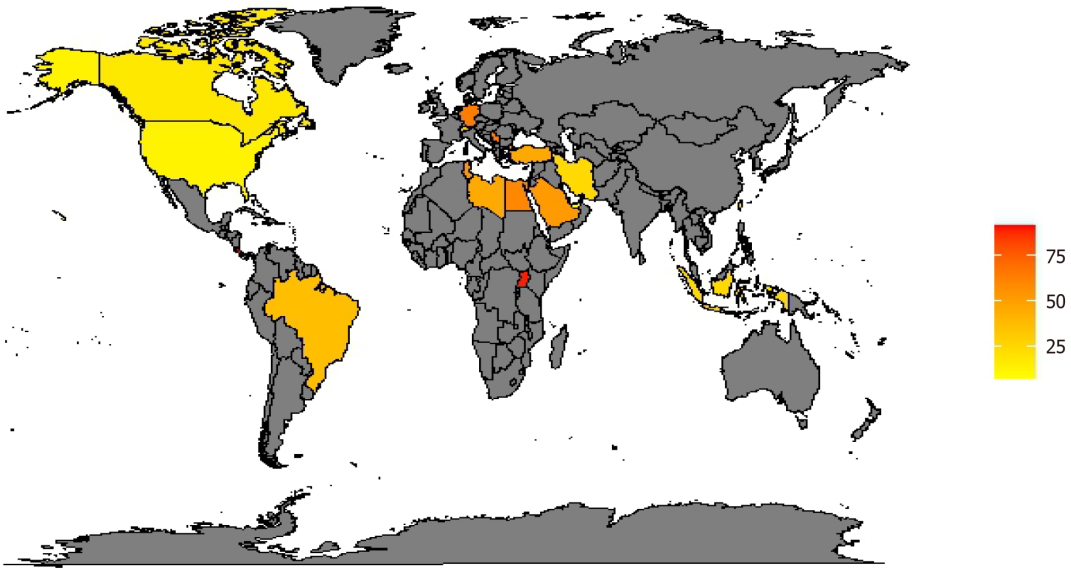
treatment and an improvement of the outcome[134]. It seems to be essential to identify protocols for the quickest identification of the germ causing the infection[135], in order not to use combination therapies whose efficacy on MDROs is not always the most effective[136,137]. A paradigmatic case seems to be the use of colistin in combination, which is the most common use in clinical practice[138], but randomized studies have not shown any benefits even in strains resistant to retrospectively identified as colistin-resistant[139]. Environmental cleaning and disinfection are other essential horizontal strategies for the control of infections and especially the prevention of cross-contamination[109]. It is important that in every hospital there is a systematic protocol for environmental cleaning and disinfection. It should address regular daily high-touch areas frequently exposed to human contact and emphasize adequate disinfection of the discharged patient's room as a terminal cleaning practice[140].

Currently, antibiotics are still the first therapeutic weapon for patients with MDROs infection in ICU [141]. Despite government efforts and incentives for pharmacological research of new molecules, few antimicrobial agents remain effective against MDROs that are available in clinical practice. New antimicrobial agents recently approved or in advanced phases of clinical development including the new beta-lactam and beta-lactamase inhibitor combinations (ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, aztreonam/avibactam), siderophore cephalosporins (cefiderocol), aminoglycosides (plazomicin) and tetracyclines (eravacycline)[142]. Numerous incentives have been provided to encourage researchers to work on alternative strategies to reverse the resistance trend. There are numerous alternative therapeutic weapons to antimicrobials in the study that could be used in the future[141]. Our microbiota remains an important ally in the battle against MDROs infections. Therefore, it must remain unaltered. Two therapeutic options are currently being investigated to remove the antibiotic residues active in the colonic space where the highest



DOI: 10.12998/wjcc.v11.i13.2874 **Copyright** ©The Author(s) 2023.

Figure 1 Worldwide prevalence of Meropenem-resistant *Acinetobacter Baumannii*.

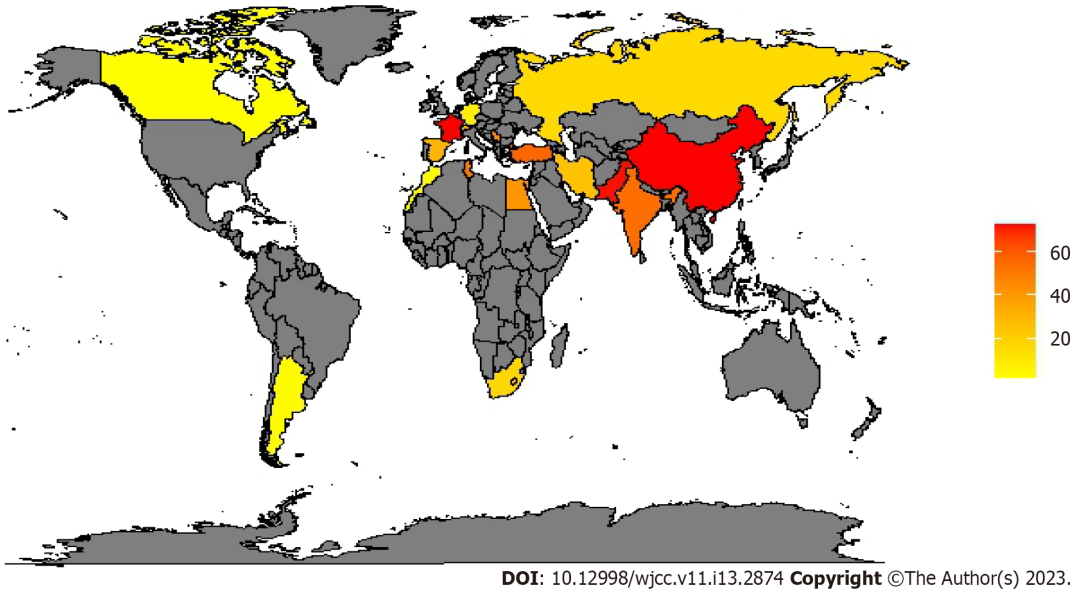


DOI: 10.12998/wjcc.v11.i13.2874 **Copyright** ©The Author(s) 2023.

Figure 2 Worldwide prevalence of Meropenem-resistant *Pseudomonas Aeruginosa*.

concentrations of intestinal bacteria are found. The first is the use of an engineered, broad-spectrum beta-lactamase that aims at decaying any beta-lactamase in the gut. The second is colon-delivered active charcoal, which aims to adsorb free colonic compounds[141]. Phage therapy is another therapeutic alternative with an interest in the future. A serious advantage of phages over antibiotics is that is highly specific. For this, they can be a perfect weapon to decontaminate MDROs from the gastrointestinal tract, as only MDROs strains would be targeted while commensal strains would be spared[141]. Like phage another specific future possibility against MDROs infection is antibodies. To overcome the issue of immune reaction against monoclonal antibodies, they are now humanized. Examples of antibodies that are being developed in this context target virulence factors: Alpha-toxin of *Staphylococcus aureus*, the type III secretion system of *Pseudomonas aeruginosa*, and the toxin B of *Clostridium difficile*[141]. In addition, a vaccine against multidrug-resistant *Acinetobacter baumannii* is also under investigation at the preclinical stage[141].

A Specific carbapenem-resistant and carbapenemase-producing Organism Prevention Program for Public Health and Healthcare is recently uploaded by the California Department of Public Health; it is clearly articulated ten different points: (1) Laboratory Identification (implement the updated laboratory breakpoints for carbapenems and *Enterobacterales*); (2) Surveillance (ensure that the laboratory rapidly notifies infection prevention and clinical staff when a patient with carbapenem resistance is identified);



DOI: 10.12998/wjcc.v11.i13.2874

Figure 3 Worldwide prevalence of Meropenem-resistant *Klebsiella pneumonia*.

(3) Colonization Testing (perform CRE colonization testing upon ICU admission of high-risk patients); (4) Infection Control Measures (place patients infected or colonized with CRE in a single room whenever possible, and implement Standard and Contact precautions); (5) Adherence Monitoring (use infection control assessment and adherence monitoring tools); (6) Environmental Cleaning (Ensure thorough daily and terminal environmental cleaning. Focus on high-touch surfaces or any shared reusable medical equipment); (7) Interfacility Communication (Communicate CRE status to the receiving facility ahead of time to ensure appropriate care is maintained when transferring a patient); (8) AS (Implement strategies to limit the use of broad-spectrum antimicrobial agents and an antimicrobial stewardship program); (9) Regional Prevention (Participate in regional efforts to prevent the spread of drug-resistant infections); and (10) Reporting (Report CPO cases through CalREDIE electronic laboratory reporting[143].

CONCLUSION

Antimicrobial resistance remains a huge public health problem on a global scale whose weight has a huge cost in terms of health expenditure and human lives. At present, antimicrobial agents remain the only causal therapeutic strategy available. Thanks to the efforts of research, in the future, we could use new therapeutic weapons as alternatives or even superior to antimicrobial agents[141]. At present, it is important to preserve the effectiveness of the last molecules put on the market, through a systematic implementation of strategies to minimize or prevent risk factors (first the pressure selection) and the spread of MDROs. For this purpose, *in primis,* the knowledge of local epidemiology and the creation of antimicrobial programs and diagnostic stewardship are mandatory to ensure the appropriateness of antimicrobial therapies. The WHO Global Action Plan on antimicrobial resistance gives strategic objectives, one of which is to strengthen knowledge through surveillance to cover the gaps in knowledge on the incidence, prevalence, and range of antimicrobial resistance across different geographical regions[144]. In our review, it is evident that there are huge differences in the epidemiology of different nations and that in most of the geographical regions, there are no data. Finally, a multidisciplinary approach including intensivists, microbiologists, pharmacists, and infectious disease specialists should play a key role to optimize antimicrobial treatment and minimizing inappropriate use of antibiotics in an era of limited pharmacological options[142]. To our knowledge, this is the first comprehensive review of the global burden of severe infections due to carbapenem-resistant pathogens focusing on ICU, as well as an evaluation of the limited availability of data. Previous reports focused on the overall antimicrobial resistance aggregating data from different inpatient wards and not exclusively from ICU[145].

FOOTNOTES

Author contributions: Corrente A and Marco F designed the study and performed the research; Pace MC, Passavanti

MB, Sansone P and Leone S supervised the manuscript; Petrou S provided critical reviews and revised the Language; Corrente A and Fiore M wrote the manuscript.

Conflict-of-interest statement: The authors have nothing to disclose.

Country/Territory of origin: Italy

ORCID number: Maria Caterina Pace 0000-0002-9352-4780; Antonio Corrente 0000-0002-8490-3148; Maria Beatrice Passavanti 0000-0002-9659-0847; Pasquale Sansone 0000-0003-0873-3586; Stephen Petrou 0000-0001-9627-5444; Sebastiano Leone 0000-0001-7852-4101; Marco Fiore 0000-0001-7263-0229.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Hussein K**, Raz-Pasteur A, Finkelstein R, Neuberger A, Shachor-Meyouhas Y, Oren I, Kassis I. Impact of carbapenem resistance on the outcome of patients' hospital-acquired bacteraemia caused by Klebsiella pneumoniae. *J Hosp Infect* 2013; **83**: 307-313 [PMID: 23313086 DOI: 10.1016/j.jhin.2012.10.012]

2 **Centers for Disease Control and Prevention (CDC)**. Vital signs: carbapenem-resistant Enterobacteriaceae. *MMWR Morb Mortal Wkly Rep* 2013; **62**: 165-170 [PMID: 23466435]

3 **World health Organization**. WHO publishes list of bacteria for which new antibiotics are urgently needed. Available from: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed

4 **Bartsch SM**, McKinnell JA, Mueller LE, Miller LG, Gohil SK, Huang SS, Lee BY. Potential economic burden of carbapenem-resistant Enterobacteriaceae (CRE) in the United States. *Clin Microbiol Infect* 2017; **23**: 48.e9-48.e16 [PMID: 27642178 DOI: 10.1016/j.cmi.2016.09.003]

5 **Ben-David D**, Kordevani R, Keller N, Tal I, Marzel A, Gal-Mor O, Maor Y, Rahav G. Outcome of carbapenem resistant Klebsiella pneumoniae bloodstream infections. *Clin Microbiol Infect* 2012; **18**: 54-60 [PMID: 21722257 DOI: 10.1111/j.1469-0691.2011.03478.x]

6 **Patel G**, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant Klebsiella pneumoniae infection and the impact of antimicrobial and adjunctive therapies. *Infect Control Hosp Epidemiol* 2008; **29**: 1099-1106 [PMID: 18973455 DOI: 10.1086/592412]

7 **van Loon K**, Voor In 't Holt AF, Vos MC. A Systematic Review and Meta-analyses of the Clinical Epidemiology of Carbapenem-Resistant Enterobacteriaceae. *Antimicrob Agents Chemother* 2018; **62** [PMID: 29038269 DOI: 10.1128/AAC.01730-17]

8 **Coppry M**, Jeanne-Leroyer C, Noize P, Dumartin C, Boyer A, Bertrand X, Dubois V, Rogues AM. Antibiotics associated with acquisition of carbapenem-resistant Pseudomonas aeruginosa in ICUs: a multicentre nested case-case-control study. *J Antimicrob Chemother* 2019; **74**: 503-510 [PMID: 30376042 DOI: 10.1093/jac/dky427]

9 **Woerther PL**, Lepeule R, Burdet C, Decousser JW, Ruppé É, Barbier F. Carbapenems and alternative β-lactams for the treatment of infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae: What impact on intestinal colonisation resistance? *Int J Antimicrob Agents* 2018; **52**: 762-770 [PMID: 30176355 DOI: 10.1016/j.ijantimicag.2018.08.026]

10 **Raman G**, Avendano EE, Chan J, Merchant S, Puzniak L. Risk factors for hospitalized patients with resistant or multidrug-resistant Pseudomonas aeruginosa infections: a systematic review and meta-analysis. *Antimicrob Resist Infect Control* 2018; **7**: 79 [PMID: 29997889 DOI: 10.1186/s13756-018-0370-9]

11 **Van Boeckel TP**, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, Laxminarayan R. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis* 2014; **14**: 742-750 [PMID: 25022435 DOI: 10.1016/S1473-3099(14)70780-7]

12 **Versporten A**, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, Jarlier V, Nathwani D, Goossens H, Global-PPS network. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *Lancet Glob Health* 2018; **6**: e619-e629 [PMID: 29681513 DOI: 10.1016/s2214-109x(18)30186-4]

13 **World Health Organization**. Implementation manual to prevent and control the spread of carbapenem-resistant organisms at the national and health care facility level. Geneva, 201. Accessed September 30, 2022. Available from: https://www.who.int/publications/i/item/WHO-UHC-SDS-2019-6

14 **Bush K**, Jacoby GA. Updated functional classification of beta-lactamases. *Antimicrob Agents Chemother* 2010; **54**: 969-976 [PMID: 19995920 DOI: 10.1128/AAC.01009-09]

15 **Ambler RP**. The structure of beta-lactamases. *Philos Trans R Soc Lond B Biol Sci* 1980; **289**: 321-331 [PMID: 6109327 DOI: 10.1098/rstb.1980.0049]

16 **Nordmann P**, Poirel L. Epidemiology and Diagnostics of Carbapenem Resistance in Gram-negative Bacteria. *Clin Infect Dis* 2019; **69**: S521-S528 [PMID: 31724045 DOI: 10.1093/cid/ciz824]

17 **CRE Technical Information**. Healthcare-Associated Infections (HAIs). Centres for Disease Control and Prevention (CDC). Accessed September 30, 2022. Available from: https://www.cdc.gov/hai/organisms/cre/technical-info.html

18 **European Centre for Disease Prevention and Control**. Expert consensus protocol on carbapenem resistance detection and characterisation for the survey of carbapenem- and/or colistin-resistant Enterobacteriaceae – Version 3.0. Stockholm: ECDC; 2019. Accessed September 30, 2022. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/expert-consensus-protocol-carbapenem-resistance.pdf

19 **European Centre for Disease Prevention and Control**. Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual Epidemiological Report 2019. Accessed September 30, 2022. Available from: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2019

20 **World Health Organization**. Regional Office for E. Central Asian and European surveillance of antimicrobial resistance: annual report 2020. Accessed September 30, 2022. Available from: https://apps.who.int/iris/handle/10665/345873

21 **Weiner-Lastinger LM**, Abner S, Edwards JR, Kallen AJ, Karlsson M, Magill SS, Pollock D, See I, Soe MM, Walters MS, Dudeck MA. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network, 2015-2017. *Infect Control Hosp Epidemiol* 2020; **41**: 1-18 [PMID: 31767041 DOI: 10.1017/ice.2019.296]

22 **Centers for Disease Control and Prevention**. About Antimicrobial Resistance. Accessed September 30, 2022. Available from: https://www.cdc.gov/drugresistance/about.html

23 **Review on Antimicrobial Resistance**. Tackling drug-resistant infections globally. Accessed September 30, 2022. Available from: https://amr-review.org/

24 **Lepape A**, Jean A, De Waele J, Friggeri A, Savey A, Vanhems P, Gustin MP, Monnet DL, Garnacho-Montero J, Kohlenberg A. European intensive care physicians' experience of infections due to antibiotic-resistant bacteria. *Antimicrob Resist Infect Control* 2020; **9**: 1 [PMID: 31908772 DOI: 10.1186/s13756-019-0662-8]

25 **Alberti C**, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, Sicignano A, Palazzo M, Moreno R, Boulmé R, Lepage E, Le Gall R. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med* 2002; **28**: 108-121 [PMID: 11907653 DOI: 10.1007/s00134-001-1143-z]

26 **MacVane SH**. Antimicrobial Resistance in the Intensive Care Unit: A Focus on Gram-Negative Bacterial Infections. *J Intensive Care Med* 2017; **32**: 25-37 [PMID: 26772199 DOI: 10.1177/0885066615619895]

27 **Magill SS**, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, Lynfield R, Maloney M, McAllister-Hollod L, Nadle J, Ray SM, Thompson DL, Wilson LE, Fridkin SK; Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med* 2014; **370**: 1198-1208 [PMID: 24670166 DOI: 10.1056/NEJMoa1306801]

28 **Vincent JL**, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K; EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; **302**: 2323-2329 [PMID: 19952319 DOI: 10.1001/jama.2009.1754]

29 **Guervil DJ**, Chau T. Trends in multidrug-resistant gram-negative bacilli and the role of prolonged β-lactam infusion in the intensive care unit. *Crit Care Nurs Q* 2013; **36**: 345-355 [PMID: 24002425 DOI: 10.1097/CNQ.0b013e3182a10d2f]

30 **Iovene MR**, Pota V, Galdiero M, Corvino G, Di Lella FM, Stelitano D, Passavanti MB, Pace MC, Alfieri A, Di Franco S, Aurilio C, Sansone P, Niyas VKM, Fiore M. First Italian outbreak of VIM-producing Serratia marcescens in an adult polyvalent intensive care unit, August-October 2018: A case report and literature review. *World J Clin Cases* 2019; **7**: 3535-3548 [PMID: 31750335 DOI: 10.12998/wjcc.v7.i21.3535]

31 **Rice LB**. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *J Infect Dis* 2008; **197**: 1079-1081 [PMID: 18419525 DOI: 10.1086/533452]

32 **Peterson LR**. Bad bugs, no drugs: no ESCAPE revisited. *Clin Infect Dis* 2009; **49**: 992-993 [PMID: 19694542 DOI: 10.1086/605539]

33 **Fish DN**, Ohlinger MJ. Antimicrobial resistance: factors and outcomes. *Crit Care Clin* 2006; **22**: 291-311, vii [PMID: 16678001 DOI: 10.1016/j.ccc.2006.02.006]

34 **Sader HS**, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalised with pneumonia in US and European hospitals: results from the SENTRY Antimicrobial Surveillance Program, 2009-2012. *Int J Antimicrob Agents* 2014; **43**: 328-334 [PMID: 24630306 DOI: 10.1016/j.ijantimicag.2014.01.007]

35 **Robicsek A**, Jacoby GA, Hooper DC. The worldwide emergence of plasmid-mediated quinolone resistance. *Lancet Infect Dis* 2006; **6**: 629-640 [PMID: 17008172 DOI: 10.1016/S1473-3099(06)70599-0]

36 **Jacoby GA**. Mechanisms of resistance to quinolones. *Clin Infect Dis* 2005; **41** Suppl 2: S120-S126 [PMID: 15942878 DOI: 10.1086/428052]

37 **Fiore M**, Di Franco S, Alfieri A, Passavanti MB, Pace MC, Petrou S, Martora F, Leone S. Spontaneous bacterial peritonitis due to carbapenemase-producing Enterobacteriaceae: Etiology and antibiotic treatment. *World J Hepatol* 2020; **12**: 1136-1147 [PMID: 33442443 DOI: 10.4254/wjh.v12.i12.1136]

38 **Baditoiu L**, Axente C, Lungeanu D, Muntean D, Horhat F, Moldovan R, Hogea E, Bedreag O, Sandesc D, Licker M. Intensive care antibiotic consumption and resistance patterns: a cross-correlation analysis. *Ann Clin Microbiol Antimicrob* 2017; **16**: 71 [PMID: 29132352 DOI: 10.1186/s12941-017-0251-8]

39 **Lăzureanu V**, Poroșnicu M, Gândac C, Moisil T, Bădițoiu L, Laza R, Musta V, Crișan A, Marinescu AR. Infection with Acinetobacter baumannii in an intensive care unit in the Western part of Romania. *BMC Infect Dis* 2016; **16** Suppl 1: 95 [PMID: 27169538 DOI: 10.1186/s12879-016-1399-0]

40 **Bado I**, Papa-Ezdra R, Delgado-Blas JF, Gaudio M, Gutiérrez C, Cordeiro NF, García-Fulgueiras V, Araújo Pirez L, Seija V, Medina JC, Rieppi G, Gonzalez-Zorn B, Vignoli R. Molecular Characterization of Carbapenem-Resistant Acinetobacter

baumannii in the Intensive Care Unit of Uruguay's University Hospital Identifies the First rmtC Gene in the Species. *Microb Drug Resist* 2018; **24**: 1012-1019 [PMID: 29920143 DOI: 10.1089/mdr.2017.0300]

41 **Denisuik AJ**, Garbutt LA, Golden AR, Adam HJ, Baxter M, Nichol KA, Lagacé-Wiens P, Walkty AJ, Karlowsky JA, Hoban DJ, Mulvey MR, Zhanel GG. Antimicrobial-resistant pathogens in Canadian ICUs: results of the CANWARD 2007 to 2016 study. *J Antimicrob Chemother* 2019; **74**: 645-653 [PMID: 30500898 DOI: 10.1093/jac/dky477]

42 **Fiorentin Vandresen D**, Carolina Lucio L, Shigueyasu Yamada R, Paula Vieira A, Ani Caovilla Follador F, Pitt Benedetti V, Pereira Bento Casaril K, Viviane Buzanello Martins C, Welter Wendt G, Elize Defante Ferreto L. Associated factors of Acinetobacter baumannii complex in hospitalized patients: A case-control study. *J Infect Dev Ctries* 2021; **15**: 73-80 [PMID: 33571148 DOI: 10.3855/jidc.13525]

43 **Chen Y**, Yang Y, Liu L, Qiu G, Han X, Tian S, Zhao J, Chen F, Grundmann H, Li H, Sun J, Han L. High prevalence and clonal dissemination of OXA-72-producing Acinetobacter baumannii in a Chinese hospital: a cross sectional study. *BMC Infect Dis* 2018; **18**: 491 [PMID: 30268099 DOI: 10.1186/s12879-018-3359-3]

44 **Aruhomukama D**, Najjuka CF, Kajumbula H, Okee M, Mboowa G, Sserwadda I, Mayanja R, Joloba ML, Kateete DP. bla(VIM)- and bla(OXA)-mediated carbapenem resistance among Acinetobacter baumannii and Pseudomonas aeruginosa isolates from the Mulago hospital intensive care unit in Kampala, Uganda. *BMC Infect Dis* 2019; **19**: 853 [PMID: 31619192 DOI: 10.1186/s12879-019-4510-5]

45 **Hurst M**, Lamb HM. Meropenem: a review of its use in patients in intensive care. *Drugs* 2000; **59**: 653-680 [PMID: 10776838 DOI: 10.2165/00003495-200059030-00016]

46 **Croughs PD**, Klaassen CHW, van Rosmalen J, Maghdid DM, Boers SA, Hays JP, Goessens WHF; Dutch Antibiotic Resistance Surveillance Group. Unexpected mechanisms of resistance in Dutch Pseudomonas aeruginosa isolates collected during 14 years of surveillance. *Int J Antimicrob Agents* 2018; **52**: 407-410 [PMID: 29772393 DOI: 10.1016/j.ijantimicag.2018.05.009]

47 **Schäfer E**, Malecki M, Tellez-Castillo CJ, Pfennigwerth N, Marlinghaus L, Higgins PG, Mattner F, Wendel AF. Molecular surveillance of carbapenemase-producing Pseudomonas aeruginosa at three medical centres in Cologne, Germany. *Antimicrob Resist Infect Control* 2019; **8**: 208 [PMID: 31893042 DOI: 10.1186/s13756-019-0665-5]

48 **Toval F**, Guzmán-Marte A, Madriz V, Somogyi T, Rodríguez C, García F. Predominance of carbapenem-resistant Pseudomonas aeruginosa isolates carrying blaIMP and blaVIM metallo-β-lactamases in a major hospital in Costa Rica. *J Med Microbiol* 2015; **64**: 37-43 [PMID: 25355933 DOI: 10.1099/jmm.0.081802-0]

49 **Park JJ**, Seo YB, Choi YK, Kym D, Lee J. Changes in the prevalence of causative pathogens isolated from severe burn patients from 2012 to 2017. *Burns* 2020; **46**: 695-701 [PMID: 31630835 DOI: 10.1016/j.burns.2019.09.008]

50 **Anggraini D**, Kemal RA, Hadi U, Kuntaman K. The susceptibility pattern and distribution of blaOXA-23 genes of clinical isolate Acinetobacter baumannii in a tertiary hospital, Indonesia. *J Infect Dev Ctries* 2022; **16**: 821-826 [PMID: 35656953 DOI: 10.3855/jidc.15902]

51 **Barnsteiner S**, Baty F, Albrich WC, Babouee Flury B, Gasser M, Plüss-Suard C, Schlegel M, Kronenberg A, Kohler P; Swiss Centre for Antibiotic Resistance (ANRESIS). Antimicrobial resistance and antibiotic consumption in intensive care units, Switzerland, 2009 to 2018. *Euro Surveill* 2021; **26** [PMID: 34794535 DOI: 10.2807/1560-7917.ES.2021.26.46.2001537]

52 **Liu Q**, Li W, Du X, Zhong T, Tang Y, Feng Y, Tao C, Xie Y. Risk and Prognostic Factors for Multidrug-Resistant Acinetobacter Baumannii Complex Bacteremia: A Retrospective Study in a Tertiary Hospital of West China. *PLoS One* 2015; **10**: e0130701 [PMID: 26083415 DOI: 10.1371/journal.pone.0130701]

53 **Chiang CH**, Pan SC, Yang TS, Matsuda K, Kim HB, Choi YH, Hori S, Wang JT, Sheng WH, Chen YC, Chang FY, Chang SC. Healthcare-associated infections in intensive care units in Taiwan, South Korea, and Japan: recent trends based on national surveillance reports. *Antimicrob Resist Infect Control* 2018; **7**: 129 [PMID: 30455867 DOI: 10.1186/s13756-018-0422-1]

54 **Ziółkowski G**, Pawłowska I, Krawczyk L, Wojkowska-Mach J. Antibiotic consumption versus the prevalence of multidrug-resistant Acinetobacter baumannii and Clostridium difficile infections at an ICU from 2014-2015. *J Infect Public Health* 2018; **11**: 626-630 [PMID: 29548877 DOI: 10.1016/j.jiph.2018.02.003]

55 **Litwin A**, Fedorowicz O, Duszynska W. Characteristics of Microbial Factors of Healthcare-Associated Infections Including Multidrug-Resistant Pathogens and Antibiotic Consumption at the University Intensive Care Unit in Poland in the Years 2011-2018. *Int J Environ Res Public Health* 2020; **17** [PMID: 32977435 DOI: 10.3390/ijerph17196943]

56 **Chang H**, Wei J, Zhou W, Yan X, Cao X, Zuo L, Chen S, Yao K, Huang R, Chen Y, Wu C. Risk factors and mortality for patients with Bloodstream infections of Klebsiella pneumoniae during 2014-2018: Clinical impact of carbapenem resistance in a large tertiary hospital of China. *J Infect Public Health* 2020; **13**: 784-790 [PMID: 31843651 DOI: 10.1016/j.jiph.2019.11.014]

57 **Zhang WX**, Chen HY, Chen C, Chen JH, Wan FS, Li LX, Chen M, Zhang J. Resistance Phenotype and Molecular Epidemiology of Carbapenem-Resistant Klebsiella pneumoniae Isolates in Shanghai. *Microb Drug Resist* 2021; **27**: 1312-1318 [PMID: 34297609 DOI: 10.1089/mdr.2020.0390]

58 **Ben Helal R**, Dziri R, Chedly M, Klibi N, Barguellil F, El Asli MS, Ben Moussa M. Occurrence and Characterization of Carbapenemase-Producing Enterobacteriaceae in a Tunisian Hospital. *Microb Drug Resist* 2018; **24**: 1361-1367 [PMID: 29596032 DOI: 10.1089/mdr.2018.0013]

59 **Kurihara MNL**, Sales RO, Silva KED, Silva GD, Mansano MCT, Mahmoud FF, Simionatto S. High lethality rate of carbapenem-resistant Acinetobacter baumannii in Intensive Care Units of a Brazilian hospital: An epidemiologic surveillance study. *Rev Soc Bras Med Trop* 2022; **55**: e05292021 [PMID: 35522809 DOI: 10.1590/0037-8682-0529-2021]

60 **Mahamat A**, Bertrand X, Moreau B, Hommel D, Couppie P, Simonnet C, Kallel H, Demar M, Djossou F, Nacher M. Clinical epidemiology and resistance mechanisms of carbapenem-resistant Acinetobacter baumannii, French Guiana, 2008-2014. *Int J Antimicrob Agents* 2016; **48**: 51-55 [PMID: 27236843 DOI: 10.1016/j.ijantimicag.2016.03.006]

61 **Uc-Cachón AH**, Gracida-Osorno C, Luna-Chi IG, Jiménez-Guillermo JG, Molina-Salinas GM. High Prevalence of Antimicrobial Resistance Among Gram-Negative Isolated Bacilli in Intensive Care Units at a Tertiary-Care Hospital in Yucatán Mexico. *Medicina (Kaunas)* 2019; **55** [PMID: 31540314 DOI: 10.3390/medicina55090588]

62 **Kumari M**, Verma S, Venkatesh V, Gupta P, Tripathi P, Agarwal A, Siddiqui SS, Arshad Z, Prakash V. Emergence of blaNDM-1 and blaVIM producing Gram-negative bacilli in ventilator-associated pneumonia at AMR Surveillance Regional Reference Laboratory in India. *PLoS One* 2021; **16**: e0256308 [PMID: 34495985 DOI: 10.1371/journal.pone.0256308]

63 **Saharman YR**, Karuniawati A, Sedono R, Aditianingsih D, Sudarmono P, Goessens WHF, Klaassen CHW, Verbrugh HA, Severin JA. Endemic carbapenem-nonsusceptible Acinetobacter baumannii-calcoaceticus complex in intensive care units of the national referral hospital in Jakarta, Indonesia. *Antimicrob Resist Infect Control* 2018; **7**: 5 [PMID: 29344351 DOI: 10.1186/s13756-017-0296-7]

64 **Pourajam S**, Kalantari E, Talebzadeh H, Mellali H, Sami R, Soltaninejad F, Amra B, Sajadi M, Alenaseri M, Kalantari F, Solgi H. Secondary Bacterial Infection and Clinical Characteristics in Patients With COVID-19 Admitted to Two Intensive Care Units of an Academic Hospital in Iran During the First Wave of the Pandemic. *Front Cell Infect Microbiol* 2022; **12**: 784130 [PMID: 35281440 DOI: 10.3389/fcimb.2022.784130]

65 **Ranjbar R**, Farahani A. Study of genetic diversity, biofilm formation, and detection of Carbapenemase, MBL, ESBL, and tetracycline resistance genes in multidrug-resistant Acinetobacter baumannii isolated from burn wound infections in Iran. *Antimicrob Resist Infect Control* 2019; **8**: 172 [PMID: 31719975 DOI: 10.1186/s13756-019-0612-5]

66 **Nazer LH**, Kharabsheh A, Rimawi D, Mubarak S, Hawari F. Characteristics and Outcomes of Acinetobacter baumannii Infections in Critically Ill Patients with Cancer: A Matched Case-Control Study. *Microb Drug Resist* 2015; **21**: 556-561 [PMID: 26430944 DOI: 10.1089/mdr.2015.0032]

67 **Viderman D**, Brotfain E, Khamzina Y, Kapanova G, Zhumadilov A, Poddighe D. Bacterial resistance in the intensive care unit of developing countries: Report from a tertiary hospital in Kazakhstan. *J Glob Antimicrob Resist* 2019; **17**: 35-38 [PMID: 30448518 DOI: 10.1016/j.jgar.2018.11.010]

68 **Aljindan R**, Bukharie H, Alomar A, Abdalhamid B. Prevalence of digestive tract colonization of carbapenem-resistant Acinetobacter baumannii in hospitals in Saudi Arabia. *J Med Microbiol* 2015; **64**: 400-406 [PMID: 25657302 DOI: 10.1099/jmm.0.000033]

69 **Al-Hamad A**, Pal T, Leskafi H, Abbas H, Hejles H, Alsubikhy F, Darwish D, Ghazawi A, Sonnevend A. Molecular characterization of clinical and environmental carbapenem resistant Acinetobacter baumannii isolates in a hospital of the Eastern Region of Saudi Arabia. *J Infect Public Health* 2020; **13**: 632-636 [PMID: 31551188 DOI: 10.1016/j.jiph.2019.08.013]

70 **Chen YP**, Liang CC, Chang R, Kuo CM, Hung CH, Liao TN, Liao CS. Detection and Colonization of Multidrug Resistant Organisms in a Regional Teaching Hospital of Taiwan. *Int J Environ Res Public Health* 2019; **16** [PMID: 30925662 DOI: 10.3390/ijerph16071104]

71 **Chusri S**, Chongsuvivatwong V, Rivera JI, Silpapojakul K, Singkhamanan K, McNeil E, Doi Y. Molecular epidemiology and spatiotemporal analysis of hospital-acquired Acinetobacter baumannii infection in a tertiary care hospital in southern Thailand. *J Hosp Infect* 2017; **95**: 53-58 [PMID: 27865634 DOI: 10.1016/j.jhin.2016.10.003]

72 **Kiddee A**, Assawatheptawee K, Na-Udom A, Treebupachatsakul P, Wangteeraprasert A, Walsh TR, Niumsup PR. Risk Factors for Gastrointestinal Colonization and Acquisition of Carbapenem-Resistant Gram-Negative Bacteria among Patients in Intensive Care Units in Thailand. *Antimicrob Agents Chemother* 2018; **62** [PMID: 29891594 DOI: 10.1128/AAC.00341-18]

73 **Le Minh V**, Thi Khanh Nhu N, Vinh Phat V, Thompson C, Huong Lan NP, Thieu Nga TV, Thanh Tam PT, Tuyen HT, Hoang Nhu TD, Van Hao N, Thi Loan H, Minh Yen L, Parry CM, Trung Nghia HD, Campbell JI, Hien TT, Thwaites L, Thwaites G, Van Vinh Chau N, Baker S. In vitro activity of colistin in antimicrobial combination against carbapenem-resistant Acinetobacter baumannii isolated from patients with ventilator-associated pneumonia in Vietnam. *J Med Microbiol* 2015; **64**: 1162-1169 [PMID: 26297024 DOI: 10.1099/jmm.0.000137]

74 **Wendel AF**, Malecki M, Otchwemah R, Tellez-Castillo CJ, Sakka SG, Mattner F. One-year molecular surveillance of carbapenem-susceptible A. baumannii on a German intensive care unit: diversity or clonality. *Antimicrob Resist Infect Control* 2018; **7**: 145 [PMID: 30505434 DOI: 10.1186/s13756-018-0436-8]

75 **Maechler F**, Peña Diaz LA, Schröder C, Geffers C, Behnke M, Gastmeier P. Prevalence of carbapenem-resistant organisms and other Gram-negative MDRO in German ICUs: first results from the national nosocomial infection surveillance system (KISS). *Infection* 2015; **43**: 163-168 [PMID: 25395161 DOI: 10.1007/s15010-014-0701-6]

76 **Karampatakis T**, Tsergouli K, Politi L, Diamantopoulou G, Iosifidis E, Antachopoulos C, Karyoti A, Mouloudi E, Tsakris A, Roilides E. Molecular Epidemiology of Endemic Carbapenem-Resistant Gram-Negative Bacteria in an Intensive Care Unit. *Microb Drug Resist* 2019; **25**: 712-716 [PMID: 30589601 DOI: 10.1089/mdr.2018.0266]

77 **Delle Rose D**, Pezzotti P, Fortunato E, Sordillo P, Gini S, Boros S, Meledandri M, Gallo MT, Prignano G, Caccese R, D'Ambrosio M, Citterio G, Rocco M, Leonardis F, Natoli S, Fontana C, Favaro M, Celeste MG, Franci T, Testore GP, Andreoni M, Sarmati L. Clinical predictors and microbiology of ventilator-associated pneumonia in the intensive care unit: a retrospective analysis in six Italian hospitals. *Eur J Clin Microbiol Infect Dis* 2016; **35**: 1531-1539 [PMID: 27272120 DOI: 10.1007/s10096-016-2694-9]

78 **Čiginskienė A**, Dambrauskienė A, Rello J, Adukauskienė D. Ventilator-Associated Pneumonia due to Drug-Resistant Acinetobacter baumannii: Risk Factors and Mortality Relation with Resistance Profiles, and Independent Predictors of In-Hospital Mortality. *Medicina (Kaunas)* 2019; **55** [PMID: 30781896 DOI: 10.3390/medicina55020049]

79 **Mayanskiy N**, Chebotar I, Alyabieva N, Kryzhanovskaya O, Savinova T, Turenok A, Bocharova Y, Lazareva A, Polikarpova S, Karaseva O. Emergence of the Uncommon Clone ST944/ST78 Carrying bla(OXA-40-like) and bla(CTX-M-like) Genes Among Carbapenem-Nonsusceptible Acinetobacter baumannii in Moscow, Russia. *Microb Drug Resist* 2017; **23**: 864-870 [PMID: 28437227 DOI: 10.1089/mdr.2016.0302]

80 **Ershova K**, Savin I, Kurdyumova N, Wong D, Danilov G, Shifrin M, Alexandrova I, Sokolova E, Fursova N, Zelman V, Ershova O. Implementing an infection control and prevention program decreases the incidence of healthcare-associated infections and antibiotic resistance in a Russian neuro-ICU. *Antimicrob Resist Infect Control* 2018; **7**: 94 [PMID: 30083313 DOI: 10.1186/s13756-018-0383-4]

81 **Djordjevic ZM**, Folic MM, Jankovic SM. Distribution and antibiotic susceptibility of pathogens isolated from adults with

hospital-acquired and ventilator-associated pneumonia in intensive care unit. *J Infect Public Health* 2017; **10**: 740-744 [PMID: 28189513 DOI: 10.1016/j.jiph.2016.11.016]

82 **Rodríguez-Lucas C**, Rodicio MR, Vázquez X, Escudero D, Quindós B, Alaguero M, Fernández J. Extensively drug-resistant Acinetobacter baumannii carrying bla(OXA-23-like) and armA in a hospital after an intervention in the intensive care unit which ended a long-standing endemicity. *Eur J Clin Microbiol Infect Dis* 2021; **40**: 385-389 [PMID: 32808109 DOI: 10.1007/s10096-020-04009-0]

83 **Al-Orphaly M**, Hadi HA, Eltayeb FK, Al-Hail H, Samuel BG, Sultan AA, Skariah S. Epidemiology of Multidrug-Resistant Pseudomonas aeruginosa in the Middle East and North Africa Region. *mSphere* 2021; **6** [PMID: 34011686 DOI: 10.1128/mSphere.00202-21]

84 **Elbaradei A**, Sayedahmed MS, El-Sawaf G, Shawky SM. Screening of mcr-1 among Gram-Negative Bacteria from Different Clinical Samples from ICU Patients in Alexandria, Egypt: One-Year Study. *Pol J Microbiol* 2022; **71**: 83-90 [PMID: 35635164 DOI: 10.33073/pjm-2022-011]

85 **de Almeida Silva KCF**, Calomino MA, Deutsch G, de Castilho SR, de Paula GR, Esper LMR, Teixeira LA. Molecular characterization of multidrug-resistant (MDR) Pseudomonas aeruginosa isolated in a burn center. *Burns* 2017; **43**: 137-143 [PMID: 27595453 DOI: 10.1016/j.burns.2016.07.002]

86 **Rodrigues YC**, Furlaneto IP, Maciel AHP, Quaresma AJPG, de Matos ECO, Conceição ML, Vieira MCDS, Brabo GLDC, Sarges EDSNF, Lima LNGC, Lima KVB. High prevalence of atypical virulotype and genetically diverse background among Pseudomonas aeruginosa isolates from a referral hospital in the Brazilian Amazon. *PLoS One* 2020; **15**: e0238741 [PMID: 32911510 DOI: 10.1371/journal.pone.0238741]

87 **Jarrell AS**, Kruer RM, Berescu LD, Pronovost PJ, Trivedi JB. Factors associated with in-hospital mortality among critically ill surgical patients with multidrug-resistant Gram-negative infections. *J Crit Care* 2018; **43**: 321-326 [PMID: 29239831 DOI: 10.1016/j.jcrc.2017.10.035]

88 **Sader HS**, Mendes RE, Streit JM, Carvalhaes CG, Castanheira M. Antimicrobial susceptibility of Gram-negative bacteria from intensive care unit and non-intensive care unit patients from United States hospitals (2018-2020). *Diagn Microbiol Infect Dis* 2022; **102**: 115557 [PMID: 34673293 DOI: 10.1016/j.diagmicrobio.2021.115557]

89 **Pelegrin AC**, Saharman YR, Griffon A, Palmieri M, Mirande C, Karuniawati A, Sedono R, Aditianingsih D, Goessens WHF, van Belkum A, Verbrugh HA, Klaassen CHW, Severin JA. High-Risk International Clones of Carbapenem-Nonsusceptible Pseudomonas aeruginosa Endemic to Indonesian Intensive Care Units: Impact of a Multifaceted Infection Control Intervention Analyzed at the Genomic Level. *mBio* 2019; **10** [PMID: 31719179 DOI: 10.1128/mBio.02384-19]

90 **Saharman YR**, Pelegrin AC, Karuniawati A, Sedono R, Aditianingsih D, Goessens WHF, Klaassen CHW, van Belkum A, Mirande C, Verbrugh HA, Severin JA. Epidemiology and characterisation of carbapenem-non-susceptible Pseudomonas aeruginosa in a large intensive care unit in Jakarta, Indonesia. *Int J Antimicrob Agents* 2019; **54**: 655-660 [PMID: 31398483 DOI: 10.1016/j.ijantimicag.2019.08.003]

91 **Emami A**, Pirbonyeh N, Keshavarzi A, Bazargani A, Hassanpour S, Javanmardi F. Evaluating the Saliva of Burn ICU Patients for Resistant Infections Harbor Metallo-β-Lactamase Genes. *J Burn Care Res* 2020; **41**: 647-651 [PMID: 31930340 DOI: 10.1093/jbcr/iraa007]

92 **Kang JS**, Moon C, Mun SJ, Lee JE, Lee SO, Lee S, Lee SH. Antimicrobial Susceptibility Trends and Risk Factors for Antimicrobial Resistance in Pseudomonas aeruginosa Bacteremia: 12-Year Experience in a Tertiary Hospital in Korea. *J Korean Med Sci* 2021; **36**: e273 [PMID: 34751008 DOI: 10.3346/jkms.2021.36.e273]

93 **Baiou A**, Elbuzidi AA, Bakdach D, Zaqout A, Alarbi KM, Bintaher AA, Ali MMB, Elarabi AM, Ali GAM, Daghfal J, Almaslamani MA, Ibrahim ASS, Alkhal A, Omrani AS. Clinical characteristics and risk factors for the isolation of multi-drug-resistant Gram-negative bacteria from critically ill patients with COVID-19. *J Hosp Infect* 2021; **110**: 165-171 [PMID: 33561503 DOI: 10.1016/j.jhin.2021.01.027]

94 **Lin KY**, Lauderdale TL, Wang JT, Chang SC. Carbapenem-resistant Pseudomonas aeruginosa in Taiwan: Prevalence, risk factors, and impact on outcome of infections. *J Microbiol Immunol Infect* 2016; **49**: 52-59 [PMID: 24662016 DOI: 10.1016/j.jmii.2014.01.005]

95 **Acar A**, Karaahmetoğlu G, Akalın H, Altay AF. Pooled prevalence and trends of antimicrobial resistance in Pseudomonas aeruginosa clinical isolates over the past 10 years in Turkey: A meta-analysis. *J Glob Antimicrob Resist* 2019; **18**: 64-70 [PMID: 30753904 DOI: 10.1016/j.jgar.2019.01.032]

96 **Kotb S**, Lyman M, Ismail G, Abd El Fattah M, Girgis SA, Etman A, Hafez S, El-Kholy J, Zaki MES, Rashed HG, Khalil GM, Sayyouh O, Talaat M. Epidemiology of Carbapenem-resistant Enterobacteriaceae in Egyptian intensive care units using National Healthcare-associated Infections Surveillance Data, 2011-2017. *Antimicrob Resist Infect Control* 2020; **9**: 2 [PMID: 31911830 DOI: 10.1186/s13756-019-0639-7]

97 **Chabah M**, Chemsi M, Zerouali K, Alloula O, Lehlimi M, Habzi A, Benomar S. Healthcare-associated infections due to carbapenemase-producing Enterobacteriaceae: Bacteriological profile and risk factors. *Med Mal Infect* 2016; **46**: 157-162 [PMID: 26897308 DOI: 10.1016/j.medmal.2015.12.015]

98 **Law T**, Chibabhai V, Nana T. Analysis and comparison of cumulative antibiograms for the Charlotte Maxeke Johannesburg Academic Hospital adult intensive care and high-care units, 2013 and 2017. *S Afr Med J* 2019; **110**: 55-64 [PMID: 31865944 DOI: 10.7196/SAMJ.2019.v110i1.13841]

99 **Lipari FG**, Hernández D, Vilaró M, Caeiro JP, Saka HA. [Clinical, epidemiological and microbiological characterization of bacteremia produced by carbapenem-resistant enterobacteria in a university hospital in Córdoba, Argentina]. *Rev Chilena Infectol* 2020; **37**: 362-370 [PMID: 33399656 DOI: 10.4067/S0716-10182020000400362]

100 **Johnson JK**, Robinson GL, Pineles LL, Ajao AO, Zhao L, Albrecht JS, Harris AD, Thom KA, Furuno JP. Carbapenem MICs in Escherichia coli and Klebsiella Species Producing Extended-Spectrum β-Lactamases in Critical Care Patients from 2001 to 2009. *Antimicrob Agents Chemother* 2017; **61** [PMID: 28167543 DOI: 10.1128/AAC.01718-16]

101 **Tamma PD**, Kazmi A, Bergman Y, Goodman KE, Ekunseitan E, Amoah J, Simner PJ. The Likelihood of Developing a Carbapenem-Resistant Enterobacteriaceae Infection during a Hospital Stay. *Antimicrob Agents Chemother* 2019; **63** [PMID: 31138574 DOI: 10.1128/AAC.00757-19]

102 **Li Y**, Sun QL, Shen Y, Zhang Y, Yang JW, Shu LB, Zhou HW, Wang Y, Wang B, Zhang R, Wang S, Shen Z. Rapid

Increase in Prevalence of Carbapenem-Resistant Enterobacteriaceae (CRE) and Emergence of Colistin Resistance Gene mcr-1 in CRE in a Hospital in Henan, China. *J Clin Microbiol* 2018; **56** [PMID: 29386265 DOI: 10.1128/JCM.01932-17]

103 **Sodhi K**, Mittal V, Arya M, Kumar M, Phillips A, Kajla B. Pattern of colistin resistance in Klebsiella isolates in an Intensive Care Unit of a tertiary care hospital in India. *J Infect Public Health* 2020; **13**: 1018-1021 [PMID: 31818712 DOI: 10.1016/j.jiph.2019.10.013]

104 **Darabi N**, Motazakker M, Khalkhali HR, Yousefi S. A multicenter study of β-lactamase-producing Klebsiella pneumoniae isolated from university teaching hospitals of Urmia, Iran. *J Infect Dev Ctries* 2019; **13**: 690-697 [PMID: 32069252 DOI: 10.3855/jidc.9985]

105 **Candevir Ulu A**, Güven Gökmen T, Kibar F, Kurtaran B, Önlen C, Kuşçu F, İnal AS, Kömür S, Yaman A, Aksu HSZ, Taşova Y. Molecular epidemiology of carbapenem-resistant Klebsiella pneumoniae at a Turkish centre: Is the increase of resistance a threat for Europe? *J Glob Antimicrob Resist* 2017; **11**: 10-16 [PMID: 28743652 DOI: 10.1016/j.jgar.2017.06.012]

106 **Davido B**, Moussiegt A, Dinh A, Bouchand F, Matt M, Senard O, Deconinck L, Espinasse F, Lawrence C, Fortineau N, Saleh-Mghir A, Caballero S, Escaut L, Salomon J. Germs of thrones - spontaneous decolonization of Carbapenem-Resistant Enterobacteriaceae (CRE) and Vancomycin-Resistant Enterococci (VRE) in Western Europe: is this myth or reality? *Antimicrob Resist Infect Control* 2018; **7**: 100 [PMID: 30123500 DOI: 10.1186/s13756-018-0390-5]

107 **Karampatakis T**, Antachopoulos C, Iosifidis E, Tsakris A, Roilides E. Molecular epidemiology of carbapenem-resistant Klebsiella pneumoniae in Greece. *Future Microbiol* 2016; **11**: 809-823 [PMID: 27206024 DOI: 10.2217/fmb-2016-0042]

108 **Partina I**, Kalinogorskaya O, Kojima S, Gostev V, Volkova M, Ageevets V, Lobzin Y, Sidorenko S. Surveillance of antimicrobial susceptibility of Enterobacteriaceae pathogens isolated from intensive care units and surgical units in Russia. *Jpn J Antibiot* 2016; **69**: 41-51 [PMID: 27290829]

109 **Riley MM**. The Rising Problem of Multidrug-Resistant Organisms in Intensive Care Units. *Crit Care Nurse* 2019; **39**: 48-55 [PMID: 31371367 DOI: 10.4037/ccn2019773]

110 **Brusselaers N**, Vogelaers D, Blot S. The rising problem of antimicrobial resistance in the intensive care unit. *Ann Intensive Care* 2011; **1**: 47 [PMID: 22112929 DOI: 10.1186/2110-5820-1-47]

111 **Umscheid CA**, Agarwal RK, Brennan PJ; Healthcare Infection Control Practices Advisory Committee. Updating the guideline development methodology of the Healthcare Infection Control Practices Advisory Committee (HICPAC). *Am J Infect Control* 2010; **38**: 264-273 [PMID: 20116133 DOI: 10.1016/j.ajic.2009.12.005]

112 **Djibré M**, Fedun S, Le Guen P, Vimont S, Hafiani M, Fulgencio JP, Parrot A, Denis M, Fartoukh M. Universal versus targeted additional contact precautions for multidrug-resistant organism carriage for patients admitted to an intensive care unit. *Am J Infect Control* 2017; **45**: 728-734 [PMID: 28285725 DOI: 10.1016/j.ajic.2017.02.001]

113 **Martín-Loeches I**, Diaz E, Vallés J. Risks for multidrug-resistant pathogens in the ICU. *Curr Opin Crit Care* 2014; **20**: 516-524 [PMID: 25188366 DOI: 10.1097/MCC.0000000000000124]

114 **Kanamori H**, Parobek CM, Juliano JJ, van Duin D, Cairns BA, Weber DJ, Rutala WA. A Prolonged Outbreak of KPC-3-Producing Enterobacter cloacae and Klebsiella pneumoniae Driven by Multiple Mechanisms of Resistance Transmission at a Large Academic Burn Center. *Antimicrob Agents Chemother* 2017; **61** [PMID: 27919898 DOI: 10.1128/AAC.01516-16]

115 **Bonten MJ**, Slaughter S, Ambergen AW, Hayden MK, van Voorhis J, Nathan C, Weinstein RA. The role of "colonization pressure" in the spread of vancomycin-resistant enterococci: an important infection control variable. *Arch Intern Med* 1998; **158**: 1127-1132 [PMID: 9605785 DOI: 10.1001/archinte.158.10.1127]

116 **Merrer J**, Santoli F, Appéré de Vecchi C, Tran B, De Jonghe B, Outin H. "Colonization pressure" and risk of acquisition of methicillin-resistant Staphylococcus aureus in a medical intensive care unit. *Infect Control Hosp Epidemiol* 2000; **21**: 718-723 [PMID: 11089656 DOI: 10.1086/501721]

117 **Harris AD**, Johnson JK, Thom KA, Morgan DJ, McGregor JC, Ajao AO, Moore AC, Comer AC, Furuno JP. Risk factors for development of intestinal colonization with imipenem-resistant Pseudomonas aeruginosa in the intensive care unit setting. *Infect Control Hosp Epidemiol* 2011; **32**: 719-722 [PMID: 21666406 DOI: 10.1086/660763]

118 **Ajao AO**, Harris AD, Roghmann MC, Johnson JK, Zhan M, McGregor JC, Furuno JP. Systematic review of measurement and adjustment for colonization pressure in studies of methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, and clostridium difficile acquisition. *Infect Control Hosp Epidemiol* 2011; **32**: 481-489 [PMID: 21515979 DOI: 10.1086/659403]

119 **Bonten MJ**, Gaillard CA, Johanson WG Jr, van Tiel FH, Smeets HG, van der Geest S, Stobberingh EE. Colonization in patients receiving and not receiving topical antimicrobial prophylaxis. *Am J Respir Crit Care Med* 1994; **150**: 1332-1340 [PMID: 7952561 DOI: 10.1164/ajrccm.150.5.7952561]

120 **Bonten MJ**. Colonization pressure: a critical parameter in the epidemiology of antibiotic-resistant bacteria. *Crit Care* 2012; **16**: 142 [PMID: 22849650 DOI: 10.1186/cc11417]

121 **Arvaniti K**, Lathyris D, Ruimy R, Haidich AB, Koulourida V, Nikolaidis P, Matamis D, Miyakis S. The importance of colonization pressure in multiresistant Acinetobacter baumannii acquisition in a Greek intensive care unit. *Crit Care* 2012; **16**: R102 [PMID: 22694969 DOI: 10.1186/cc11383]

122 **Ang H**, Sun X. Risk factors for multidrug-resistant Gram-negative bacteria infection in intensive care units: A meta-analysis. *Int J Nurs Pract* 2018; **24**: e12644 [PMID: 29575345 DOI: 10.1111/ijn.12644]

123 **Popovich KJ**. Another success story for horizontal infection control strategies--which one? *Crit Care Med* 2014; **42**: 2292-2293 [PMID: 25226120 DOI: 10.1097/CCM.0000000000000566]

124 **Septimus E**, Weinstein RA, Perl TM, Goldmann DA, Yokoe DS. Approaches for preventing healthcare-associated infections: go long or go wide? *Infect Control Hosp Epidemiol* 2014; **35**: 797-801 [PMID: 24915206 DOI: 10.1086/676535]

125 **Wenzel RP**, Edmond MB. Infection control: the case for horizontal rather than vertical interventional programs. *Int J Infect Dis* 2010; **14** Suppl 4: S3-S5 [PMID: 20851010 DOI: 10.1016/j.ijid.2010.05.002]

126 **Calfee DP**, Salgado CD, Milstone AM, Harris AD, Kuhar DT, Moody J, Aureden K, Huang SS, Maragakis LL, Yokoe DS; Society for Healthcare Epidemiology of America. Strategies to prevent methicillin-resistant Staphylococcus aureus transmission and infection in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol* 2014; **35**: 772-796 [PMID:

24915205 DOI: 10.1086/676534]
127 **World Health Organization**. WHO guidelines on hand hygiene in health care. Accessed September 30, 2022. Available from: https://www.who.int/publications/i/item/9789241597906
128 **Erasmus V**, Daha TJ, Brug H, Richardus JH, Behrendt MD, Vos MC, van Beeck EF. Systematic review of studies on compliance with hand hygiene guidelines in hospital care. *Infect Control Hosp Epidemiol* 2010; **31**: 283-294 [PMID: 20088678 DOI: 10.1086/650451]
129 **Kowitt B**, Jefferson J, Mermel LA. Factors associated with hand hygiene compliance at a tertiary care teaching hospital. *Infect Control Hosp Epidemiol* 2013; **34**: 1146-1152 [PMID: 24113597 DOI: 10.1086/673465]
130 **Luyt CE**, Bréchot N, Trouillet JL, Chastre J. Antibiotic stewardship in the intensive care unit. *Crit Care* 2014; **18**: 480 [PMID: 25405992 DOI: 10.1186/s13054-014-0480-6]
131 **Onorato L**, Macera M, Calò F, Monari C, Russo F, Iovene MR, Signoriello G, Annibale R, Pace MC, Aurilio C, Gaeta GB, Coppola N. The effect of an antimicrobial stewardship programme in two intensive care units of a teaching hospital: an interrupted time series analysis. *Clin Microbiol Infect* 2020; **26**: 782.e1-782.e6 [PMID: 31678230 DOI: 10.1016/j.cmi.2019.10.021]
132 **Tabah A**, Bassetti M, Kollef MH, Zahar JR, Paiva JA, Timsit JF, Roberts JA, Schouten J, Giamarellou H, Rello J, De Waele J, Shorr AF, Leone M, Poulakou G, Depuydt P, Garnacho-Montero J. Antimicrobial de-escalation in critically ill patients: a position statement from a task force of the European Society of Intensive Care Medicine (ESICM) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Critically Ill Patients Study Group (ESGCIP). *Intensive Care Med* 2020; **46**: 245-265 [PMID: 31781835 DOI: 10.1007/s00134-019-05866-w]
133 **Ventola CL**. The antibiotic resistance crisis: part 1: causes and threats. *P T* 2015; **40**: 277-283 [PMID: 25859123]
134 **Hranjec T**, Rosenberger LH, Swenson B, Metzger R, Flohr TR, Politano AD, Riccio LM, Popovsky KA, Sawyer RG. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study. *Lancet Infect Dis* 2012; **12**: 774-780 [PMID: 22951600 DOI: 10.1016/S1473-3099(12)70151-2]
135 **Fiore M**, Maraolo AE, Leone S, Gentile I, Cuomo A, Schiavone V, Bimonte S, Pace MC, Cascella M. Spontaneous peritonitis in critically ill cirrhotic patients: a diagnostic algorithm for clinicians and future perspectives. *Ther Clin Risk Manag* 2017; **13**: 1409-1414 [PMID: 29081656 DOI: 10.2147/TCRM.S144262]
136 **Fiore M**, Alfieri A, Di Franco S, Pace MC, Simeon V, Ingoglia G, Cortegiani A. Ceftazidime-Avibactam Combination Therapy Compared to Ceftazidime-Avibactam Monotherapy for the Treatment of Severe Infections Due to Carbapenem-Resistant Pathogens: A Systematic Review and Network Meta-Analysis. *Antibiotics (Basel)* 2020; **9** [PMID: 32645986 DOI: 10.3390/antibiotics9070388]
137 **Fiore M**, Corrente A, Pace MC, Alfieri A, Simeon V, Ippolito M, Giarratano A, Cortegiani A. Ceftolozane-Tazobactam Combination Therapy Compared to Ceftolozane-Tazobactam Monotherapy for the Treatment of Severe Infections: A Systematic Review and Meta-Analysis. *Antibiotics (Basel)* 2021; **10** [PMID: 33467508 DOI: 10.3390/antibiotics10010079]
138 **Giacobbe DR**, Saffioti C, Losito AR, Rinaldi M, Aurilio C, Bolla C, Boni S, Borgia G, Carannante N, Cassola G, Ceccarelli G, Corcione S, Dalla Gasperina D, De Rosa FG, Dentone C, Di Bella S, Di Lauria N, Feasi M, Fiore M, Fossati S, Franceschini E, Gori A, Granata G, Grignolo S, Grossi PA, Guadagnino G, Lagi F, Maraolo AE, Marinò V, Mazzitelli M, Mularoni A, Oliva A, Pace MC, Parisini A, Patti F, Petrosillo N, Pota V, Raffaelli F, Rossi M, Santoro A, Tascini C, Torti C, Trecarichi EM, Venditti M, Viale P, Signori A, Bassetti M, Del Bono V, Giannella M, Mikulska M, Tumbarello M, Viscoli C; SITA GIOVANI (Young Investigators Group of the Società Italiana Terapia Antinfettiva) and the COLI-CROSS Study Group. Use of colistin in adult patients: A cross-sectional study. *J Glob Antimicrob Resist* 2020; **20**: 43-49 [PMID: 31207379 DOI: 10.1016/j.jgar.2019.06.009]
139 **Dickstein Y**, Lellouche J, Ben Dalak Amar M, Schwartz D, Nutman A, Daitch V, Yahav D, Leibovici L, Skiada A, Antoniadou A, Daikos GL, Andini R, Zampino R, Durante-Mangoni E, Mouton JW, Friberg LE, Dishon Benattar Y, Bitterman R, Neuberger A, Carmeli Y, Paul M; AIDA Study Group. Treatment Outcomes of Colistin- and Carbapenem-resistant Acinetobacter baumannii Infections: An Exploratory Subgroup Analysis of a Randomized Clinical Trial. *Clin Infect Dis* 2019; 69: 769-776 [PMID: 30462182 DOI: 10.1093/cid/ciy988]
140 **Gupta R**, Hannon E, Huprikar S, Bassily-Marcus A, Manasia A, Oropello J, Kohli-Seth R. Getting to zero: Reduction in the incidence of multidrug-resistant organism infections using an integrated infection control protocol in an intensive care unit. *Am J Infect Control* 2016; 44: 1695-1697 [PMID: 27575774 DOI: 10.1016/j.ajic.2016.07.003]
141 **Bassetti M**, Poulakou G, Ruppe E, Bouza E, Van Hal SJ, Brink A. Antimicrobial resistance in the next 30 years, humankind, bugs and drugs: a visionary approach. *Intensive Care Med* 2017; 43: 1464-1475 [PMID: 28733718 DOI: 10.1007/s00134-017-4878-x]
142 **Leone S**, Damiani G, Pezone I, Kelly ME, Cascella M, Alfieri A, Pace MC, Fiore M. New antimicrobial options for the management of complicated intra-abdominal infections. *Eur J Clin Microbiol Infect Dis* 2019; 38: 819-827 [PMID: 30903538 DOI: 10.1007/s10096-019-03533-y]
143 **Healthcare-Associated Infections (Hai) Program**. Carbapenem-resistant and Carbapenemase-producing Organisms for Public Health and Healthcare Providers. Accessed September 30, 2022. Available from: https://www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/CRE_InfectionPreventionStrategies.aspx
144 **World Health Organization**. Global action plan on antimicrobial resistance. Accessed February 1, 2023. Available from: https://www.who.int/publications/i/item/9789241509763
145 **Antimicrobial Resistance Collaborators**. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022; **399**: 629-655 [PMID: 35065702 DOI: 10.1016/S0140-6736(21)02724-0]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 2890-2902

DOI: 10.12998/wjcc.v11.i13.2890

ISSN 2307-8960 (online)

MINIREVIEWS

Individualized diabetes care: Lessons from the real-world experience

Xiao Ying Khor, Joseph M Pappachan, Mohammad Sadiq Jeeyavudeen

Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Arumugam VA, India; Cigrovski Berkovic M, Croatia

Received: December 17, 2022
Peer-review started: December 17, 2022
First decision: February 17, 2023
Revised: February 25, 2023
Accepted: March 30, 2023
Article in press: March 30, 2023
Published online: May 6, 2023

Xiao Ying Khor, Joseph M Pappachan, Department of Endocrinology and Metabolism, Lancashire Teaching Hospitals NHS Trust, Preston PR2 9UT, United Kingdom

Joseph M Pappachan, Faculty of Science, Manchester Metropolitan University, Manchester M15 6BH, United Kingdom

Joseph M Pappachan, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester M13 9PL, United Kingdom

Mohammad Sadiq Jeeyavudeen, Department of Endocrinology and Metabolism, University Hospitals of Edinburgh, Edinburgh EH16 4SA, United Kingdom

Corresponding author: Joseph M Pappachan, MD, FRCP, Academic Editor, Consultant Endocrinologist, Professor, Senior Researcher, Department of Endocrinology and Metabolism, Lancashire Teaching Hospitals NHS Trust, Sharoe Green Lane, Preston PR2 9HT, United Kingdom. drpappachan@yahoo.co.in

Abstract

Diabetes care is often difficult without a proper collaboration between the patient and the care provider as the disease is mostly self-managed by patients through adjustments in their lifestyles, and medication doses to optimise glycaemic control. Most clinical guidelines on the management of diabetes mellitus (DM) provide only broad principles on diabetes care, and the blind follow-up of such principles without a proper review and consideration of patient characteristics often results in inadequate glycaemic control and diabetes complications consequently. Therefore, a proper understanding of the pathobiology, clinical situation, and comorbidities of the individual case is of paramount importance to tailoring the most appropriate management strategy in real-world diabetes care. With the aid of five unique cases of DM [(1) Medically managed type 2 diabetes mellitus (T2DM) with severe obesity; (2) Management of T2DM with unreliable glycated haemoglobin (HbA1c); (3) Obesity in a patient with type 1 diabetes mellitus (T1DM); and (4) Late diagnosis and subsequent management of monogenic diabetes and 5. Sudden worsening of well-controlled T2DM)] we elaborate on the importance of individualised diabetes care and the practicalities in these situations. The review also provides an evidence update on the management of different forms of DM to guide physicians in optimising the care of their patients in day-to-day clinical practice.

Key Words: Individualised diabetes care; Diabesity; Double diabetes; Monogenic diabetes; Diabetes in pancreatic cancer

Core Tip: Diabetes mellitus (DM) is a chronic disease mostly self-managed by patients as glucose control is largely related to lifestyle adjustments with appropriate dietary habits and physical activities. A proper understanding of the pathobiology of DM, associated comorbidities, the clinical situation, and the socio-cultural background of each patient is of paramount importance in planning the optimal management strategies for diabetes care. With the aid of 5 interesting real-world case scenarios, we elaborate on the importance of individualised diabetes care in this evidence-based review to empower physicians in optimising the care of their diabetes patients in day-to-day clinical practice.

Citation: Khor XY, Pappachan JM, Jeeyavudeen MS. Individualized diabetes care: Lessons from the real-world experience. *World J Clin Cases* 2023; 11(13): 2890-2902
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/2890.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.2890

INTRODUCTION

According to the most recent update of the International Diabetes Federation (IDF) in the year 2021, DM has affected 537 million adults across the globe[1]. Patients with DM are often not well-informed about the pathophysiology, natural course, potential complications, and the plan for optimal management of their illness from the outset which is the most important reason for poor disease outcomes. Although diabetes professional bodies such as the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), the Diabetes United Kingdom (DUK), and IDF commonly involve patient support groups and produce publications on structured diabetes education programs, empowerment of diabetes patients by the healthcare professionals during clinic reviews is often inadequate at an individual level. Figure 1 shows a graphical summary of the importance of individualised diabetes care.

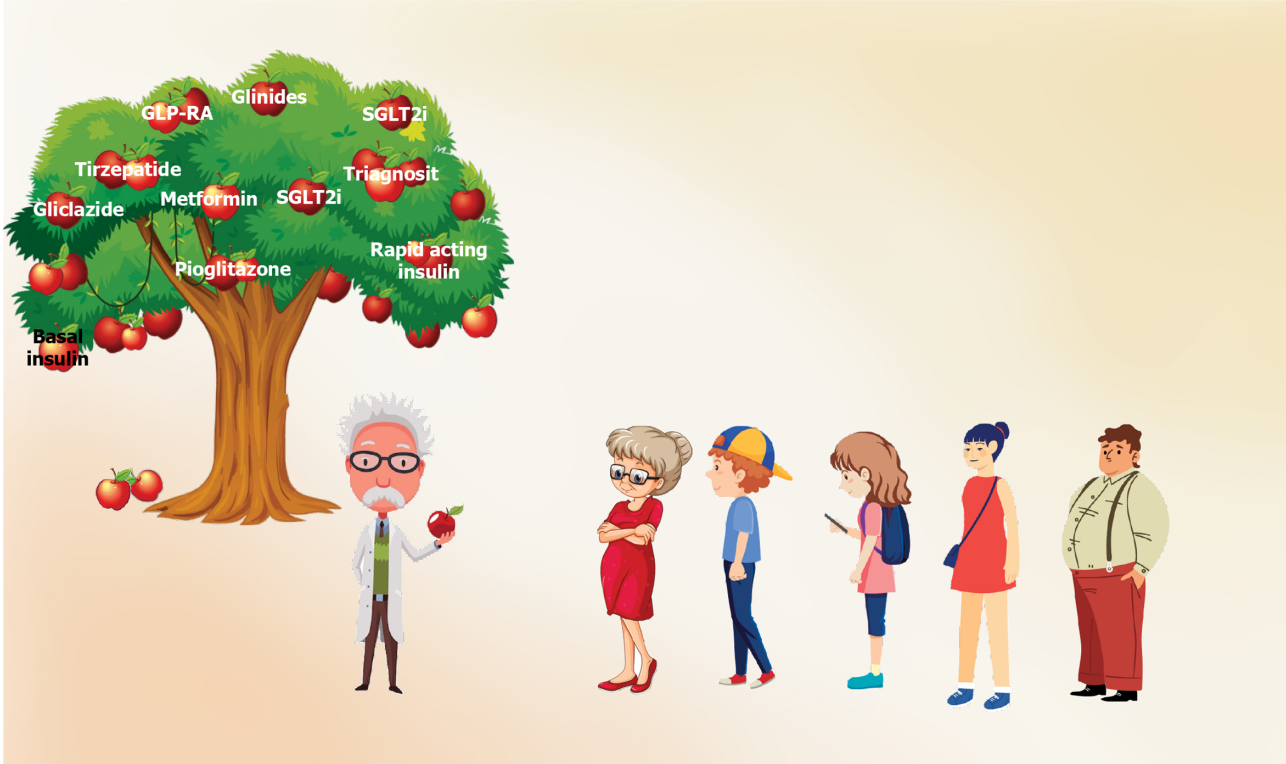
As DM is a chronic disease mostly self-managed by patients, individualised diabetes care plans and self-management support (SMS) systems are expected to improve adherence to therapy and thereby, the disease outcomes. Multiple studies have shown that SMS interventions and personalised care plans result in an improvement in clinical outcomes, quality of life, knowledge about the disease, and the efficiency of self-care among patients with DM[2-4]. However, this approach is often overlooked in the day-to-day clinical practice in most healthcare systems which can contribute to adverse disease outcomes in DM cases. With the aid of 5 unique real-world clinical case scenarios, we outline the importance of individualised diabetes care in this evidence-based review.

CASE SCENARIOS AND MANAGEMENT

Case 1

A 58-year-old woman with a 10-year history of T2DM, initially managed with Metformin 1 g twice a day (BID), Gliclazide 160 mg BID, and insulin Glargine 60 units at night, was referred to the diabetes specialist clinic for improvement of her metabolic control due to inadequate glycaemic control despite a gradual increase in the insulin doses. Her body weight was 118 kg with a body mass index (BMI) of 41 kg/m^2, and her blood pressure (BP) was 156/88 mmHg. Her biochemical profile showed: HbA1c 76 mmol/mol, creatinine 86 mmol/L, total cholesterol 5.6 mmol/L, high-density lipoprotein (HDL) 0.88 mmol/L, low-density lipoprotein (LDL) 3.1 mmol/L, triglycerides (TG) 2.3 mmol/L, gamma-glutamyl transferase (GGT) 168 U/L, and alkaline phosphatase (ALP) 146 U/L. Other biochemical tests such as thyroid functions and urine microalbumin were normal.

After a discussion about the importance of managing her gradually increasing body weight which was getting worse after the initiation of insulin 2 years ago (when her body weight was 102 kg), she agreed to start an injection of Semaglutide 0.25 mg subcutaneously weekly after stopping the Gliclazide. She tolerated the Semaglutide well with good suppression of her appetite and the dose was escalated to 0.5 mg weekly after 4 wk, and then to 1 mg weekly after 8 weeks. She started losing weight steadily and managed to reduce the dose of her insulin Glargine by 4-6 units periodically and discontinued the insulin completely in 9 mo following the initiation of Semaglutide. She achieved a total weight loss of 36 kg and her HbA1c dropped to 58 mmol/moL at the 9-mo follow-up visit. After another discussion about the potential for further improvements in her diabetes and body weight, she has been commenced on Canagliflozin 100 mg daily, the dose of which was increased to 300 mg daily after a month.



DOI: 10.12998/wjcc.v11.i13.2890

Figure 1 Individualised diabetes care - graphical abstract. GLP-RA; SGLT2 inhibitor.

At her subsequent review 6 months later, she had a further weight loss of 20 kg but had been feeling depressed as people have not been recognizing her because of her massive weight loss and demanded to stop her antidiabetic medications completely. Her biochemical profile revealed: HbA1c 42 mmol/moL, creatinine 64 mmol/L, total cholesterol 3.8 mmol/L, HDL 0.98 mmol/L, LDL 2.8 mmol/L, TG 2.3 mmol/L, GGT 168 U/L, and ALP 146 U/L. Although her T2DM was in remission, she was cautioned about the high risk of relapse when the medications that resulted in massive weight loss (combination of Semaglutide and Canagliflozin) were discontinued. She agreed to continue Metformin 1 g BID on a long-term basis.

Case 2

A 64-year-old man was referred to the diabetes clinic by his general practitioner as he could not explain the disproportionately low HbA1c of 52 mmol/moL while the patient was showing capillary blood glucose (CBG) readings of 18–24 mmol/L regularly on his home glucose monitor. He had been on mixed Isophane human insulin/regular insulin (70/30) BID (20 units before breakfast and 15 units before evening meals). He was getting monthly iron transfusions and occasional infusions of packed red blood cells for chronic anaemia related to angiodysplasia of the small intestine.

Evaluation from the hospital clinic revealed haemoglobin of 105 g/L and a fructosamine level of 564 μmol/L (reference range: 215-310). The falsely low HbA1c levels in the patient were considered a reflection of rapid red cell turnover from chronic intestinal blood loss and accelerated erythropoiesis. He was advised to up-titrate the insulin doses gradually to bring down the CBGs to < 10 mmol/L consistently. After three months of treatment under close supervision, his fructosamine levels came down to 384 μmol/L, acceptable for his age and co-morbidities. The referring physician and the patient were advised to rely upon the CBGs for optimal management of diabetes without periodic monitoring of HbA1c because of its unreliability.

Case 3

A 72-year-old woman was referred to the diabetes clinic for consideration of adding an antidiabetic medication with weight loss potential. She had a background of longstanding inadequately controlled T1DM of 15 years duration. She was on treatment with insulin Aspart 36 units with main meals three times a day (TID), insulin Glargine 90 units at night, and Metformin 1 g BID for her diabetes management. Her HbA1c level was 68 mmol/moL without other major abnormalities in her biochemical tests. Her body weight was 94 kg with a BMI of 36 kg/m^2 and was quite motivated to try any medications to improve her body weight and high insulin dose requirements.

After counselling about the potential gastrointestinal side effects and the lack of license for routine use in patients with T1DM, the patient agreed to try an injection of liraglutide as an add-on therapy for her diabetes management at a dose of 0.6 mg subcutaneously daily. The daily dose was up-titrated by 0.6 mg every month to a maximum of 1.8 mg daily in 2 months. She tolerated the medication well and started losing weight with her CBG readings consistently < 10 mmol/L without significant hypoglycemic episodes. She managed to reduce the dose of her insulins gradually, and at the end of one year, she was only taking insulin Aspart 10 units TID with her main meals and insulin Glargine 40 units at night. Her final body weight was 72 kg and her HbA1c was 57 mmol/moL. She also reported significant improvement in her mobility which was previously restricted by knee joint osteoarthritis.

Case 4

A 42-year-old woman was reviewed in the diabetes clinic as requested by her primary care physician for the optimisation of diabetes control. She had a 12-year history of diabetes which was initially managed by oral hypoglycaemic agents (OHA). Metformin was stopped because of severe diarrhoea. She did not tolerate Gliclazide because of hypoglycaemic episodes. Subsequently, she was managed with mixed Isophane human insulin/regular insulin (70/30) BID- 30 units before breakfast and 42 units before evening meals. The CBG readings ranged between 6–16 mmol/L with occasional mild symptomatic hypoglycaemic episodes. Her latest HbA1c was 72 mmol/moL, indicating poor glycaemic control for her age although she had no established microvascular complications of diabetes.

When she reported a recent diagnosis of diabetes in her 22-year-old son and a previous history of hypoglycaemic episodes with Gliclazide, the probability of monogenic diabetes was considered. She was unwilling to undergo genetic testing for monogenic diabetes initially. Therefore, a sulphonylurea challenge test was performed. She responded very well to the sulphonylurea challenge with a marked reduction in her plasma glucose. This was suggestive of monogenic diabetes. Subsequently, she had a genetic test that showed an *HNF-1A* mutation. Her glycemic control improved significantly with her HbA1c level reaching 49 mmol/moL within three months of treatment with oral Gliclazide 40 mg BID only.

Case 5

A 66-year-old woman with an 8-year history of well-controlled T2DM on diet and lifestyle modifications presented with a one-month duration of osmotic symptoms and weight loss of 6 kg. Her CBGs were consistently between 16–22 mmol/L for nearly three weeks before her evaluation. Her HbA1c rose to 66 mmol/moL from 51 mmol/moL three months earlier indicating that her hyperglycaemia was of very recent onset. She weighed 66 kg with a BMI of 28 kg/m^2. Her liver function tests (LFT) showed elevated GGT of 240 U/L, ALP of 196 U/L, and alanine transaminase level of 68 U/L with normal bilirubin and albumin levels. She has commenced on Metformin 500 mg BID and mixed Isophane human insulin/regular insulin (70/30) 10 units BID with a plan to increase the dose every 2–3 d to reduce the glucose readings to mostly single figures without hypoglycaemia.

Blood samples for screening of T1DM antibodies [antibodies against islet cells, insulinoma antigen 2 (IA2), glutamic acid decarboxylase (GAD), and zinc transporter 8 [ZnT8)], and an outpatient ultrasound scan of the liver for investigating the presumed metabolic-associated fatty liver disease as a cause of abnormal LFT were ordered. Although her antibody screening for T1DM was reported as negative 2 d later, the liver USS showed numerous nodular lesions suggestive of metastatic cancer. A subsequent computed tomography scan of the chest, abdomen, and pelvis revealed advanced metastatic pancreatic cancer. The patient and family understood that her prognosis was very poor and declined further evaluation and interventions for the cancer. She was discharged to a palliative care facility for symptom control and end-of-life support where she died a few weeks later.

DISCUSSION

Diabetes is a unique disease entity with very different clinical presentations and courses of illness largely influenced by the patient's biological characteristics, environmental factors, and comorbid illnesses. Therefore, formulating a management plan requires consideration of all these factors at a personal level to individualise treatment options through the SMS mentioned above. The case snippets discussed in this paper are some unique examples of this paradigm. The scientific rationale for this individualised DM care and the importance of SMS systems are discussed below.

The concept of "Diabesity"

Obesity, defined by the World Health Organisation (WHO) as having a BMI of ≥ 30 kg/m^2, is an excessive accumulation of fat that poses a risk to health. The prevalence of obesity worldwide has almost tripled since 1975 with > 650 million adults being obese in 2016[5]. More concerningly, the percentage of children and adolescents aged 5-19 who are overweight, and obese has increased significantly from just 4% in 1975 to a whopping > 18% in 2016. This obesity epidemic, which is a major risk factor for noncommunicable diseases such as diabetes, cardiovascular diseases, musculoskeletal

disorders, and some forms of cancers, is largely preventable through lifestyle changes with the consumption of a low-energy diet and regular physical activities.

"Diabesity" is a terminology used to describe the pathophysiological interlink between obesity/overweight and T2DM. This phenomenon is a complex molecular cascade, involving lifestyle factors, abnormal genetic heterogenicity background as well as biochemical and hormonal mechanisms.

The development of T2DM in an overweight or obese individual can be annotated by the presence of visceral adiposity leading to the development of peripheral insulin resistance. There are three hypotheses proposed in the pathophysiology of diabesity[6]:

The "inflammatory hypothesis" advocates a causal link between the pro-inflammatory cytokines produced by the excess adipose tissues and insulin resistance.

The "lipid overflow hypothesis" suggests that lipid metabolites released from the adipose tissues cause inhibition of insulin signal transduction and increased insulin resistance.

The "adipokine hypothesis" suggests that the adipokines secreted from the adipose tissues made up of several hormones and chemical substances, induce inflammatory and metabolic cascades, resulting in insulin resistance.

As insulin resistance progresses, an individual will require a higher amount of plasma insulin to achieve the same insulin effect due to a downregulation of the insulin receptors on cell membranes. However, insulin is an anabolic hormone that slows basal metabolism, inhibits protein catabolism, stimulates lipogenesis, and increases the accumulation of adiposity. In addition, the exogenous insulin does not have the first pass hepatic metabolism through the portal vein to suppress hepatic gluconeogenesis. This results in further weight gain associated with exogenous insulin use. The vicious cycle due to hyperinsulinemia can cause worsening of the diabesity[6,7]. Figure 2 shows the schematic diagram of the mechanism of insulin resistance and the development of diabesity.

Clinical and management approach to diabesity

In case 1, the patient presented with a classical picture of diabesity and metabolic syndrome (dyslipidaemia and hypertension). Her initial treatment which consisted of Metformin, sulphonylurea, and insulin had resulted in the worsening of her diabesity. Metformin, which remained as the first-line treatment in T2DM, is thought to be a weight-neutral antidiabetic medication. Although its exact mechanism of action is yet to be fully understood, it is known to inhibit hepatic glucose production and gluconeogenesis, improve peripheral insulin resistance, and it has an anorexiant effect which is beneficial in the context of managing diabesity. On the other hand, the risks and benefits of using sulphonylurea and exogenous insulin need to be carefully considered owing to their side effect of weight gain. On balance, exogenous insulin remained an important treatment in patients with uncontrolled hyperglycaemia when oral antidiabetic medications alone would not have worked sufficiently. Insulin, in addition to Metformin, is especially useful when the HbA1c level is ≥ 75 mmol/moL to achieve a rapid improvement in glycaemic control. Combination therapy is preferred as less insulin is required compared to insulin monotherapy[6,7].

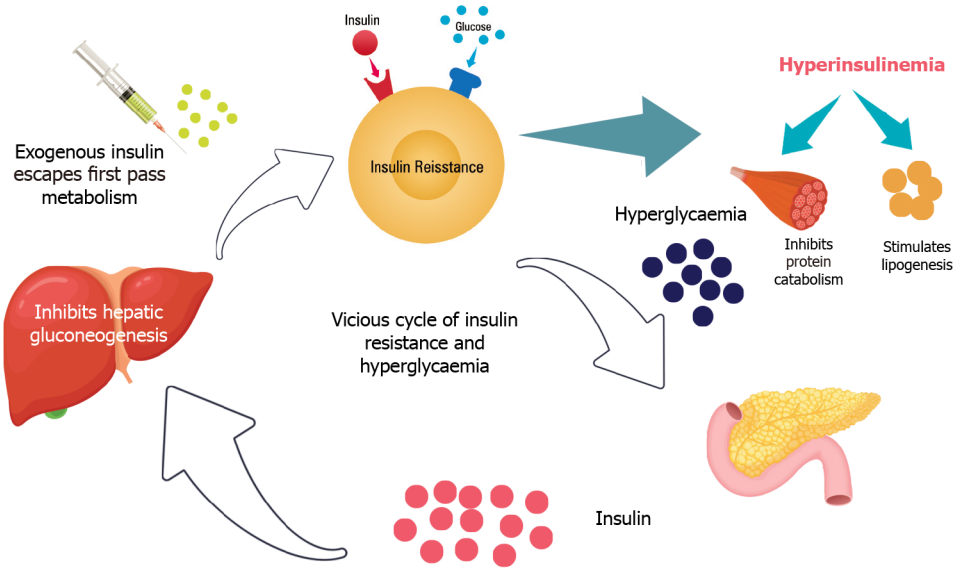
The clinicians should review and rationalise antidiabetic regimes from time to time. For example, in the case we described, the insulin regime was gradually titrated down following the addition of antidiabetic medications to prevent adverse effects such as hypoglycaemia.

Antidiabetic medications specifically for the management of diabesity

Glucagon-like peptide-1 receptor agonists: GLP-1 is a short-lived incretin hormone that is produced in response to food intake, and it controls feeding behaviour and glucose homeostasis[6,7]. The binding of GLP-1 to its receptor stimulates the release of insulin from beta-cells and suppresses the release of glucagon from alpha cells in the pancreas. Therefore, the glucagon-like peptide-1 receptor agonists (GLP-1RA), which mimics the action of endogenous GLP-1 but escapes the degradation by the dipeptidyl peptidase-4 (DPP-4) enzyme, acts by stimulating the insulin secretion, inhibiting gastric emptying in a dose-dependent manner, suppressing the appetite and altering the feeding behaviour[8].

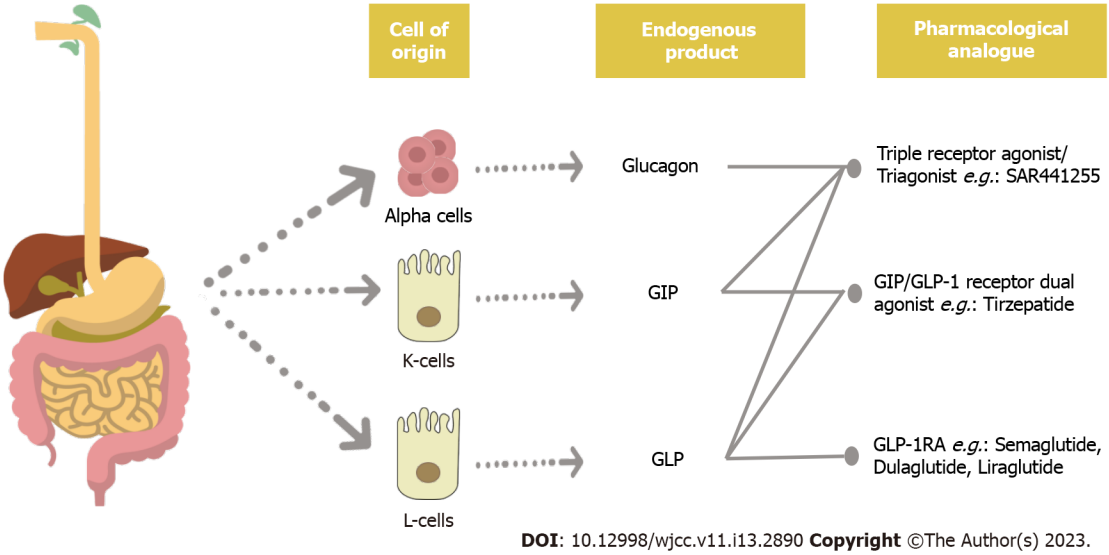
Several studies reviewed that various preparations of GLP-1RA such as Liraglutide, Dulaglutide, Semaglutide, and Exenatide demonstrated a significant reduction in HbA1c, at least if not more than when basal insulin was used, and with significant weight reduction[9-13]. Liraglutide has been shown to achieve a significantly greater mean HbA1c reduction when compared to the placebo: 11.9 mmol/moL *vs* 6.0 mmol/moL[14]. A mean weight change of -5.8% was observed at the end of this 56-wk SCALE Insulin study with 51.8% of patients on Liraglutide achieving ≥ 5% weight loss. In addition, 22% of the patients had managed to lose ≥ 10% of their weight. It was thought that the delay in gastric emptying, satiety, and reduced dose of insulin or sulfonylurea may have contributed to this. Figure 3 shows a schematic diagram of the physiology of incretins and glucagon and the pharmacological manipulation for the management of diabesity.

A greater mean weight loss of 15.8% in the Semaglutide group compared to only 6.4% in the Liraglutide group was observed in a head-to-head study to compare the efficacy of GLP-1RA in weight loss[15]. The proportion of patients achieving ≥ 10%, ≥ 15%, and ≥ 20% of weight loss was significantly larger in the Semaglutide group. The study on Semaglutide also showed the benefit of continuing treatment following weight loss can result in further weight loss, with improvement in waist circumference, lipid profile, and glucose metabolism.



DOI: 10.12998/wjcc.v11.i13.2890 **Copyright** ©The Author(s) 2023.

Figure 2 Vicious cycle of insulin resistance and weight gain.



DOI: 10.12998/wjcc.v11.i13.2890 **Copyright** ©The Author(s) 2023.

Figure 3 Gut glucagon-like peptide, gastric inhibitory peptide and glucagon system and its pharmacological analogues. GLP: Gut glucagon-like peptide; GIP: Gastric inhibitory peptide; GLP-1RA: Glucagon-like peptide-1 receptor agonist.

Moreover, the GLP-1RA has also been shown to offer cardiorenal protection, which is particularly relevant to this group of patients who are already at high risk of developing micro- and macrovascular diabetic complications. A meta-analysis demonstrated a significant 14% reduction in the risk of major cardiovascular events among the diabetic population, with the effect noted to be greater in patients with established cardiovascular disease[16].

The most common side effect from the GLP-1RA was gastrointestinal events of mild to moderate severity, which were more frequently observed following the dose escalation[10,11]. Table 1 shows the landmark clinical trials with the GLP-1RA group of drugs currently in worldwide use for the management of diabesity.

Sodium-glucose cotransporter 2 inhibitors: Sodium-glucose cotransporter 2 (SGLT2) accounts for about 90% of glucose reabsorption in the kidney with its inhibition leading to a significant amount of glucose (50-100 g daily) filtered by the renal glomeruli being excreted through the urinary system[6,17]. SGLT2 inhibitors group of drugs, therefore, helps to improve diabetes with an insulin-independent glucose-lowering mechanism. SGLT2 inhibitors also act by reducing leptin and increasing the adiponectin level, resulting in lipolysis, weight loss, and reduced accumulation of adipose tissue in the myocardium[6,17,18].

Table 1 Landmark clinical trials with glucagon-like peptide-1 receptor agonists and the efficacy on diabesity management

Study name	Year	Drug molecule	Mean weight reduction (95%CI/SD)	Mean HbA1c reduction in % (95%CI/SD)	Ref.
Exenatide-113 Clinical Study	2004	Exenatide 10 mcg twice daily	-1.6 kg (SD +/-0.3)	-0.86 (SD +/- 0.11)	[10]
EXSCEL study	2017	Exenatide (ER) Once weekly	-1.27 kg (-1.40 to -1.13)	-0.53 (-0.57 to -0.50)	[11]
LEAD 3 (Mono) Trial	2009	Liraglutide 1.2 mg daily	-1.6 kg (-2.43 to -0.88)	-1.21 (-1.35 to -1.06)	[12]
SUSTAIN 7 Trial	2018	Dulaglutide 1.5 mg weekly	-3.0 kg (SD: 0.27)	-1.4 (SD: -0.06)	[12]
SUSTAIN 7 Trial	2018	Semaglutide 1 mg weekly	-6.5 kg (SD: -0.28)	-1.8 (SD: -0.06)	[12]

Effects in comparison to placebo. HbA1c: Glycated hemoglobin; CI: Confidence interval; SD: Standard deviation; ER: Extended-release.

Four commonly available SGLT2 inhibitors worldwide, namely Canagliflozin, Dapagliflozin, Empagliflozin, and Ertugliflozin have all demonstrated significant efficacy in lowering the HbA1c and promoting weight loss which is crucial in tackling diabesity. In addition, SGLT2 inhibitors have also been shown to confer a benefit against high blood pressure, cardiovascular diseases, heart failure, and renal disease[7,17-21]. Especially prominent benefits on cardiovascular profile with SGLT2 inhibitors therapy include the reduced risk of hospitalisation from heart failure, myocardial infarction, and cardiovascular deaths among patients with T2DM.

Studies have further demonstrated the increased efficacy in glycaemic control and weight loss but not blood pressure control when SGLT2 inhibitors and metformin are used as combination therapy[15]. On the other hand, a greater reduction in HbA1c, weight, systolic blood pressure, and total and LDL cholesterol were observed with the combined use of the SGLT2 inhibitors and GLP-1RA[16]. Potential drug synergism of this combination therapy was proposed because of the differences in the mechanism of action at different sites of the body's glucose regulation[6,21].

The current National Institute for Health and Clinical Care Excellence (NICE) guidance of the United Kingdom (UK) has recommended the SGLT2 inhibitors (Canagliflozin, Dapagliflozin, or Empagliflozin) to be used as first-line monotherapy in circumstances where Metformin is contraindicated or not tolerated while lifestyle modification alone has not provided the adequate glycaemic control[22]. It can also be used as an add-on therapy in diabetic patients who has a history of chronic heart failure or established atherosclerotic cardiovascular disease.

The common adverse effects encountered with the use of SGLT2 inhibitors are genital thrush and urinary tract infections which can result in treatment discontinuation. Augmented glycosuria resulting from drug therapy may be the reason for these infections[23]. Table 2 shows the landmark clinical trials showing the benefits of managing diabesity with the SGLT2 inhibitors group of drugs commonly used in clinical practice across the world[24-26].

Biochemical monitoring of diabetes management

HbA1c has been widely used as a biomarker for long-term glucose monitoring in patients with T2DM as it reflects glycaemic control over a period of approximately 90-120 d[27,28]. It is convenient to perform, and fasting is not required. The availability of standardised assays and calibration of measurement according to the International Federation of Clinical Chemistry allow comparisons of results between the laboratories. In addition, the HbA1c level has been shown to correlate with diabetic-related complications[27,29]. As a result, the practice nowadays is still very much reliant on HbA1c in titrating antidiabetic treatment. Its use has been supported by several guidelines such as the NICE guidance in the UK and the guidelines from the ADA and the EASD, which recommended the utilisation of individualised HbA1c targets for monitoring control and antidiabetic treatment optimisation[30].

However, the accuracy of HbA1c can be affected in several conditions, resulting in falsely low or high readings which do not correlate with the clinical picture of glycaemic control in real life, as demonstrated in our case 2 described above. For instance, disorders that lead to a reduction in the lifespan of red blood cells such as haemolytic anaemia and chronic kidney disease, haemodilution in the context of blood transfusion or pregnancy, and decreased glycation of haemoglobin due to alcohol use, high doses of vitamins C and E, certain antiviral agents, and antibiotics use can lead to falsely low HbA1c level[27,29]. On the other hand, HbA1c can be falsely elevated due to increased lifespan of the red blood cells, decreased percentage of reticulocytes and increased glycation rates such as in the context of iron deficiency. Therefore, a patient's clinical history needs to be carefully sought to identify any underlying conditions which can interfere with the HbA1c readings.

There are several methods for glycaemic monitoring to use in patients whose HbA1c cannot be reliably interpreted.

Table 2 Landmark clinical trials with sodium-glucose cotransporter 2 inhibitor inhibitors and the efficacy on diabesity management

Study name	Year	Drug molecule	Mean weight reduction (95%CI)	Mean % reduction of HbA1c (95%CI)	Ref.
EMPA-REG Trial	2015	Empagliflozin 25 mg	-1.9 kg (-2.1 to -1.7)	-0.60 (-0.64 to -0.55)	[24]
CANVAS Trial	2017	Canagliflozin 300 mg	-2.8 kg (-3.21 to -2.39)	-0.80 (-0.62 to -0.98)	[25]
DECLARE-TIMI-58 Trial	2019	Dapagliflozin 10 mg	-1.51 kg (-1.81 to -1.21)	-0.55 (-0.62 to -0.53)	[26]

HbA1c: Glycated hemoglobin; CI: Confidence interval.

CBG profiling was used in our case for example. Post-meal hyperglycaemia normally precedes significant basal hyperglycaemia contributing to overall hyperglycaemia in individuals with T2DM[28]. Therefore, measuring the post-meal glucose concentrations is a helpful tool in addition to HbA1c results when there is a discrepancy between the premeal glucose profile and predicted HbA1c level. In the UK, self-monitoring of CBG device is not routinely offered to all T2DM patients. It is only available for T2DM patients who are on insulin therapy, suspected or confirmed hypoglycaemia, on oral medications that carry an increased risk of hypoglycaemia, who are pregnant or planning to conceive, or when started on glucocorticoid treatment[22]. This could potentially miss detecting T2DM patients who have poor glycaemic control but a falsely low HbA1c. The quality-controlled plasma glucose profile is recommended by the NICE, UK where HbA1c monitoring is invalid due to abnormal haemoglobin variants or disturbed erythrocyte turnover[22]. The guidelines from the ADA and the EASD recommended combining the use of plasma glucose measurement with HbA1c in T2DM patients treated with insulin[30].

Alternatively, the total glycated haemoglobin estimation, fructosamine, or glycated albumin measurement can be considered when there is an issue with HbA1c monitoring[22,27,28]. The total glycated haemoglobin estimation uses the boronate-affinity chromatography method to measure the HbA1c based on the separation of proteins resulting from structural differences. Although it is demonstrated to have the least analytical interference from the haemoglobin variants, it can be affected by the abnormal glycation of proteins. The fructosamine is obtained by measuring all the glycated proteins including albumin in plasma while the glycated albumin is measured and expressed as a percentage of total serum albumin. Both the fructosamine and glycated albumin are much shorter-term markers correlating to the glycaemic control over a 2–4-wk period, owing to their relatively rapid turnover rate. They are convenient and cost-effective to use. The reference range for both is assay, age, gender, and race dependent. While fructosamine reference intervals are now widely available, this is not the case for glycated albumin. The results for both the fructosamine and glycated albumin can be significantly affected in several conditions associated with altered protein metabolism and protein loss such as nephrotic syndrome, a hepatic disease with diminished protein synthesis, thyroid disease, and malnutrition states. In addition, glycated albumin can underestimate glycaemic control in overweight patients, particularly in those with BMI > 30 kg/m^2[23,28,31]. The total HbA1c estimation or fructosamine estimation is currently recommended for use in the UK[22].

Continuous glucose monitoring (CGM) is an emerging method to monitor ambient glucose concentrations. It reveals the glycaemic variability which may have an association with an increased risk of micro- and macrovascular complications[32]. The CGM is being increasingly recommended in patients with T2DM who are on multiple daily injections and experience recurrent or severe hypoglycaemia, impaired hypoglycaemia awareness, conditions or disabilities impacting their ability to perform self-CBG monitoring or those who self-measure at least 8 times a day. This could be an option in the future but is not currently recommended for use in glycaemic control monitoring in the context of inaccurate HbA1c in the UK[22].

Approach type 1 DM and obesity

The obesity epidemic is affecting the T1DM population much greater than the general population. Its prevalence continues to be trending up in recent decades, with a rate of between 2.8% and 37.1% across the lifetime of T1DM patients. The associated incidence of metabolic syndrome increased from 4.9% among patients with normal weight to 35.3% among obese patients[33]. Several studies demonstrated that individuals with T1DM and obesity are at higher risk of micro- and macrovascular complications [34].

Double diabetes is a terminology used to describe patients with T1DM who are also showing clinical signs of T2DM such as obesity and insulin resistance. In addition to the state of insulin deficiency, the increased adiposity leads to the production of inflammatory cytokines and adipokines, resulting in a worsening of peripheral insulin resistance. Consequently, these patients require a higher amount of exogenous insulin to achieve satisfactory glycaemic control which is crucial in reducing the risk of long-term complications from diabetes. However, insulin is an anabolic hormone that slows basal metabolism, inhibits protein catabolism, and stimulates lipogenesis. The exogenous insulin also does not have first pass through the liver as in the case of endogenous insulin which suppresses hepatic glucon-

eogenesis in a non-diabetic individual. Hence, the use of intensive insulin therapy over time can cause increased fat accumulation and weight gain which further exacerbates the issue of obesity[33,34].

In addition to lifestyle modifications, several pharmacological approaches can be considered in the management of patients with double diabetes.

Metformin is known to decrease hepatic glucose production, increase insulin sensitivity, and decrease glucose absorption. The REMOVAL trial revealed a reduction in body weight, LDL cholesterol, and insulin dose requirement when Metformin was used in T1DM patients[35]. However, it did not result in a sustained effect in glycaemic control as measured with HbA1c or alter the atherosclerosis progression. Metformin is currently being used off-licensed in the UK as additional therapy in T1DM patients who have a BMI of > 25 kg/m^2 and in the context of improving glycaemic control while minimising the insulin dosage[36].

In our case, the patient was also trialled on the maximum dose of Liraglutide, a GLP-1RA usually used for treating patients with T2DM. The GLP-1RA has extensively demonstrated to have a good profile in promoting weight loss in both diabetic and non-diabetic populations[34,37,38]. However, there are relatively few studies that recruited patients with T1DM. The 2 Large trials: ADJUNCT ONE [37] and ADJUNCT TWO[38] which studied the efficacy and safety of the use of Liraglutide in the T1DM population showed benefits in HbA1c, insulin dose, and body weight reduction. Both these studies showed a statistically significant reduction in HbA1c with all doses of Liraglutide compared to placebo. However, the ADJUNCT 2 study observed no significant difference in the mean fasting plasma glucose. This could be explained by the mode of action of the GLP-1RA. In line with this, the studies demonstrated a dose-dependent reduction in total daily insulin dose, mainly contributed by a reduction in the bolus insulin requirement. Both studies also revealed a statistically significant weight loss in a dose-dependent manner, with a mean reduction in body weight of 5.1 kg with Liraglutide 1.8 mg being observed. The occurrence of adverse events associated with Liraglutide use is observed to be dose-dependent. Higher rates of hypoglycaemia and hyperglycaemia with ketosis were also reported[37,38].

The use of SGLT2 inhibitors in T1DM remained an area to be explored. A review of 8 randomised placebo-controlled trials which studied the use of SGLT2 inhibitors (Canagliflozin, Dapagliflozin, Empagliflozin, and Sotagliflozin) in T1DM patients have shown its effectiveness in lowering the HbA1c, averaging at 0.35%–0.54% after 24-26 weeks of treatment when added to the insulin therapy[39]. However, the benefit of sustained glycaemic efficacy beyond 1 year of therapy remained uncertain. All the studies also found a positive outcome in terms of weight loss and reduced requirement for a total daily dose of insulin. All the trials cut down on the insulin regime by 10%-30% at the initiation of treatment to mitigate the risk of SGLT2 inhibitors induced hypoglycaemia. Studies that used Dapagliflozin, Empagliflozin, and Sotagliflozin reported no increase in the risk of developing severe hypoglycaemia. However, a 5.8- fold increase in the risk of ketoacidosis was found in these studies and this occurred in a dose-dependent manner[39].

Overall, the experience of using other antidiabetic medications as add-on therapy to insulin in T1DM remained limited with all uses being unlicensed. The pros and cons of treatment need to be carefully weighed and discussed with patients. The individualised use of these medications especially in the management of double diabetes can achieve some good outcomes such as in the patient we showcased here. Largescale multicentre clinical trials are needed to provide us with more robust evidence of the benefits of such an approach and the risks associated.

Monogenic diabetes

Monogenic diabetes accounts for about 1%-3% of patients with young-onset diabetes[40]. These rare forms of diabetes caused by a single gene defect are mostly inherited in an autosomal dominant pattern, giving rise to 2 main clinical phenotypes: the maturity-onset diabetes of young (MODY) and neonatal diabetes. MODY, being the most common form of monogenic diabetes, is estimated to be present at 1 in 10000 adults and 1 in 23000 children according to studies that comprised mostly of the White European population[41]. 14 different gene mutations in MODY have been identified so far with the *HNF1A, HNF4A, HNF1B,* and *GCK* being the most common mutations[40,42]. Nearly all genes implicated in monogenic diabetes correspondingly encode a protein which involves in pancreatic beta cell development or function. For example, a mutation in *HNF1A, HNF4A,* and *HNF1B* leads to transcription factor defects disrupting the beta cell development and function while the *GCK* mutation accounts for impaired beta cell glucose sensing[43].

Detecting monogenic diabetes in clinical practice has remained challenging as it relies on a collection of clinical characteristics with no universally recognised criteria to prompt suspicion and investigations into the presence of the disease[43,44]. Investigations for monogenic diabetes should be considered in children who receive a diagnosis of diabetes within the first 6 mo of life, children, and young adults (< 25 years of age) who have hyperglycaemia without the typical characteristics of type 1 or type 2 diabetes. Other clinical characteristics that could be suggestive of monogenic diabetes include the presence of a personal or family history of transient neonatal hypoglycaemia or neonatal diabetes, absence of pancreatic antibodies, prolonged "honeymoon" phase with detectable C- peptide after more than 3-5 years and lack of ketoacidosis when insulin is omitted or is extremely sensitive to the sulphonylurea treatment[40,44]. It is recommended that a minimum of 3 antibodies, preferably GAD, IA2, and ZnT8 should be checked with the presence of any positive antibodies essentially excluding the

diagnosis of MODY[41]. Due to the pattern of inheritance, a family history of diabetes in successive generations is a good pointer to prompt further investigations. The MODY calculator is a clinical prediction tool developed by the University of Exeter group which takes into account the current age, age at diagnosis, gender, ethnicity, BMI, HbA1c, treatment regimen, parental history of diabetes, and presence of certain medical conditions to calculate the post-test probability of MODY. The calculator is validated in individuals of < 35 years old and has a limitation of detecting MODY across different ethnic groups as it is developed based on the Caucasian group[41,42].

Diagnosing monogenic diabetes *via* molecular genetic testing enables the practice of precision medicine in diabetes which allows future care and management to be tailored accordingly. This has a significant implication of allowing cost and treatment effectiveness with targeted therapies, as well as the cascade effect of identifying other family members who may have a similar diagnosis[42,44]. As portrayed in this case, achieving the diagnosis has allowed the patient's glycaemic control to be optimised with sulfonylurea only. It has prevented the unnecessary use of exogenous insulin and its associated complications with prolonged use. Besides, achieving the right diagnosis enables her son to be investigated and managed appropriately at a younger age. Patients with *HNF-1A* mutation have a similar risk as patients with T2DM in all-cause mortality and cardiovascular disease. They are also at risk of developing microvascular complications such as retinopathy, nephropathy, and neuropathy[40]. Patients with *HNF-1A* MODY respond well to sulphonylurea, which acts on the potassium-sensitive ATP channels leading to increased insulin secretion. However, monotherapy with sulphonylurea may not be sufficient to control hyperglycaemia over time. Exogenous insulin or GLP-1RA can be considered at this point. GLP-1RA can act by stimulating insulin secretion and reducing postprandial glucose elevation. On the other hand, SGLT2-i is thought to cause a higher risk of dehydration, glycosuria, genital infections, and diabetic ketoacidosis in *HNF-A1* MODY and therefore, not a choice of treatment currently[40,41].

Sudden deterioration of well-controlled diabetes

A significant glycaemic deterioration in a diabetic patient with longstanding stable disease control should prompt screening for other causes of sudden hyperglycaemia. In addition to the common T1DM and T2DM, other causes of diabetes which could be considered depending on the clinical history and examination include: (1) Disorders of the pancreas such as pancreatitis, pancreatic neoplasm, or following pancreatectomy; (2) endocrinopathies such as Cushing's syndrome or acromegaly; (3) drug-induced diabetes; (4) various infections; and (5) systemic diseases such as haemochromatosis[45].

Type 3C diabetes describes diabetes caused by the destruction of the pancreas. Its prevalence was approximately 1%-9% of all forms of diabetes. The majority of type 3C diabetes was due to chronic pancreatitis with only 8% of it being caused by pancreatic ductal adenocarcinoma[45]. The presence of diabetes was found to be significantly higher at 68% in patients with pancreatic ductal adenocarcinoma when compared to other types of cancers, such as lung, breast, colorectal, and prostate cancer[46]. New-onset of diabetes has been commonly reported preceding the diagnosis of pancreatic ductal adenocarcinoma. The incidence of impaired fasting glucose or glucose intolerance irrespective of the size and stage of the underlying pancreatic ductal adenocarcinoma was estimated to be about 80%[47]. Although the exact mechanism is yet to be fully understood, insulin resistance, the presence of adrenomedullin, beta cell loss, and dysfunction were among the proposed elements which are thought to be contributing to diabetes in patients with pancreatic ductal adenocarcinoma[47]. However, due to the high incidence of diabetes relative to the incidence of pancreatic cancer, routine screening for the presence of cancer in patients with new-onset diabetes is currently not deemed to be cost-effective[45].

There is no consensus on managing diabetes in this group of patients. The primary aim of antidiabetic treatment is to avoid acute metabolic complications due to uncontrolled hyperglycaemia rather than prevention of long-term complications considering the limited life expectancy associated with the diagnosis[47]. Symptomatic hyperglycaemia has a negative impact on the quality of life. Patients with diabetes who are on cancer treatment are at higher risk of infection. The glucocorticoid treatment which is commonly used in advanced cancer for symptom management and appetite stimulation can lead to worsening glycaemic control. It was also found that the concordance to antidiabetic treatment was lower in patients with cancer.

Most cases of pancreatic ductal adenocarcinoma are associated with a poor prognosis due to late diagnosis and limited treatment options. Patients with pancreatic malignancy with concurrent diabetes are observed to have poorer overall survival[48]. In addition to physical illness, the patient and families also undergo psychological distress. Palliative care involvement is therefore vital in supporting the management of the symptoms and preserving the quality of life as best as possible[49]. Diabetes care during the end-of-life requires a holistic approach and acknowledgement that the focus and principles of treatment have now changed to avoid hypoglycaemia, diabetic ketoacidosis, hyperosmolar hyperglycaemic state, or symptomatic hyperglycaemia. Discussions with patients and families to provide reassurance, respect, support, and preserve one's ability to self-manage their diabetes are pivotal[50]. During the last days of life, a CBG range of 6-15 mmol/L is generally well accepted to accommodate the minimal number of glucose testings as possible.

CONCLUSION

The diabetes epidemic continues to grow. Over the recent decades, there have been many advances in diabetes research leading to more sophisticated diabetes care algorithms in the modern world. As the complexity of the disease unfolded such as with the discovery of some rarer causes of diabetes *via* genomic testing and recognising diabetes as part of a bigger picture of the metabolic disease, having a better understanding of the underlying pathophysiology contributing to various forms of diabetes enables the practice of precision medicine in diabetes. Acknowledging diabetes as a multifaceted disease and the development of various newer hypoglycaemic agents are important milestones in the paradigm of enhanced diabetes care. This should always be reflected in our clinical practice to individualise diabetes care with the best evidence-based approach.

Although we presented 5 unique case scenarios to highlight the importance of individualized diabetes care in day-to-day clinical practice with this paper, we cannot make any firm recommendations for the management of every patient that physicians come across in their diabetes clinics based on this paper. We need to adhere to appropriate clinical guidelines from various professional bodies for the usual care of diabetes patients. However, when the situation demands as in the case snippets discussed above, we need to "think out of the box" to change the usual algorithms to ensure that our patients get the optimal benefit from scientific medicine based on the latest evidence available to us.

FOOTNOTES

Author contributions: Khor XY performed the literature search, interpreted the relevant literature, and drafted the initial manuscript with guidance from Pappachan JM and Jeeyavudeen MS who conceived the idea and designed the paper; In addition, Jeeyavudeen MS prepared the figures and supervised the revision of the article critically for important intellectual content; All authors have read and approved the final version of the manuscript.

Conflict-of-interest statement: Professor Pappachan and co-authors have nothing to disclose.

Country/Territory of origin: United Kingdom

ORCID number: Joseph M Pappachan 0000-0003-0886-5255; Mohammad Sadiq Jeeyavudeen 0000-0002-1461-0534.

S-Editor: Liu JH
L-Editor: A
P-Editor: Yuan YY

REFERENCES

1 **IDF Diabetes Atlas 2021**. IDF Atlas 10th Edition, International Diabetes Federation. IDF Diabetes Atlas 2021 | IDF Diabetes Atlas. Accessed on 20th September 2022
2 **Dineen-Griffin S**, Garcia-Cardenas V, Williams K, Benrimoj SI. Helping patients help themselves: A systematic review of self-management support strategies in primary health care practice. *PLoS One* 2019; **14**: e0220116 [PMID: 31369582 DOI: 10.1371/journal.pone.0220116]
3 **Coulter A**, Entwistle VA, Eccles A, Ryan S, Shepperd S, Perera R. Personalised care planning for adults with chronic or long-term health conditions. *Cochrane Database Syst Rev* 2015; **2015**: CD010523 [PMID: 25733495 DOI: 10.1002/14651858.CD010523.pub2]
4 **Ray JG**, O'Brien TE, Chan WS. Preconception care and the risk of congenital anomalies in the offspring of women with diabetes mellitus: a meta-analysis. *QJM* 2001; **94**: 435-444 [PMID: 11493721 DOI: 10.1093/qjmed/94.8.435]
5 **World Health Organisation**. Obesity. Assessed on 22nd September 2022. Available from: https://www.who.int/health-topics/obesity#tab=tab_1
6 **Pappachan JM**, Viswanath AK. Medical Management of Diabesity: Do We Have Realistic Targets? *Curr Diab Rep* 2017; **17**: 4 [PMID: 28101792 DOI: 10.1007/s11892-017-0828-9]
7 **Pappachan JM**, Fernandez CJ, Chacko EC. Diabesity and antidiabetic drugs. *Mol Aspects Med* 2019; **66**: 3-12 [PMID: 30391234 DOI: 10.1016/j.mam.2018.10.004]
8 **Jakhar K**, Vaishnavi S, Kaur P, Singh P, Munshi A. Pharmacogenomics of GLP-1 receptor agonists: Focus on pharmacological profile. *Eur J Pharmacol* 2022; **936**: 175356 [PMID: 36330902 DOI: 10.1016/j.ejphar.2022.175356]
9 **Sarma S**, Palcu P. Weight loss between glucagon-like peptide-1 receptor agonists and bariatric surgery in adults with obesity: A systematic review and meta-analysis. *Obesity (Silver Spring)* 2022; **30**: 2111-2121 [PMID: 36321278 DOI:

10.1002/oby.23563]

10 **Buse JB**, Henry RR, Han J, Kim DD, Fineman MS, Baron AD; Exenatide-113 Clinical Study Group. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 2004; **27**: 2628-2635 [PMID: 15504997 DOI: 10.2337/diacare.27.11.2628]

11 **Holman RR**, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Öhman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF; EXSCEL Study Group. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2017; **377**: 1228-1239 [PMID: 28910237 DOI: 10.1056/NEJMoa1612917]

12 **Garber A**, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, Hale PM, Zdravkovic M, Bode B; LEAD-3 (Mono) Study Group. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009; **373**: 473-481 [PMID: 18819705 DOI: 10.1016/S0140-6736(08)61246-5]

13 **Pratley RE**, Aroda VR, Lingvay I, Lüdemann J, Andreassen C, Navarria A, Viljoen A; SUSTAIN 7 investigators. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol* 2018; **6**: 275-286 [PMID: 29397376 DOI: 10.1016/S2213-8587(18)30024-X]

14 **Garvey WT**, Birkenfeld AL, Dicker D, Mingrone G, Pedersen SD, Satylganova A, Skovgaard D, Sugimoto D, Jensen C, Mosenzon O. Efficacy and Safety of Liraglutide 3.0 mg in Individuals With Overweight or Obesity and Type 2 Diabetes Treated With Basal Insulin: The SCALE Insulin Randomized Controlled Trial. *Diabetes Care* 2020; **43**: 1085-1093 [PMID: 32139381 DOI: 10.2337/dc19-1745]

15 **Rubino DM**, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sørrig R, Wadden TA, Wizert A, Garvey WT; STEP 8 Investigators. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. *JAMA* 2022; **327**: 138-150 [PMID: 35015037 DOI: 10.1001/jama.2021.23619]

16 **Giugliano D**, Scappaticcio L, Longo M, Caruso P, Maiorino MI, Bellastella G, Ceriello A, Chiodini P, Esposito K. GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs. *Cardiovasc Diabetol* 2021; **20**: 189 [PMID: 34526024 DOI: 10.1186/s12933-021-01366-8]

17 **Blüher M**, Ceriello A, Davies M, Rodbard H, Sattar N, Schnell O, Tonchevska E, Giorgino F. Managing weight and glycaemic targets in people with type 2 diabetes-How far have we come? *Endocrinol Diabetes Metab* 2022; **5**: e00330 [PMID: 35298097 DOI: 10.1002/edm2.330]

18 **Lazzaroni E**, Ben Nasr M, Loretelli C, Pastore I, Plebani L, Lunati ME, Vallone L, Bolla AM, Rossi A, Montefusco L, Ippolito E, Berra C, D'Addio F, Zuccotti GV, Fiorina P. Anti-diabetic drugs and weight loss in patients with type 2 diabetes. *Pharmacol Res* 2021; **171**: 105782 [PMID: 34302978 DOI: 10.1016/j.phrs.2021.105782]

19 **Milder TY**, Stocker SL, Abdel Shaheed C, McGrath-Cadell L, Samocha-Bonet D, Greenfield JR, Day RO. Combination Therapy with an SGLT2 Inhibitor as Initial Treatment for Type 2 Diabetes: A Systematic Review and Meta-Analysis. *J Clin Med* 2019; **8** [PMID: 30621212 DOI: 10.3390/jcm8010045]

20 **Castellana M**, Cignarelli A, Brescia F, Perrini S, Natalicchio A, Laviola L, Giorgino F. Efficacy and safety of GLP-1 receptor agonists as add-on to SGLT2 inhibitors in type 2 diabetes mellitus: A meta-analysis. *Sci Rep* 2019; **9**: 19351 [PMID: 31852920 DOI: 10.1038/s41598-019-55524-w]

21 **Deol H**, Lekkakou L, Viswanath AK, Pappachan JM. Combination therapy with GLP-1 analogues and SGLT-2 inhibitors in the management of diabesity: the real world experience. *Endocrine* 2017; **55**: 173-178 [PMID: 27696231 DOI: 10.1007/s12020-016-1125-0]

22 **National Institute for Health and Clinical Care Excellence**. Type 2 diabetes in adults: management [NICE guideline no. 28]; Assessed on 24th September 2022. Available from: https://www.nice.org.uk/guidance/ng28

23 **Liu J**, Li L, Li S, Jia P, Deng K, Chen W, Sun X. Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: a systematic review and meta-analysis. *Sci Rep* 2017; **7**: 2824 [PMID: 28588220 DOI: 10.1038/s41598-017-02733-w]

24 **Zinman B**, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; **373**: 2117-2128 [PMID: 26378978 DOI: 10.1056/NEJMoa1504720]

25 **Wiviott SD**, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2019; **380**: 347-357 [PMID: 30415602 DOI: 10.1056/NEJMoa1812389]

26 **Neal B**, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017; **377**: 644-657 [PMID: 28605608 DOI: 10.1056/NEJMoa1611925]

27 **Sodi R**, McKay K, Dampetla S, Pappachan JM. Monitoring glycaemic control in patients with diabetes mellitus. *BMJ* 2018; **363**: k4723 [PMID: 30459149 DOI: 10.1136/bmj.k4723]

28 **Bergman M**, Abdul-Ghani M, DeFronzo RA, Manco M, Sesti G, Fiorentino TV, Ceriello A, Rhee M, Phillips LS, Chung S, Cravalho C, Jagannathan R, Monnier L, Colette C, Owens D, Bianchi C, Del Prato S, Monteiro MP, Neves JS, Medina JL, Macedo MP, Ribeiro RT, Filipe Raposo J, Dorcely B, Ibrahim N, Buysschaert M. Review of methods for detecting glycemic disorders. *Diabetes Res Clin Pract* 2020; **165**: 108233 [PMID: 32497744 DOI: 10.1016/j.diabres.2020.108233]

29 **Radin MS**. Pitfalls in hemoglobin A1c measurement: when results may be misleading. *J Gen Intern Med* 2014; **29**: 388-394 [PMID: 24002631 DOI: 10.1007/s11606-013-2595-x]

30 **Inzucchi SE**, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; **35**: 1364-1379 [PMID: 22517736 DOI: 10.2337/dc12-0413]

31 **Danese E**, Montagnana M, Nouvenne A, Lippi G. Advantages and pitfalls of fructosamine and glycated albumin in the diagnosis and treatment of diabetes. *J Diabetes Sci Technol* 2015; **9**: 169-176 [PMID: 25591856 DOI: 10.1177/1932296814567227]

32 **Umpierrez GE**, P Kovatchev B. Glycemic Variability: How to Measure and Its Clinical Implication for Type 2 Diabetes. *Am J Med Sci* 2018; **356**: 518-527 [PMID: 30447705 DOI: 10.1016/j.amjms.2018.09.010]

33 **Vilarrasa N**, San Jose P, Rubio MÁ, Lecube A. Obesity in Patients with Type 1 Diabetes: Links, Risks and Management Challenges. *Diabetes Metab Syndr Obes* 2021; **14**: 2807-2827 [PMID: 34188505 DOI: 10.2147/DMSO.S223618]

34 **Mottalib A**, Kasetty M, Mar JY, Elseaidy T, Ashrafzadeh S, Hamdy O. Weight Management in Patients with Type 1 Diabetes and Obesity. *Curr Diab Rep* 2017; **17**: 92 [PMID: 28836234 DOI: 10.1007/s11892-017-0918-8]

35 **Petrie JR**, Chaturvedi N, Ford I, Brouwers MCGJ, Greenlaw N, Tillin T, Hramiak I, Hughes AD, Jenkins AJ, Klein BEK, Klein R, Ooi TC, Rossing P, Stehouwer CDA, Sattar N, Colhoun HM; REMOVAL Study Group. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2017; **5**: 597-609 [PMID: 28615149 DOI: 10.1016/S2213-8587(17)30194-8]

36 **National Institute for Health and Care Excellence**. Type 1 diabetes in adults: diagnosis and management [NICE guideline no. 17]; Assessed on 26th September 2022. Available from: https://www.nice.org.uk/guidance/ng17

37 **Mathieu C**, Zinman B, Hemmingsson JU, Woo V, Colman P, Christiansen E, Linder M, Bode B; ADJUNCT ONE Investigators. Efficacy and Safety of Liraglutide Added to Insulin Treatment in Type 1 Diabetes: The ADJUNCT ONE Treat-To-Target Randomized Trial. *Diabetes Care* 2016; **39**: 1702-1710 [PMID: 27506222 DOI: 10.2337/dc16-0691]

38 **Ahrén B**, Hirsch IB, Pieber TR, Mathieu C, Gómez-Peralta F, Hansen TK, Philotheou A, Birch S, Christiansen E, Jensen TJ, Buse JB; ADJUNCT TWO Investigators. Efficacy and Safety of Liraglutide Added to Capped Insulin Treatment in Subjects With Type 1 Diabetes: The ADJUNCT TWO Randomized Trial. *Diabetes Care* 2016; **39**: 1693-1701 [PMID: 27493132 DOI: 10.2337/dc16-0690]

39 **Taylor SI**, Blau JE, Rother KI, Beitelshees AL. SGLT2 inhibitors as adjunctive therapy for type 1 diabetes: balancing benefits and risks. *Lancet Diabetes Endocrinol* 2019; **7**: 949-958 [PMID: 31585721 DOI: 10.1016/S2213-8587(19)30154-8]

40 **Naylor RN**, Philipson LH. Diagnosis and Clinical Management of Monogenic Diabetes. 2020 Nov 5. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000– [PMID: 33180404]

41 **Broome DT**, Pantalone KM, Kashyap SR, Philipson LH. Approach to the Patient with MODY-Monogenic Diabetes. *J Clin Endocrinol Metab* 2021; **106**: 237-250 [PMID: 33034350 DOI: 10.1210/clinem/dgaa710]

42 **Tosur M**, Philipson LH. Precision diabetes: Lessons learned from maturity-onset diabetes of the young (MODY). *J Diabetes Investig* 2022; **13**: 1465-1471 [PMID: 35638342 DOI: 10.1111/jdi.13860]

43 **Zhang H**, Colclough K, Gloyn AL, Pollin TI. Monogenic diabetes: a gateway to precision medicine in diabetes. *J Clin Invest* 2021; **131** [PMID: 33529164 DOI: 10.1172/JCI142244]

44 **Colclough K**, Patel K. How do I diagnose Maturity Onset Diabetes of the Young in my patients? *Clin Endocrinol (Oxf)* 2022; **97**: 436-447 [PMID: 35445424 DOI: 10.1111/cen.14744]

45 **Feingold KR**. Atypical Forms of Diabetes. 2022 Feb 24. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000– [PMID: 25905351]

46 **Aggarwal G**, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. *Pancreas* 2013; **42**: 198-201 [PMID: 23000893 DOI: 10.1097/MPA.0b013e3182592c96]

47 **Hart PA**, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark CE, Goodarzi MO, Habtezion A, Korc M, Kudva YC, Pandol SJ, Yadav D, Chari ST; Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer(CPDPC). Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. *Lancet Gastroenterol Hepatol* 2016; **1**: 226-237 [PMID: 28404095 DOI: 10.1016/S2468-1253(16)30106-6]

48 **Joharatnam-Hogan N**, Carter TJ, Reynolds N, Ho JH, Adam S, Board R. Diabetes Mellitus in People with Cancer. 2021 Dec 12. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000– [PMID: 34965060]

49 **Chung V**, Sun V, Ruel N, Smith TJ, Ferrell BR. Improving Palliative Care and Quality of Life in Pancreatic Cancer Patients. *J Palliat Med* 2022; **25**: 720-727 [PMID: 34704841 DOI: 10.1089/jpm.2021.0187]

50 **Diabetes UK**. For Healthcare Professionals: End of Life Guidance for Diabetes Care. November 2021. Assessed on 29th November 2022https://diabetes-resources-production.s3.eu-west-1.amazonaws.com/resources-s3/public/2021-11/EoL_TREND_FINAL2_0.pdf

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 2903-2915

DOI: 10.12998/wjcc.v11.i13.2903

ISSN 2307-8960 (online)

MINIREVIEWS

Clinical management of dural defects: A review

Rong-Peng Dong, Qi Zhang, Li-Li Yang, Xue-Liang Cheng, Jian-Wu Zhao

Specialty type: Orthopedics

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Chrastina J, Czech Republic; Kung WM, Taiwan

Received: December 28, 2022
Peer-review started: December 28, 2022
First decision: February 20, 2023
Revised: March 3, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 6, 2023

Rong-Peng Dong, Qi Zhang, Li-Li Yang, Xue-Liang Cheng, Jian-Wu Zhao, Department of Spinal Surgery, The Second Hospital of Jilin University, Changchun 130000, Jilin Province, China

Corresponding author: Jian-Wu Zhao, MD, PhD, Chief Doctor, Professor, Department of Spinal Surgery, The Second Hospital of Jilin University, No. 218 Ziqiang Street, Nanguan District, Changchun 130000, Jilin Province, China. jianwu@jlu.edu.cn

Abstract

Dural defects are common in spinal and cranial neurosurgery. A series of complications, such as cerebrospinal fluid leakage, occur after rupture of the dura. Therefore, treatment strategies are necessary to reduce or avoid complications. This review comprehensively summarizes the common causes, risk factors, clinical complications, and repair methods of dural defects. The latest research progress on dural repair methods and materials is summarized, including direct sutures, grafts, biomaterials, non-biomaterial materials, and composites formed by different materials. The characteristics and efficacy of these dural substitutes are reviewed, and these materials and methods are systematically evaluated. Finally, the best methods for dural repair and the challenges and future prospects of new dural repair materials are discussed.

Key Words: Dural defect; Cerebrospinal fluid leak; Incidental durotomy; Causes of dural defect; Dural repair

Core Tip: Dural defects are common in spinal surgery and may cause a series of complications, so it is necessary to actively prevent and treat them. In this paper, we reviewed issues related to dural defects and discussed their clinical management.

Citation: Dong RP, Zhang Q, Yang LL, Cheng XL, Zhao JW. Clinical management of dural defects: A review. *World J Clin Cases* 2023; 11(13): 2903-2915
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/2903.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.2903

INTRODUCTION

The surface of the brain and spinal cord is covered by three layers of capsular membrane, including the soft membrane, arachnoid membrane, and dural membrane, from the inside to the outside, respectively, with the function of protecting and supporting the brain and spinal cord. The dura, which is the outermost layer of the meninges that protects the brain or spinal cord, can be damaged in situations such as accidental trauma and spinal surgery. In a meta-analysis of 23 studies, the incidence of dural injury related to spinal surgery was 5.8%[1]. Dural damage can result in persistent cerebrospinal fluid (CSF) leakage, which can lead to serious complications including severe headache, pseudomeningocele, nerve root entrapment, and intracranial hemorrhage[2]. In existing research and clinical practice, whether the damaged dura mater should be repaired is debated[3], and research on the repair methods of dural defects has progressed[4,5]. Therefore, this review aimed to summarize the clinical treatment of dural defects, to help doctors better treat dural defects and reduce the occurrence and sequelae of dural injuries.

ANATOMY OF THE DURA MATER

Although the dura mater spinalis and dura mater encephalin are anatomically continuous, they exhibit several differences. The dura mater encephalin is a thick, tough, double-layer membrane. The outer part of the dura is the periosteum on the inner surface of the skull, which stops at the foramen magnum and becomes the periosteum in the spinal canal. The inner part continues and becomes the dura mater spinalis. In some parts of the dura, the two layers are separated and the inner surface is lined with endothelial cells, known as the dural sinus, which is connected to the extracranial vein by the guiding vein. The dura mater of the spine extends to the dura mater, gradually thinning at the level of the second lumbar vertebra, surrounding the terminal filament, and its lower end is connected to the coccyx. The space between the dura mater and the periosteum of the spinal canal is called the epidural space, which contains loose connective tissue, fat, lymphatic vessels, the venous plexus, and spinal nerve roots. The epidural space is often used for epidural anesthesia in clinical practice. The middle layer of the meninges is referred to as the arachnoid membrane, while the inner layer is referred to as the soft membrane, and CSF is found between these two spaces. The generation, flow, absorption, and circulation of CSF provide the basis for maintaining local homeostasis. Under physiological conditions, CSF fluctuates within a reasonable range. When the dura is torn or damaged, the decrease in CSF pressure leads to a series of clinical symptoms and later complications, such as intracranial hypotension, infectious complications, delayed wound healing, and neurological dysfunction[2,6,7].

CAUSES OF DURAL DEFECTS

Dural tears are common in spinal and neurosurgery. Depending on the course of the disease, dural tears can be classified as either acute or chronic and primary or secondary. Most dural tears are accidental, while others are intentional. Intentional dural tears, including diagnostic lumbar puncture, therapeutic puncture, removal of intradural tumors or cysts, and selective shunt among others are often required for treatment and diagnosis of various disorders of the brain and spinal cord[8]. Meanwhile, accidental dural tears may be caused by trauma, neurosurgery, or spinal surgery. Multiple studies have shown that patients with a history of lumbar surgery tend to be more prone to dural tears[1,9-12]. For example, Telfeian *et al*[13] found that patients who underwent secondary minimally invasive lumbar surgery were more likely to develop dural defects. Takahashi *et al*[14] found that patients with degenerative lumbar spondylolisthesis and juxtafacet cysts were more likely to undergo an unintended durotomy. In addition, Lukas reported a case of a dural defect caused by a positioning needle during spinal surgery, indicating that caution is needed during needle placement in unilateral surgery[15]. Our research team also found a case of dural damage caused by continuous negative pressure suction after spinal laminectomy in daily clinical work. In addition, dural defects have many risk factors, including obesity. Therefore, we comprehensively summarized the causes and risk factors of dural breakage in Table 1. The clinical symptoms vary by the type of dural defect, and dural defects may cause destruction of the arachnoid membrane and CSF leakage.

COMPLICATIONS OF DURAL DEFECTS

Dural tears can cause CSF leakage and increase the risk of infection; therefore, they are often associated with acute or chronic complications. Due to CSF leakage, dural tears may cause a persistent decrease in intracranial pressure, leading to symptoms of low cranial pressure, including postural headache[2]. Persistent low cranial pressure can also cause adult migraine, nausea, photophobia, and ataxia, and

Table 1 Etiology of dural defect

Relationship	Classification	Etiology
Immediate factors	Operation	Lumbar anesthesia, puncture[8]
		Analgesia in labor[8]
		Chiropractic[82]
		Negative pressure suction
	Trauma	Skull fracture[83]
		Spinal burst fracture[84]
		Subdural hematoma cleared[85]
	Surgery	Discectomy/artificial disc replacement[86-88]
		laminectomy[86-88]
		Late-presenting dural tear[89]
		minimally invasive surgery[90]
		Secondary intervention after surgical intervention[9,10,14,92]
		Intradural mass resection/cyst removal[9,14]
Indirect factors	Connective tissue disorders	Marfan syndrome[91]
		Ehlers-Danlos syndrome type II[92]
	Miscellaneous	Dural ossification[86]
		Spontaneous fistula
		The use of bone morphoprotein 2[93]
		Older age[1,10,14]
		Diabetes[1]
		Obesity (Body mass index ≥ 30)[87]
		Corticosteroid use[87]
		Ankylosing spondylitis[87]

severe low cranial pressure can even cause pseudomeningocele, nerve root entrapment, and intracranial hemorrhage, among other symptoms[2,6,16]. Furthermore, the patient's life is at risk when low pressure in the damaged dural area causes the spinal cord or brain tissue to protrude from the injured opening, resulting in spinal or brain herniation. When dural defects lead to long-term CSF leakage, CSF accumulation in the tissue space can form pseudocysts, sinuses, or fistulas, increasing the risk of infection[6,7,17,18]. Intradural infections caused by dural defects from spinal surgery include meningitis, adhesive arachnoiditis, and dural annulus fibrosus. A high index of suspicion for meningitis should be maintained in patients with a clinical triad of fever, neck stiffness, and disturbance of consciousness after spinal surgery[7]. The spread of the infection can also lead to complications such as sepsis, pneumonia, urinary tract infections, thromboembolism, and acute kidney injury[8]. Moreover, damage to the dura can lead to prolonged bed rest, which may result in a series of long-term bed complications such as bedsores, pendant pneumonia, skin ulcers, and deep venous thrombosis of the lower extremities.

CLINICAL MANAGEMENT OF DURAL DEFECTS

Direct suture

The common techniques of direct suture are summarized as follows: (1) Direct suture for dural tears or small dural defects; (2) Continuous suture or figure-8 suture; (3) Leaving a small suture hole using GORE-TEX suture material; and (4) Making the distance between two sutures < 3 mm and placing each suture line 1 mm from the edge[19]. One-stage repair is the first choice of treatment, because if it is successful, it can obtain ideal long-term clinical outcomes[20,21]. However, direct suture has a high failure rate of 5%–9%[22]. Failure is affected by many factors, including the surgeon's treatment experience, the size of the defect, the location of the defect, minimally invasive spinal surgery that

increases the challenge of suturing, and brittle surgical dural tissue. Long-term exposure of the dura during operation, irradiation with surgical light, and other factors also lead to dural contraction caused by dural dehydration[23,24]. Several reports have described the development and use of a new device called DuraStat, which deploys a double-armed suture in a controlled manner through the dura to facilitate repair in difficult clinical scenarios. Compared to traditional techniques, this new dural repair device allows surgeons at all levels of training to quickly and successfully repair simulated dural tears [25]. In summary, in clinical settings, primary sutures are mainly used as a basic technique for repairing dural injury combined with other repair methods, rather than simple sutures. Among 11 published reviews of different methods of repairing dural injuries found on PubMed, primary closure was the basis for repairing all 148 intentional durotomies[4].

Biomaterials

Grafts: Large dural defects often occur in patients undergoing skull base surgery. When the dural defect is too large to be repaired directly, it can be repaired by transplanting other tissues in autotransplantation, allotransplantation, or xenografts. Autografts used to repair dural defects include fat, muscle tissue, fascia, and the periosteum. Neurosurgeons often prefer fascia lata transplantation to repair the dura mater, as it is convenient for dural reconstruction[5]. The transplanted free fascia lata is highly tolerant to infection and can be nourished not only through the scalp, but also through the surrounding dura. Nakano *et al*[26] used fascia lata transplantation to treat postoperative infection of an artificial dura mater and achieved good results. Dural tears from spinal endoscopic surgery are often treated by autologous muscle or fat transplantation using a piece of muscle or fat beside the spine the same size as the damaged dura. To reduce the risk of CSF-related complications after intradural tumor surgery, Arnautovic *et al*[27] used autologous fat transplantation to fill the dead space and close the dura during the operation, and no postoperative CSF-related complications were observed in patients who underwent this procedure. The use of autogenous skull periosteum has been reported to effectively prevent CSF leakage and is feasible in terms of preventing further complications, as well as the time and cost of operation[28]. However, the uses of the periosteum are limited, as it is hard, fragile, and difficult to manage, and it is not suitable for repairing large dural defects. Autologous tissue used to repair dural defects has the advantages of no disinfection, rejection, transmission of disease, or burden on patients; however, additional surgery with local materials increases the surgical trauma, operation time, and risk of adhesion.

Previously, surgeons have used allogeneic materials, including the cadaveric dura, for dural repair [29]. The use of a cadaveric dura reduces pathogens to the greatest extent through freeze-drying and inactivation, but its clinical effect is not optimistic. Moreover, due to limited sources and ethical limitations, this material is no longer common in current clinical practice. At present, the amniotic membrane (AM) is the primary allogeneic material used in clinical settings[30]. The guiding role of the AM as a material for dural repair is based on its non-immunogenicity, anti-inflammatory properties, and promotion of collagen remodeling. The AM promotes the proliferation and migration of epithelial cells and reduces scar formation, thereby playing a role in dural repair. Furthermore, previous studies have compared the use of the AM and an autograft (fascia) in dural repair. They found that in dural repair, the AM could perfectly combine with autologous dura, accompanied by the disappearance of the epithelium and the formation of new connective tissue, fibrous tissue lamina, no inflammatory reaction or necrosis, and no adhesion[31]. In addition, clinicians have used acellular human dermis for dural repair and found no significant difference in the incidence of complications between the use of this material and autografts[32].

Xenogeneic biomaterials from animals, such as the pericardium, mesentery, and peritoneum can also be used to repair dural defects. These heterogeneous biomaterials must be treated by removing the antigen and adding a cross-linking agent before they can be used in medical products. Bovine pericardium was used earlier in clinical settings and welcomed by surgeons. At present, pigs and horses are animal sources of pericardia[32,33]. In animal experiments, He *et al*[34] found that the small intestinal submucosa can stimulate the response of connective and epithelial tissue to dural regeneration and functional recovery without immune rejection, which can provide long-term dural repair and prevent complications. However, the incidence of complications in dural repair, including pseudomeningocele and meningitis, was significantly higher with xenografts than with autografts[32].

Protein-based adhesives: In addition to dural repair materials directly derived from human or animal tissues, those made of collagen and fibrin from human or animal tissues are also useful as dural substitutes. Collagen exhibits good biocompatibility and low antigenicity. Currently, DuraGen® (Integra, NJ, United States) and TissuDura® from bovine and equine Achilles tendon collagen respectively are commonly used. DuraGen® is a chemically cross-linked collagen sponge composed of collagen type 1 in the Achilles tendon. Clinical trials have reported that DuraGen® can be used in patients with significantly larger dural defects and can prevent postoperative epidural effusion to ensure that the dura is completely sealed[35]. However, because DuraGen® is mainly placed on the damaged dura using a "mosaic" technique without suture, it can easily lead to complications such as CSF leakage and infection[36]. TissuDura® is an elastic, chemically inert, and adaptable collagen-based biological matrix [37]. In a rat model experiment, glial hyperplasia and inflammation in the bone and parenchyma foreign

bodies were significantly decreased in the TissuDura® group, indicating that this material is more biocompatible in dural meningioplasty[38]. Based on the previous use of collagen, researchers added fibrinogen, which results in blood coagulation and a better repair effect. Generally, fibrinogen is extracted from the blood and is an important protein involved in blood coagulation and hemostasis. At present, fibrin glue products contain two main components: fibrinogen and thrombin, which are mixed to form fibrin clots in a liquid glue or dry patch[39]. The first fibrin glue product used was Tisseel/Tissucol glue (Baxter, Deerfield, IL, United States). Later, researchers developed Evicel (Ethicon US, LLC) and dry patch products such as TachoSil (Baxter) and Tachocomb (CSL Behring, Tokyo, Japan). TachoSil, whose fibrinogen product is made from horse collagen, bovine thrombin, bovine aprotinin, and human fibrinogen, is widely used in clinical practice. To eliminate the risks associated with bovine materials, TachoSil has gradually replaced all bovine materials with those of human origin[40]. TachoSil, which was approved for clinical use long ago, is widely used for surgical hemostasis. Later studies also found that TachoSil not only acts as a mechanical barrier between surfaces during mesothelial recovery, but also reduces adhesion by inhibiting the level of plasminogen activator inhibitor-1, which can effectively prevent intra-abdominal, gynecological, and pleural adhesions. Therefore, TachoSil can repair dural defects, prevent postoperative dural adhesions, and provide good satisfaction among surgeons[40,41]. An analysis of 35 patients with spinal intradural tumors using TachoSil to treat dural defects showed that only 1 patient had CSF leakage, and no other complications were observed[42]. Gazzeri *et al*[43] successfully treated CSF leakage with TachoSil after anterior cervical discectomy and fusion. While the effectiveness of TachoSil in spinal surgery has been well established, this material poses potential risks of infection, including human parvovirus B19, alloimmunity, and allergic reactions. Thus, surgeons are developing fully autologous fibrin glue as a dural sealant[44]. To treat 17 patients with CSF leakage, Taniguchi *et al*[44] simultaneously prepared cold precipitates and thrombin from the patient's own blood within 90 min before surgery and did not add any allogeneic components or other exogenous additives. Fully autologous fibrin glue was prepared to repair and prevent CSF leakage. Full autologous fibrin glue can eliminate the risk of virus or prion transmission and alloimmunity; however, this material comes from patients themselves. Thus, patients must meet the requirements to prepare a sufficient amount of autologous fibrin glue.

Bacterial cellulose membrane: Researchers have also noted the excellent mechanical and biological properties of the bacterial cellulose (BC) membrane, including good biocompatibility and low host inflammatory response. Therefore, this material has been employed for dural repair[45]. Xu *et al*[45] found that the BC membrane could repair dural defects in rabbits, and the inflammatory response was lower than that of traditional materials (NormalGEN, biological dural repair patch in Guangzhou, China). Through mouse experiments, Lima *et al*[46] verified that BC membranes showed suitable biocompatibility in repairing the dura without inducing an immune response, chronic inflammatory response, or loss of neurotoxic signals. Jing *et al*[47] developed a new type of electrospun BC (EBC) membrane. Compared with BC, the inflammatory reaction was lower, more collagen fibers were uniformly distributed on the outside of the EBC membrane, and brain tissue adhesion and epidural scarring were reduced in the EBC group. Additionally, through animal experiments, Xu *et al*[48] found that the continuous release of vancomycin BC could effectively improve central nervous system infection after implantation. Moreover, BC is strong in the hygroscopic state, exhibits good biocompatibility, is relatively simple and cost-effective, and has the ability to carry drugs or growth factors. Therefore, the BC membrane can be used as a new artificial dural material, but the long-term effects of BC on dural repair remain to be studied[49,50].

Non-biological materials

Biological materials have many advantages in dural repair; however, they are difficult to prepare, limited in shape and size, differ among batches, and lack mechanical strength. In contrast, synthetic materials are easier to prepare than biological materials, can be repeatedly synthesized in large quantities and adjusted according to demand, and are relatively cheaper than natural materials. Two main types of synthetic materials can be used for dural repair[5]: (1) Non-degradable polytetrafluoroethylene and polyurethane; and (2) Degradable polyglycolic acid, polycaprolactone, and poly (L-lactic acid) (PLLA). Although these sealants are effective for watertight dura, a number of retrospective analyses have found no significant difference in CSF leakage between the sealant and suture groups. Nevertheless, some studies suggest that the use of sealant can reduce infection[51], while others suggest no significant difference in the infection rate[52].

Therefore, in recent years, researchers have derived a variety of new dural repair materials on this basis and achieved good repair results in human or animal models (Table 2). Under the condition that the dura could not be repaired directly after craniocerebral surgery, four patients underwent dural reconstruction with a new graft material, CerafixDura, a synthetic porous polymer matrix composed of spun poly (lactic acid-glycolic acid) and poly (p-dioxane). Satisfactory results were obtained without complications[53]. Researchers often combine various polymers to experiment with their characteristics [54-56]. For example, Chuan *et al*[57] prepared a three-dimensional composite nanofiber membrane based on enantiomeric polylactic acid and poly(d-lactic acid)-grafted tetracalcium phosphate. The

Table 2 Non-biological materials and their effect evaluation

Ref.	Year	Restorative materials	Object of application	Evaluation of clinical / laboratory effect
Ramot *et al* [94]	2020	Novel synthetic and fibrous Dural graft: Poly (L-lactic-cocaprolactone acid) and poly (D-lactic-co-caprolactone acid)	Rabbits	12 mo after operation, there was no animal death, and the new dura mater, dura mater injury and upper bone healing were formed at the implantation site. The advantage for this material is favorable local tolerability and biodegradability
Schmalz *et al*[53]	2018	Cerafix dura substitute: Spun poly (lactic-coglycolic acid) and poly-p-dioxanone	Human: Four patients after resection of brain tumor	In all patients wound healing proceeded without complication. There was no imaging evidence of persistent fluid collection to suggest cerebrospinal fluid leakage or pseudomeningocele formation, nor was there evidence of meningeal enhancement to suggest the development of subclinical chemical meningitis
Li *et al*[60]	2022	bioactive patch composed of alginate and polyacrylamide hydrogel matrix cross-linked by calcium ions, and chitosan adhesive	*In vitro* experiment and *in vivo* experiment in rabbit model	The bioactive patch have the good properties of withstanding high pressure, promoting defect closure, exerting the effects of anti-inflammatory, analgesic, adhesion prevention and inhibiting postoperative infection
Kinaci *et al* [58]	2021	Liqoseal, a dural sealant patch comprising a watertight polyester-urethane layer and an adhesive layer consisting of poly (DL-lactide-co-ε-caprolactone) copolymer and multi-armed N-hydroxylsuccinimide function-alized polyethylene glycol	Computer-assisted models, fresh porcine dura and In vitro experiment	The mean burst pressure of Liqoseal in the spinal model (233 ± 81 mmHg) was higher than that of Tachosil (123 ± 63 mmHg) and Tisseel (23 ± 16 mmHg). Compared with Adherus, Duraseal, Tachosil, and Tisseel, Liqoseal was able to achieve a strong watertight seal on dura defects in the *in vitro* model
Yamaguchi *et al*[56]	2019	Durawave: Polyglycolic acid felt	Human: 36 cases of tumor resection *via* transpetrosal approach	The cerebrospinal fluid leakage rate of patients treated with polyglycolic acid felt was lower than that of autogenous fascia fixation, and the time of intraoperative dural reconstruction was significantly shortened. Using polyglycolic acid felt to reconstruct dura mater simplifies the operation and may prevent cerebrospinal fluid-related complications after transpetrosal approach
Huang *et al* [61]	2022	Photo-Crosslinked Hyaluronic Acid/Car-b oxymethyl Cellulose Composite Hydrogel	*In vitro* experiment and *in vivo* experiment in rabbit model	It has biocompatibility, biodegradability and mechanical strength. By drastically reducing attachment and penetration of adhesion-forming fibroblasts *in vitro*, HC hydrogel can be used as an anti-adhesion barrier to prevent postoperative adhesion
Zhu *et al* [95]	2021	Tetra-PEG hydrogel sealants	*In vitro* experiment and *in vivo* experiment in rabbit model	It has the advantages of simple operation, high safety, fast solidification time, easy injection, good mechanical strength and strong tissue adhesion. In the liquid environment, the tetra-PEG hydrogel sealants can also instantly adhere to the irregular tissue surface
Chuan *et al* [57]	2020	Stereocomplex nanofiber membranes based on enantiomeric poly (lactic acid) and poly (D-lactic acid)-grafted tetracalcium phosphate	*In vitro* experiment	It has heat resistance, stretching similar to human dura mater, non-toxic to cells, and neuron compatibility
Yu *et al*[62]	2015	Two layers of novel electrospun membranes, dermal fibroblasts and mussel adhesive protein for repairing spinal dural defect. Inner layer: Lactide-co-glycolide other layer: Chitosan-coated electrospun nonwoven poly(lactide-co-glycolide) membrane	Goats	Seamless and quick sealing of the defect area with the implants was realized by mussel adhesive protein. Effective cerebrospinal fluid containment and anti-adhesion of the regenerated tissue to the surrounding tissue could be achieved in the current animal model
Masuda *et al*[96]	2016	Suture or nonpenetrating titanium clips, followed by reinforcement with a polyglycolic acid mesh and fibrin glue intraoperatively	75 patients (34 males and 41 females; age range, 16e80 years; mean age, 57.1 years)	Only one patient out of 75 (1.3%) required reoperation for dural repair
Terasaka *et al*[64]	2017	Fibrin glue and polyglycolic acid felt (GM111)	Sixty patients were enrolled. The craniotomy site was supratentorial in 77.2%, infratentorial in 12.3% and sellar in 10.5%	Cerebrospinal fluid leakage and subcutaneous cerebrospinal fluid retention throughout the postoperative period were found in four patients. Adverse events for which a causal relationship with GM111 could not be ruled out occurred in 8.8% of the patients. There were no instances of postoperative infection due to GM111
Liao *et al* [97]	2021	Triple-layered composite: Poly (L-lactic acid), chitosan, gelatin, and acellular small intestinal submucosa	*In vitro* experiment	Satisfactory multifunction of leakage blockade, adhesion prevention, antibacterial property, and dura reconstruction potential
Deng *et al* [66]	2017	Absorbable materials Poly (L-lactic acid) and gelatin	*In vitro* experiment	More biomimetic to native extracellular matrix than collagen substitute did, together with better cytocompat-ibility, tissue ingrowth, and neoangiogenesis

PLLA: Poly (L-lactic acid).

tensile strength of the composite membrane was close to that of a human dura, and no cytotoxicity was observed. Liqossee, a dural sealant patch composed of a watertight polyester urethane layer and an adhesive layer consisting of poly (DL-lactide-co-ε-caprolactone) copolymer and multiarmed N-hydroxylsuccinimide-functionalized polyethylene glycol, exhibited stronger watertight sealing ability than Adherus, Duraseal, TachoSil, and Tisseel[58]. Other researchers have developed double-layer oxidized regenerated cellulose knitted fabric/poly (ε-caprolactone) knitted fabric-reinforced composites and compared them with human cadaveric membranes and three commercial dura mater substitutes (two collagen substrates, DuraGenPlus and TissuDura, and a synthetic poly-L-lactide patch, ReDura). Although slightly inferior to human cadaveric membranes, this new composite exhibited better functional properties than typical dural substitutes[59]. Bioactive patches composed of calcium-cross-linked alginate, polyacrylamide hydrogel matrix, and chitosan adhesive have been proven to have anti-inflammatory, analgesic, and anti-adhesive effects[60]. Photo-cross-linked hyaluronic acid/carboxymethyl cellulose composite hydrogels can also be used as a dural substitute to prevent postoperative adhesion[61].

Composite materials

Different materials have different advantages and disadvantages; therefore, the combination of various materials to form composites may result in better dural repair. Yu *et al*[62] developed a package that includes two layers of novel electrospun membranes, dermal fibroblasts, and mussel adhesive proteins to repair spinal dural defects. This compound material effectively curbed CSF leakage and resisted adhesion between regenerated and surrounding tissues in a goat animal model. Additionally, autologous human muscle or fat transplantation can be combined with fibrin glue or fibrin-sealed collagen sponges. Surgeons collected autologous muscles from patients during total endoscopic surgery and transplanted them into several layers of dural defects. The graft was then fixed and sealed watertight with fibrin sealant and a gelatin sponge[63]. In a multicenter clinical trial, a new dura mater substitute (GM111) composed of polyglycolic acid felt and fibrin glue was used for non-suture dural repair. Of the 60 patients in the group, 4 experienced CSF leakage and subcutaneous CSF retention after surgery, and no postoperative infections resulted from the use of GM111. Therefore, GM111 showed good closure ability and safety for dural closure without sutures[64]. Similarly, in a review of 409 patients who underwent reconstruction of the sellar region, a single synthetic dura mater substitute was used to cover the damaged area, and then a dural sealant was applied to the repaired epidural surface. Postoperative results showed that this technique can effectively prevent postoperative CSF leakage[65]. Another composite, named NeoduraTM (MedprinBiotechGmbH, Germany), was made of absorbable PLLA and gelatin. Compared with the control DuraGen group, the surface properties of the composite substitute were more bionic to the natural extracellular matrix and exhibited better cell compatibility, inward tissue growth, and neovascularization. In clinical trials, this substitute further proved its ideal repair effects without CSF leakage or other adverse reactions[66].

Other repair methods

A non-penetrating titanium clip is commonly used for dural repair in clinics. Compared with the primary suture, the non-penetrating anastomotic clip has the advantages of simple operation, rapid process, reduced dura exposure, no pinhole, and no risk of pinhole leakage. Additionally, compared with the foreign body inflammatory reaction caused by sutures, the use of a titanium clip significantly reduces local acute or chronic inflammation, as well as the risk of postoperative adhesion[67-69]. Shahrestani *et al*[67] used non-penetrating anastomotic clips to repair dural defects in children, and the incidence of postoperative CSF leakage and non-penetrating titanium clip infection was very low. Ito *et al*[70] used non-penetrating titanium clips to prevent postoperative CSF leakage during spinal surgery, and only 1 of the 31 patients exhibited postoperative CSF leakage. These studies suggest that non-penetrating anastomotic titanium clips are a good auxiliary tool in the treatment of dura breakage. However, because they are made of metal, these clips may lead to metal artifacts and affect the discrimination of structure in the future. Nevertheless, some studies think that they are small enough to not produce obvious artifacts[71]. In addition, the use of non-penetrating titanium clips exhibits several issues, including dural tears caused by the clips, displacement and non-reusability of the clips, high medical costs, and non-degradable materials. Additionally, the long-term effects of the use of titanium clips have not been observed. Whether these clips will eventually lead to progressive stenosis of the dural space, among other issues, require further exploration.

Epidural or intrathecal injection of saline has also been considered to alleviate the complications of CSF leakage caused by dural injury. Saline injection can improve the symptoms of intracranial hypotension by restoring CSF pressure in the subarachnoid space, which can immediately improve symptoms. However, this is only a temporary solution[72,73].

In addition, clinical adjuvant treatments, such as fluid replacement, caffeine, sphenopalatine ganglion block, greater occipital nerve block, local pressure bandaging, surgical closure of the space, and short-term bed rest after surgery are reasonable in current clinical practice, as these methods can increase the pressure in the dural defect area and avoid postural low intracranial pressure[74-77]. Through animal experiments, Ahmadi *et al*[78] found that local or systemic supplementation with L-arginine is beneficial for the treatment of dural tears. Systemic supplementation with L-arginine can promote collagen deposition and vascularization and increase the level of granulation tissue formation to accelerate dural healing.

Systematic evaluation of dural repair technology

Many types of dural repair techniques and the continuous emergence of dural repair materials provide clinicians with more choices in the face of dural damage. A Canadian medical questionnaire examined clinicians' choice of repair methods in the face of different dural defects[79]. The results showed that when the diameter of the damage was less than 1 mm, the surgeon often chose sealant or even no treatment. When the diameter of the damaged opening was greater than 1 mm, the combination of suture and sealant was found to be a more popular option. Additionally, the larger the diameter of the damaged opening, the greater the proportion of the combined application. On the other hand, surgeons preferred to use sealants or do nothing when the damage was located in the anterior area, most surgeons chose to use a combination of sutures and sealants in the posterior area, and use more sealants in the nerve root area. However, the results also showed that at least 20% of doctors chose a different repair method than the mainstream for different conditions. Therefore, the combined use of dural repair techniques and materials should be evaluated. Alshameeri *et al*[80] conducted a systematic review and meta-analysis on the management of accidental dural tears during spinal surgery in 2020. A total of 3822 cases of dural tears were included among 49 studies. Compared with different dural repair techniques, the risk of dural tears was 5.2% (4%-6.5%). Regardless of the type of treatment, the total combined proportion of dural tear treatment failure was 6.1%(4.4%-8.3%). In other words, little difference was observed among the different repair methods. Among them, the total failure rate of direct suture repair (with or without any other reinforcing material) was lower than that of indirect repair (with sealant and/or a patch)[80]. In a systematic review in 2021, a summary analysis of 11 studies showed that among the 776 enrolled patients, the most common technique was primary suture, patch, or a combination of graft and sealant (22.7%, 176/776). The incidence of CSF leakage was the lowest in the primary suture plus patch or bone graft group (5.5%, 7/128). In addition, compared with the use of an occluder alone (17.6%, 18/102), sealant as an aid to primary closure (13.7%, 18/131) did not significantly reduce the incidence of CSF leakage. Moreover, regardless of the repair technique, no significant difference was observed in the rate of infection or postoperative neurological deficits[4]. A total of 106 patients with dural tears, CSF leakage, dural incisions, or pseudomeningocele in the online databases of Southampton General Hospital from 2016 to 2019 were enrolled in the study[81]. The authors compared the combination of preliminary suture closure, artificial patch, sealant, autologous repair, and drainage in patients with dural ruptures. By comparing the length of hospitalization, number of readmissions or revision surgeries, time of readmission, postoperative infection rate, and neurological symptoms related to dural tear, the authors concluded that primary suture plus an artificial dural patch was the most effective method for repair.

CONCLUSION

In summary, one-stage suture is essential for all types of dural damage and partial dural damage repair surgeries, and primary suture plus patch repair is recommended. If the damage is too large for direct repair, indirect repair should be considered. Additionally, as the overall failure rate of spinal dural repair is 6.1%, dural repair materials should be constantly updated in clinical practice. In the development and testing phases, the new repair materials should be further adapted to special occasions, such as when a large, damaged area cannot be directly sutured or when patients with other diseases cannot tolerate secondary surgical sutures. In addition, many of the new repair materials are still in the *in vitro* or animal experiment stage, and further clinical trials are expected to obtain more clinical data.

FOOTNOTES

Author contributions: Dong RP, Zhang Q contributed to this paper with design of the study, literature review and analysis, and manuscript drafting; Yang LL collected relevant information; Zhao JW and Cheng XL guided the writing and reviewing of this paper and put forward suggestions for the article; all authors have read and approved the final manuscript.

Supported by Jilin Health Science and Technology Capability Improvement Project, No. 2022C107.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Country/Territory of origin: China

ORCID number: Rong-Peng Dong 0000-0002-0578-353X; Qi Zhang 0000-0003-1593-575X; Xue-Liang Cheng 0000-0001-6285-1175; Jian-Wu Zhao 0000-0003-0574-9742.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Guo X

REFERENCES

1 **Alshameeri ZAF**, Jasani V. Risk Factors for Accidental Dural Tears in Spinal Surgery. *Int J Spine Surg* 2021; **15**: 536-548 [PMID: 33986000 DOI: 10.14444/8082]
2 **Ishikura H**, Ogihara S, Oka H, Maruyama T, Inanami H, Miyoshi K, Matsudaira K, Chikuda H, Azuma S, Kawamura N, Yamakawa K, Hara N, Oshima Y, Morii J, Saita K, Tanaka S, Yamazaki T. Risk factors for incidental durotomy during posterior open spine surgery for degenerative diseases in adults: A multicenter observational study. *PLoS One* 2017; **12**: e0188038 [PMID: 29190646 DOI: 10.1371/journal.pone.0188038]
3 **Kamenova M**, Leu S, Mariani L, Schaeren S, Soleman J. Management of Incidental Dural Tear During Lumbar Spine Surgery. To Suture or Not to Suture? *World Neurosurg* 2016; **87**: 455-462 [PMID: 26700751 DOI: 10.1016/j.wneu.2015.11.045]
4 **Choi EH**, Chan AY, Brown NJ, Lien BV, Sahyouni R, Chan AK, Roufail J, Oh MY. Effectiveness of Repair Techniques for Spinal Dural Tears: A Systematic Review. *World Neurosurg* 2021; **149**: 140-147 [PMID: 33640528 DOI: 10.1016/j.wneu.2021.02.079]
5 **Bi X**, Liu B, Mao Z, Wang C, Dunne N, Fan Y, Li X. Applications of materials for dural reconstruction in pre-clinical and clinical studies: Advantages and drawbacks, efficacy, and selections. *Mater Sci Eng C Mater Biol Appl* 2020; **117**: 111326 [PMID: 32919680 DOI: 10.1016/j.msec.2020.111326]
6 **Barber SM**, Fridley JS, Konakondla S, Nakhla J, Oyelese AA, Telfeian AE, Gokaslan ZL. Cerebrospinal fluid leaks after spine tumor resection: avoidance, recognition and management. *Ann Transl Med* 2019; **7**: 217 [PMID: 31297382 DOI: 10.21037/atm.2019.01.04]
7 **Lin TY**, Chen WJ, Hsieh MK, Lu ML, Tsai TT, Lai PL, Fu TS, Niu CC, Chen LH. Postoperative meningitis after spinal surgery: a review of 21 cases from 20,178 patients. *BMC Infect Dis* 2014; **14**: 220 [PMID: 24755138 DOI: 10.1186/1471-2334-14-220]
8 **Epstein NE**. A review article on the diagnosis and treatment of cerebrospinal fluid fistulas and dural tears occurring during spinal surgery. *Surg Neurol Int* 2013; **4**: S301-S317 [PMID: 24163783 DOI: 10.4103/2152-7806.111427]
9 **Chen Z**, Shao P, Sun Q, Zhao D. Risk factors for incidental durotomy during lumbar surgery: a retrospective study by multivariate analysis. *Clin Neurol Neurosurg* 2015; **130**: 101-104 [PMID: 25600349 DOI: 10.1016/j.clineuro.2015.01.001]
10 **Smorgick Y**, Baker KC, Herkowitz H, Montgomery D, Badve SA, Bachison C, Ericksen S, Fischgrund JS. Predisposing factors for dural tear in patients undergoing lumbar spine surgery. *J Neurosurg Spine* 2015; **22**: 483-486 [PMID: 25700240 DOI: 10.3171/2015.1.SPINE13864]
11 **Strömqvist F**, Jönsson B, Strömqvist B; Swedish Society of Spinal Surgeons. Dural lesions in decompression for lumbar spinal stenosis: incidence, risk factors and effect on outcome. *Eur Spine J* 2012; **21**: 825-828 [PMID: 22146791 DOI: 10.1007/s00586-011-2101-2]
12 **Yokogawa N**, Murakami H, Demura S, Kato S, Yoshioka K, Tsuchiya H. Incidental durotomy during total en bloc spondylectomy. *Spine J* 2018; **18**: 381-386 [PMID: 28735765 DOI: 10.1016/j.spinee.2017.07.169]
13 **Telfeian AE**, Shen J, Ali R, Oyelese A, Fridley J, Gokaslan ZL. Incidence and Implications of Incidental Durotomy in Transforaminal Endoscopic Spine Surgery: Case Series. *World Neurosurg* 2020; **134**: e951-e955 [PMID: 31734429 DOI: 10.1016/j.wneu.2019.11.045]
14 **Takahashi Y**, Sato T, Hyodo H, Kawamata T, Takahashi E, Miyatake N, Tokunaga M. Incidental durotomy during lumbar spine surgery: risk factors and anatomic locations: clinical article. *J Neurosurg Spine* 2013; **18**: 165-169 [PMID: 23199434 DOI: 10.3171/2012.10.SPINE12271]
15 **Andereggen L**, Luedi MM. Dural leakage due to ipsilateral needle placement for spinal level localization in unilateral decompression surgery: A case report. *Surg Neurol Int* 2021; **12**: 205 [PMID: 34084632 DOI: 10.25259/SNI_245_2021]
16 **Allouch H**, Abu Nahleh K, Mursch K, Shousha M, Alhashash M, Boehm H. Symptomatic Intracranial Hemorrhage after Dural Tear in Spinal Surgery-A Series of 10 Cases and Review of the Literature. *World Neurosurg* 2021; **150**: e52-e65 [PMID: 33640532 DOI: 10.1016/j.wneu.2021.02.071]
17 **Bydon M**, De la Garza-Ramos R, Abt NB, Macki M, Sciubba DM, Wolinsky JP, Bydon A, Gokaslan ZL, Witham TF. Durotomy is associated with pseudoarthrosis following lumbar fusion. *J Clin Neurosci* 2015; **22**: 544-548 [PMID: 25532509 DOI: 10.1016/j.jocn.2014.08.023]

18 **Lopes M**, Faillot T. [Dural tears: Regarding a series of 100 cases]. *Neurochirurgie* 2015; **61**: 329-332 [PMID: 26409571 DOI: 10.1016/j.neuchi.2015.06.005]

19 **Bosacco SJ**, Gardner MJ, Guille JT. Evaluation and treatment of dural tears in lumbar spine surgery: a review. *Clin Orthop Relat Res* 2001; 238-247 [PMID: 11501817 DOI: 10.1097/00003086-200108000-00033]

20 **Desai A**, Ball PA, Bekelis K, Lurie J, Mirza SK, Tosteson TD, Weinstein JN. SPORT: does incidental durotomy affect long-term outcomes in cases of spinal stenosis? *Neurosurgery* 2011; **69**: 38-44; discussion 44 [PMID: 21358354 DOI: 10.1227/NEU.0b013e3182134171]

21 **Desai A**, Ball PA, Bekelis K, Lurie J, Mirza SK, Tosteson TD, Zhao W, Weinstein JN. Surgery for lumbar degenerative spondylolisthesis in Spine Patient Outcomes Research Trial: does incidental durotomy affect outcome? *Spine (Phila Pa 1976)* 2012; **37**: 406-413 [PMID: 21971123 DOI: 10.1097/BRS.0b013e3182349bc5]

22 **Fang Z**, Tian R, Jia YT, Xu TT, Liu Y. Treatment of cerebrospinal fluid leak after spine surgery. *Chin J Traumatol* 2017; **20**: 81-83 [PMID: 28336418 DOI: 10.1016/j.cjtee.2016.12.002]

23 **Lewandrowski KU**, Hellinger S, De Carvalho PST, Freitas Ramos MR, Soriano-SáNchez JA, Xifeng Z, Calderaro AL, Dos Santos TS, Ramírez León JF, de Lima E SilvA MS, Dowling Á, DataR G, Kim JS, Yeung A. Dural Tears During Lumbar Spinal Endoscopy: Surgeon Skill, Training, Incidence, Risk Factors, and Management. *Int J Spine Surg* 2021; **15**: 280-294 [PMID: 33900986 DOI: 10.14444/8038]

24 **Kinaci A**, Van Doormaal TPC. Dural sealants for the management of cerebrospinal fluid leakage after intradural surgery: current status and future perspectives. *Expert Rev Med Devices* 2019; **16**: 549-553 [PMID: 31144544 DOI: 10.1080/17434440.2019.1626232]

25 **Shenoy K**, Donnally CJ 3rd, Sheha ED, Khanna K, Prasad SK. An Investigation of a Novel Dural Repair Device for Intraoperative Incidental Durotomy Repair. *Front Surg* 2021; **8**: 642972 [PMID: 34291076 DOI: 10.3389/fsurg.2021.642972]

26 **Nakano T**, Yoshikawa K, Kunieda T, Arakawa Y, Kikuchi T, Yamawaki S, Naitoh M, Kawai K, Suzuki S. Treatment for infection of artificial dura mater using free fascia lata. *J Craniofac Surg* 2014; **25**: 1252-1255 [PMID: 25006907 DOI: 10.1097/SCS.0000000000000929]

27 **Arnautovic KI**, Kovacevic M. CSF-Related Complications After Intradural Spinal Tumor Surgery: Utility of an Autologous Fat Graft. *Med Arch* 2016; **70**: 460-465 [PMID: 28210022 DOI: 10.5455/medarh.2016.70.460-465]

28 **Sabatino G**, Della Pepa GM, Bianchi F, Capone G, Rigante L, Albanese A, Maira G, Marchese E. Autologous dural substitutes: a prospective study. *Clin Neurol Neurosurg* 2014; **116**: 20-23 [PMID: 24300745 DOI: 10.1016/j.clineuro.2013.11.010]

29 **Meddings N**, Scott R, Bullock R, French DA, Hide TA, Gorham SD. Collagen vicryl--a new dural prosthesis. *Acta Neurochir (Wien)* 1992; **117**: 53-58 [PMID: 1514429 DOI: 10.1007/BF01400636]

30 **Turchan A**, Rochman TF, Ibrahim A, Fauziah D, Wahyuhadi J, Parenrengi MA, Fauzi AA, Sufarnap E, Bajamal AH, Ferdiansyah, Suroto H, Purwati, Rantam FA, Paramadini AW, Lumenta CB. Duraplasty using amniotic membrane *vs* temporal muscle fascia: A clinical comparative study. *J Clin Neurosci* 2018; **50**: 272-276 [PMID: 29428266 DOI: 10.1016/j.jocn.2018.01.069]

31 **Marton E**, Giordan E, Gallinaro P, Curzi C, Trojan D, Paolin A, Guerriero A, Rossi S, Bendini M, Longatti P, Canova G. Homologous amniotic membrane as a dural substitute in decompressive craniectomies. *J Clin Neurosci* 2021; **89**: 412-421 [PMID: 34052070 DOI: 10.1016/j.jocn.2021.05.030]

32 **Yahanda AT**, Adelson PD, Akbari SHA, Albert GW, Aldana PR, Alden TD, Anderson RCE, Bauer DF, Bethel-Anderson T, Brockmeyer DL, Chern JJ, Couture DE, Daniels DJ, Dlouhy BJ, Durham SR, Ellenbogen RG, Eskandari R, George TM, Grant GA, Graupman PC, Greene S, Greenfield JP, Gross NL, Guillaume DJ, Hankinson TC, Heuer GG, Iantosca M, Iskandar BJ, Jackson EM, Johnston JM, Keating RF, Krieger MD, Leonard JR, Maher CO, Mangano FT, McComb JG, McEvoy SD, Meehan T, Menezes AH, O'Neill BR, Olavarria G, Ragheb J, Selden NR, Shah MN, Shannon CN, Shimony JS, Smyth MD, Stone SSD, Strahle JM, Torner JC, Tuite GF, Wait SD, Wellons JC, Whitehead WE, Park TS, Limbrick DD. Dural augmentation approaches and complication rates after posterior fossa decompression for Chiari I malformation and syringomyelia: a Park-Reeves Syringomyelia Research Consortium study. *J Neurosurg Pediatr* 2021; **27**: 459-468 [PMID: 33578390 DOI: 10.3171/2020.8.PEDS2087]

33 **Centonze R**, Agostini E, Massaccesi S, Toninelli S, Morabito L. A novel equine-derived pericardium membrane for dural repair: A preliminary, short-term investigation. *Asian J Neurosurg* 2016; **11**: 201-205 [PMID: 27366245 DOI: 10.4103/1793-5482.179645]

34 **He SK**, Guo JH, Wang ZL, Zhang Y, Tu YH, Wu SZ, Huang FG, Xie HQ. Efficacy and safety of small intestinal submucosa in dural defect repair in a canine model. *Mater Sci Eng C Mater Biol Appl* 2017; **73**: 267-274 [PMID: 28183608 DOI: 10.1016/j.msec.2016.12.077]

35 **Nakayama Y**, Tanaka T, Teshigawara A, Nogami R, Tachi R, Fuga M, Tochigi S, Hasegawa Y, Murayama Y. [Technical "Tips" for Epidural Tenting Using DuraGen(®) for Surgical Management of Large Dural Defects:A Technical Note]. *No Shinkei Geka* 2020; **48**: 903-907 [PMID: 33071225 DOI: 10.11477/mf.1436204294]

36 **Sade B**, Oya S, Lee JH. Non-watertight dural reconstruction in meningioma surgery: results in 439 consecutive patients and a review of the literature. Clinical article. *J Neurosurg* 2011; **114**: 714-718 [PMID: 20707618 DOI: 10.3171/2010.7.JNS10460]

37 **Parlato C**, di Nuzzo G, Luongo M, Parlato RS, Accardo M, Cuccurullo L, Moraci A. Use of a collagen biomatrix (TissuDura) for dura repair: a long-term neuroradiological and neuropathological evaluation. *Acta Neurochir (Wien)* 2011; **153**: 142-147 [PMID: 20623361 DOI: 10.1007/s00701-010-0718-2]

38 **Karkucak A**, Turkoz D, Bayraktar B, Turkoz A, Cokluk C. Comparison of TachoComb and TissuDura in Terms of Adverse Effects and Complications in Duraplasty in Rats. *Turk Neurosurg* 2021; **31**: 680-685 [PMID: 33978197 DOI: 10.5137/1019-5149.JTN.30444-20.2]

39 **Esposito F**, Angileri FF, Kruse P, Cavallo LM, Solari D, Esposito V, Tomasello F, Cappabianca P. Fibrin Sealants in Dura Sealing: A Systematic Literature Review. *PLoS One* 2016; **11**: e0151533 [PMID: 27119993 DOI: 10.1371/journal.pone.0151533]

40 **Toro A**, Mannino M, Reale G, Di Carlo I. TachoSil use in abdominal surgery: a review. *J Blood Med* 2011; **2**: 31-36 [PMID: 22287861 DOI: 10.2147/JBM.S13061]

41 **Kuschel TJ**, Gruszka A, Hermanns-Sachweh B, Elyakoubi J, Sachweh JS, Vázquez-Jiménez JF, Schnoering H. Prevention of postoperative pericardial adhesions with TachoSil. *Ann Thorac Surg* 2013; **95**: 183-188 [PMID: 23084416 DOI: 10.1016/j.athoracsur.2012.08.057]

42 **Montano N**, Pignotti F, Auricchio AM, Fernandez E, Olivi A, Papacci F. Results of TachoSil® associated with fibrin glue as dural sealant in a series of patients with spinal intradural tumors surgery. Technical note with a review of the literature. *J Clin Neurosci* 2019; **61**: 88-92 [PMID: 30414810 DOI: 10.1016/j.jocn.2018.10.138]

43 **Gazzeri R**, Galarza M, Callovini G. Use of tissue sealant patch (TachoSil) in the management of cerebrospinal fluid leaks after anterior cervical spine discectomy and fusion. *Br J Neurosurg* 2021; 1-8 [PMID: 33538190 DOI: 10.1080/02688697.2021.1881444]

44 **Taniguchi Y**, Matsubayashi Y, Ikeda T, Kato S, Doi T, Oshima Y, Okazaki H, Tanaka S. Clinical Feasibility of Completely Autologous Fibrin Glue in Spine Surgery. *Spine Surg Relat Res* 2022; **6**: 388-394 [PMID: 36051679 DOI: 10.22603/ssrr.2021-0190]

45 **Xu C**, Ma X, Chen S, Tao M, Yuan L, Jing Y. Bacterial cellulose membranes used as artificial substitutes for dural defection in rabbits. *Int J Mol Sci* 2014; **15**: 10855-10867 [PMID: 24937688 DOI: 10.3390/ijms150610855]

46 **Lima FM**, Pinto FC, Andrade-da-Costa BL, Silva JG, Campos Júnior O, Aguiar JL. Biocompatible bacterial cellulose membrane in dural defect repair of rat. *J Mater Sci Mater Med* 2017; **28**: 37 [PMID: 28144849 DOI: 10.1007/s10856-016-5828-9]

47 **Jing Y**, Ma X, Xu C, Tian HL, Chen SW. Repair of dural defects with electrospun bacterial cellulose membranes in a rabbit experimental model. *Mater Sci Eng C Mater Biol Appl* 2020; **117**: 111246 [PMID: 32919624 DOI: 10.1016/j.msec.2020.111246]

48 **Xu C**, Zhao J, Gong Q, Chen S. Sustained release of vancomycin from bacterial cellulose membrane as dural substitutes for anti-inflammatory wound closure in rabbits. *J Biomater Appl* 2020; **34**: 1470-1478 [PMID: 32070189 DOI: 10.1177/0885328220908027]

49 **Mensah A**, Chen Y, Christopher N, Wei Q. Membrane Technological Pathways and Inherent Structure of Bacterial Cellulose Composites for Drug Delivery. *Bioengineering (Basel)* 2021; **9** [PMID: 35049712 DOI: 10.3390/bioengineering9010003]

50 **Picheth GF**, Pirich CL, Sierakowski MR, Woehl MA, Sakakibara CN, de Souza CF, Martin AA, da Silva R, de Freitas RA. Bacterial cellulose in biomedical applications: A review. *Int J Biol Macromol* 2017; **104**: 97-106 [PMID: 28587970 DOI: 10.1016/j.ijbiomac.2017.05.171]

51 **Kinaci A**, Algra A, Heuts S, O'Donnell D, van der Zwan A, van Doormaal T. Effectiveness of Dural Sealants in Prevention of Cerebrospinal Fluid Leakage After Craniotomy: A Systematic Review. *World Neurosurg* 2018; **118**: 368-376.e1 [PMID: 29969744 DOI: 10.1016/j.wneu.2018.06.196]

52 **Kinaci A**, Moayeri N, van der Zwan A, van Doormaal TPC. Effectiveness of Sealants in Prevention of Cerebrospinal Fluid Leakage after Spine Surgery: A Systematic Review. *World Neurosurg* 2019; **127**: 567-575.e1 [PMID: 30928579 DOI: 10.1016/j.wneu.2019.02.236]

53 **Schmalz P**, Griessenauer C, Ogilvy CS, Thomas AJ. Use of an Absorbable Synthetic Polymer Dural Substitute for Repair of Dural Defects: A Technical Note. *Cureus* 2018; **10**: e2127 [PMID: 29607275 DOI: 10.7759/cureus.2127]

54 **Wang J**, Li K, Xu J, Liu M, Li P, Li X, Fan Y. A biomimetic hierarchical small intestinal submucosa-chitosan sponge/chitosan hydrogel scaffold with a micro/nano structure for dural repair. *J Mater Chem B* 2021; **9**: 7821-7834 [PMID: 34586141 DOI: 10.1039/d1tb00948f]

55 **Diab A**, Al-Shami H, Negida A, Gadallah A, Farag H, Elkadi DM, Gaber MM, Ebada MA. Efficacy and safety of polyethylene glycol dural sealant system in cranial and spinal neurosurgical procedures: Meta-analysis. *Surg Neurol Int* 2021; **12**: 182 [PMID: 34084610 DOI: 10.25259/SNI_132_2021]

56 **Yamaguchi S**, Terasaka S, Okamoto M, Ishi Y, Motegi H, Kobayashi H, Houkin K. Simplified Dural Reconstruction Procedure Using Biocompatible Polyglycolic Acid Felt with Autologous Abdominal Fat Grafts after a Transpetrosal Approach. *World Neurosurg* 2019; **132**: e710-e715 [PMID: 31421296 DOI: 10.1016/j.wneu.2019.08.033]

57 **Chuan D**, Wang Y, Fan R, Zhou L, Chen H, Xu J, Guo G. Fabrication and Properties of a Biomimetic Dura Matter Substitute Based on Stereocomplex Poly(Lactic Acid) Nanofibers. *Int J Nanomedicine* 2020; **15**: 3729-3740 [PMID: 32547025 DOI: 10.2147/IJN.S248998]

58 **Kinaci A**, van Thoor S, Redegeld S, Tooren M, van Doormaal TPC. Ex vivo evaluation of a multilayered sealant patch for watertight dural closure: cranial and spinal models. *J Mater Sci Mater Med* 2021; **32**: 85 [PMID: 34297226 DOI: 10.1007/s10856-021-06552-4]

59 **Hemstapat R**, Suvannapruk W, Thammarakcharoen F, Chumnanvej S, Suwanprateeb J. Performance evaluation of bilayer oxidized regenerated cellulose/poly ε-caprolactone knitted fabric-reinforced composites for dural substitution. *Proc Inst Mech Eng H* 2020; **234**: 854-863 [PMID: 32423302 DOI: 10.1177/0954411920926071]

60 **Li J**, Tian J, Li C, Chen L, Zhao Y. A hydrogel spinal dural patch with potential anti-inflammatory, pain relieving and antibacterial effects. *Bioact Mater* 2022; **14**: 389-401 [PMID: 35386815 DOI: 10.1016/j.bioactmat.2022.01.043]

61 **Huang YC**, Liu ZH, Kuo CY, Chen JP. Photo-Crosslinked Hyaluronic Acid/Carboxymethyl Cellulose Composite Hydrogel as a Dural Substitute to Prevent Post-Surgical Adhesion. *Int J Mol Sci* 2022; **23** [PMID: 35682853 DOI: 10.3390/ijms23116177]

62 **Yu F**, Li Q, Yin S, Liao X, Huang F, Chen D, Cao Y, Cen L. Reconstructing spinal dura-like tissue using electrospun poly(lactide-co-glycolide) membranes and dermal fibroblasts to seamlessly repair spinal dural defects in goats. *J Biomater Appl* 2015; **30**: 311-326 [PMID: 26041755 DOI: 10.1177/0885328215589205]

63 **Oertel JM**, Burkhardt BW. Full endoscopic treatment of dural tears in lumbar spine surgery. *Eur Spine J* 2017; **26**: 2496-2503 [PMID: 28528480 DOI: 10.1007/s00586-017-5105-8]

64 **Terasaka S**, Taoka T, Kuroda S, Mikuni N, Nishi T, Nakase H, Fujii Y, Hayashi Y, Murata JI, Kikuta KI, Kuroiwa T, Shimokawa S, Houkin K. Efficacy and safety of non-suture dural closure using a novel dural substitute consisting of

polyglycolic acid felt and fibrin glue to prevent cerebrospinal fluid leakage-A non-controlled, open-label, multicenter clinical trial. *J Mater Sci Mater Med* 2017; **28**: 69 [PMID: 28357687 DOI: 10.1007/s10856-017-5877-8]

65 **Chaskes MB**, Khoury T, Chitguppi C, Lavergne P, Nyquist GG, Rabinowitz MR, Rosen MR, Evans JJ. A Single Layer Synthetic Dural Substitute Inlay is an Effective Sellar Reconstruction Technique in Endoscopic Transsphenoidal Pituitary Surgery. *J Neurol Surg B Skull Base* 2022; **83**: 291-295 [PMID: 35769799 DOI: 10.1055/s-0040-1721822]

66 **Deng K**, Yang Y, Ke Y, Luo C, Liu M, Deng Y, Tian Q, Yuan Y, Yuan T, Xu T. A novel biomimetic composite substitute of PLLA/gelatin nanofiber membrane for dura repairing. *Neurol Res* 2017; **39**: 819-829 [PMID: 28701072 DOI: 10.1080/01616412.2017.1348680]

67 **Shahrestani S**, Brown NJ, Loya J, Patel NA, Gendreau JL, Himstead AS, Pierzchajlo N, Singh R, Sahyouni R, Diaz-Aguilar LD, Rennert RC, Levy ML. Novel use of nonpenetrating titanium clips for pediatric primary spinal dural closure: A technical note. *Clin Neurol Neurosurg* 2022; **222**: 107422 [PMID: 36084429 DOI: 10.1016/j.clineuro.2022.107422]

68 **Marin Laut FM**, Gómez Cárdenas EA, Dormido JR, Molina NM, López López JA. Spinal dural closure without suture: Minimizing the risk of CSF leakage with a flat non-penetrating titanium U-clip. *Neurocirugia (Astur : Engl Ed)* 2019; **30**: 173-178 [PMID: 30782504 DOI: 10.1016/j.neucir.2018.12.002]

69 **Cheng YP**, Lin PY, Huang AP, Cheng CY, Chen CM, Hueng DY. Durotomy repair in minimally invasive transforaminal lumbar interbody fusion by nonpenetrating clips. *Surg Neurol Int* 2014; **5**: 36 [PMID: 24818043 DOI: 10.4103/2152-7806.129161]

70 **Ito K**, Aoyama T, Horiuchi T, Hongo K. Utility of nonpenetrating titanium clips for dural closure during spinal surgery to prevent postoperative cerebrospinal fluid leakage. *J Neurosurg Spine* 2015; **23**: 812-819 [PMID: 26315957 DOI: 10.3171/2015.3.SPINE141215]

71 **Ito K**, Seguchi T, Nakamura T, Chiba A, Hasegawa T, Nagm A, Horiuchi T, Hongo K. Evaluation of Metallic Artifacts Caused by Nonpenetrating Titanium Clips in Postoperative Neuroimaging. *World Neurosurg* 2016; **96**: 16-22 [PMID: 27586178 DOI: 10.1016/j.wneu.2016.08.086]

72 **Che X**, Zhang W, Xu M. Continuous epidural pumping of saline contributes to prevent and treat postdural puncture headache. *J Clin Anesth* 2016; **34**: 154-158 [PMID: 27687364 DOI: 10.1016/j.jclinane.2016.03.066]

73 **Abdulla S**, Abdulla W, Eckhardt R. Caudal normal saline injections for the treatment of post-dural puncture headache. *Pain Physician* 2011; **14**: 271-279 [PMID: 21587330]

74 **Niraj G**, Kelkar A, Girotra V. Greater occipital nerve block for postdural puncture headache (PDPH): a prospective audit of a modified guideline for the management of PDPH and review of the literature. *J Clin Anesth* 2014; **26**: 539-544 [PMID: 25441250 DOI: 10.1016/j.jclinane.2014.03.006]

75 **Patel R**, Urits I, Orhurhu V, Orhurhu MS, Peck J, Ohuabunwa E, Sikorski A, Mehrabani A, Manchikanti L, Kaye AD, Kaye RJ, Helmstetter JA, Viswanath O. A Comprehensive Update on the Treatment and Management of Postdural Puncture Headache. *Curr Pain Headache Rep* 2020; **24**: 24 [PMID: 32323013 DOI: 10.1007/s11916-020-00860-0]

76 **Zorrilla-Vaca A**, Makkar JK. Effectiveness of Lateral Decubitus Position for Preventing Post-Dural Puncture Headache: A Meta-Analysis. *Pain Physician* 2017; **20**: E521-E529 [PMID: 28535561]

77 **Li H**, Wang Y, Oprea AD, Li J. Postdural Puncture Headache-Risks and Current Treatment. *Curr Pain Headache Rep* 2022; **26**: 441-452 [PMID: 35353358 DOI: 10.1007/s11916-022-01041-x]

78 **Ahmadi SA**, Jafari M, Darabi MR, Chehrei A, Rezaei M, Mirsalehi M. The Effect of l-Arginine on Dural Healing After Experimentally Induced Dural Defect in a Rat Model. *World Neurosurg* 2017; **97**: 98-103 [PMID: 27717775 DOI: 10.1016/j.wneu.2016.09.091]

79 **Oitment C**, Aref M, Almenawar S, Reddy K. Spinal Dural Repair: A Canadian Questionnaire. *Global Spine J* 2018; **8**: 359-364 [PMID: 29977720 DOI: 10.1177/2192568217724132]

80 **Alshameeri ZAF**, El-Mubarak A, Kim E, Jasani V. A systematic review and meta-analysis on the management of accidental dural tears in spinal surgery: drowning in information but thirsty for a clear message. *Eur Spine J* 2020; **29**: 1671-1685 [PMID: 32296949 DOI: 10.1007/s00586-020-06401-y]

81 **Taylor C**, Khan A, Shenouda E, Brooke N, Nader-Sepahi A. Dural tear repair surgery comparative analysis: a stitch in time saves nine. *Eur Spine J* 2022; **31**: 575-595 [PMID: 34889999 DOI: 10.1007/s00586-021-07081-y]

82 **Suh SI**, Koh SB, Choi EJ, Kim BJ, Park MK, Park KW, Yoon JS, Lee DH. Intracranial hypotension induced by cervical spine chiropractic manipulation. *Spine (Phila Pa 1976)* 2005; **30**: E340-E342 [PMID: 15959358 DOI: 10.1097/01.brs.0000166511.59868.b7]

83 **Singhal GD**, Atri S, Suggala S, Jaluka D, Singhal S, Shrivastava AK. Growing Skull Fractures; Pathogenesis and Surgical Outcome. *Asian J Neurosurg* 2021; **16**: 539-548 [PMID: 34660366 DOI: 10.4103/ajns.AJNS_183_18]

84 **Lofrese G**, Visani J, Cultrera F, De Bonis P, Tosatto L, Scerrati A. Anterior Dural Tear in Thoracic and Lumbar Spinal Fractures: Single-Center Experience with Coating Technique and Literature Review of the Available Strategies. *Life (Basel)* 2021; **11** [PMID: 34575024 DOI: 10.3390/life11090875]

85 **Li C**, Raza HK, Chansysouphanthong T, Zu J, Cui G. A clinical analysis on 40 cases of spontaneous intracranial hypotension syndrome. *Somatosens Mot Res* 2019; **36**: 24-30 [PMID: 30870079 DOI: 10.1080/08990220.2019.1566122]

86 **Du YQ**, Duan WR, Chen Z, Wu H, Jian FZ. Risk Factors and Management of Dural Defects in Anterior Surgery for Cervical Ossification of the Posterior Longitudinal Ligament. *World Neurosurg* 2018; **111**: e527-e538 [PMID: 29288856 DOI: 10.1016/j.wneu.2017.12.113]

87 **Murphy ME**, Kerezoudis P, Alvi MA, McCutcheon BA, Maloney PR, Rinaldo L, Shepherd D, Ubl DS, Krauss WE, Habermann EB, Bydon M. Risk factors for dural tears: a study of elective spine surgery(). *Neurol Res* 2017; **39**: 97-106 [PMID: 27908218 DOI: 10.1080/01616412.2016.1261236]

88 **O'Neill KR**, Neuman BJ, Peters C, Riew KD. Risk factors for dural tears in the cervical spine. *Spine (Phila Pa 1976)* 2014; **39**: E1015-E1020 [PMID: 24859583 DOI: 10.1097/BRS.0000000000000416]

89 **Durand WM**, DePasse JM, Kuris EO, Yang J, Daniels AH. Late-presenting dural tear: incidence, risk factors, and associated complications. *Spine J* 2018; **18**: 2043-2050 [PMID: 29679726 DOI: 10.1016/j.spinee.2018.04.004]

90 **Xu JX**, Zhou CW, Wang CG, Tang Q, Li JW, Zhang LL, Xu HZ, Tian NF. Risk Factors for Dural Tears in Thoracic and Lumbar Burst Fractures Associated With Vertical Laminar Fractures. *Spine (Phila Pa 1976)* 2018; **43**: 774-779 [PMID:

28953708 DOI: 10.1097/BRS.0000000000002425]

91 **Reinstein E**, Pariani M, Bannykh S, Rimoin DL, Schievink WI. Connective tissue spectrum abnormalities associated with spontaneous cerebrospinal fluid leaks: a prospective study. *Eur J Hum Genet* 2013; **21**: 386-390 [PMID: 22929030 DOI: 10.1038/ejhg.2012.191]

92 **Bassani L**, Graffeo CS, Behrooz N, Tyagi V, Wilson T, Penaranda S, Zagzag D, Rifkin DB, Barcellos-Hoff MH, Fatterpekar G, Placantonakis D. Noninvasive diagnosis and management of spontaneous intracranial hypotension in patients with marfan syndrome: Case Report and Review of the Literature. *Surg Neurol Int* 2014; **5**: 8 [PMID: 24575323 DOI: 10.4103/2152-7806.125629]

93 **Glassman SD**, Gum JL, Crawford CH 3rd, Shields CB, Carreon LY. Complications with recombinant human bone morphogenetic protein-2 in posterolateral spine fusion associated with a dural tear. *Spine J* 2011; **11**: 522-526 [PMID: 20598649 DOI: 10.1016/j.spinee.2010.05.016]

94 **Ramot Y**, Harnof S, Klein I, Amouyal N, Steiner M, Manassa NN, Bahar A, Rousselle S, Nyska A. Local Tolerance and Biodegradability of a Novel Artificial Dura Mater Graft Following Implantation Onto a Dural Defect in Rabbits. *Toxicol Pathol* 2020; **48**: 738-746 [PMID: 32812521 DOI: 10.1177/0192623320947075]

95 **Zhu T**, Wang H, Jing Z, Fan D, Liu Z, Wang X, Tian Y. High efficacy of tetra-PEG hydrogel sealants for sutureless dural closure. *Bioact Mater* 2022; **8**: 12-19 [PMID: 34541383 DOI: 10.1016/j.bioactmat.2021.06.022]

96 **Masuda S**, Fujibayashi S, Otsuki B, Kimura H, Neo M, Matsuda S. The dural repair using the combination of polyglycolic acid mesh and fibrin glue and postoperative management in spine surgery. *J Orthop Sci* 2016; **21**: 586-590 [PMID: 27519623 DOI: 10.1016/j.jos.2016.07.016]

97 **Liao J**, Li X, He W, Guo Q, Fan Y. A biomimetic triple-layered biocomposite with effective multifunction for dura repair. *Acta Biomater* 2021; **130**: 248-267 [PMID: 34118449 DOI: 10.1016/j.actbio.2021.06.003]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 2916-2924

DOI: 10.12998/wjcc.v11.i13.2916

ISSN 2307-8960 (online)

MINIREVIEWS

Potential impact of music interventions in managing diabetic conditions

Chiedu Eseadi, Amos Nnaemeka Amedu

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Dolińska-Kaczmarek K, Poland; Gluvic Z, Serbia

Received: December 29, 2022
Peer-review started: December 29, 2022
First decision: February 20, 2023
Revised: March 1, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 6, 2023

Chiedu Eseadi, Department of Educational Psychology, Faculty of Education, University of Johannesburg, Johannesburg 2006, Gauteng, South Africa

Amos Nnaemeka Amedu, Social Science Education, University of Nigeria, Nsukka 41001, Enugu State, Nigeria

Corresponding author: Chiedu Eseadi, PhD, Research Fellow, Department of Educational Psychology, Faculty of Education, University of Johannesburg, B-Ring 3, Auckland Park Campus, Johannesburg 2006, Gauteng, South Africa. chiedu.eseadi@unn.edu.ng

Abstract

Diabetes is one of the most prevalent diseases, characterized by an insufficiency in insulin secretion as well as chronic hyperglycemia and disturbances in carbohydrate, lipid, and protein metabolism. The major aim of this study was to conduct a literature review on the impact of music intervention on the management of diabetic conditions among patients. Available studies on the impact of music interventions on the management of diabetic conditions were reviewed and analysed using descriptive literature review approach. This review showed that music intervention plays a dual role in managing patients' diabetic conditions. First, music intervention is impactful in managing the health condition of diabetic patients through enhancing the patient's compliance with exercise, improving lower limb blood circulation, and enhancing health parameters that increase autonomous balance among diabetic patients. Second, music therapy is impactful in the management of diabetic conditions through lowering blood sugar, heart rate, glucose levels, and stress among patients. However, with the number of empirical studies available in this regard, the impact of music intervention is still growing, and longer-term studies and randomised controlled trials with robust sample size are recommended to reach a more valid conclusion.

Key Words: Diabetes; Management of diabetes; Music intervention; Music therapy

Core Tip: The use of music intervention has been found effective in treating a wide range of health issues. This study demonstrates that music intervention is impactful in the management of diabetic conditions through reduction in blood sugar, heart rate, glucose level, and stress. These symptoms have been widely associated with diabetic conditions among patients. It is imperative to further examine the significant effects of music intervention in curtailing these symptoms through the selection of specific music that reduces these specific symptoms in diabetics.

Citation: Eseadi C, Amedu AN. Potential impact of music interventions in managing diabetic conditions. *World J Clin Cases* 2023; 11(13): 2916-2924
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/2916.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.2916

INTRODUCTION

Music therapy is a non-drug-assisted intervention that has a significant impact on diabetic patients' management, comfort, and recovery. Music intervention has been perceived as a resolute musical exercise in which music listening and singing are central. Music intervention is the clinical and evidence-based application of music in a therapeutic intervention by a certified professional who has completed a recognized music therapy programme[1]. Additionally, music interventions are delivered by licensed music therapists and are distinguished by the utilization of personalized musical experiences and the inclusion of a therapeutic approach[2]. In music therapy history, music intervention may include listening to music, playing music, or writing songs[3]. Music features have been shown to have a significant impact on the management and reduction of stress experienced by patients with illnesses[4].

Music of different types, such as high and low tempos, with and without lyrics, live or recorded, has a different degree of impact on managing the health conditions of patients. In the context of music, the tempo of a piece is regarded as one of the most significant moderators of arousal and relaxation. Meditative music with a slow tempo of 60-80 beats per minute is commonly linked with decreases in heart rate, resulting in greater relaxation[5,6]. When instrumental music is used, it is found to have a more profound impact on reducing stress as music that includes lyrics is more distracting and stimulating rather than calming[7]. As a result of the possible comforting effects of lyrics, music with lyrics may enhance the positive impact of music interventions when managing stress associated with ailments[8]. Additionally, the manner in which music is played (on stage or recorded) has a significant impact on patients. Since live music therapists tailor their programmes in order to capture patients' specific needs, live music has been revealed to be more impactful than "music as medicine" in lessening patient pain[9]. There is evidence that music therapists in hospice and palliative care utilize a variety of techniques, including song writing, lyric analysis, instrumental playing, guided imagery and music, singing, and music therapy relaxation techniques in order to address the immediate and personified needs of their patients[10]. The goal of this study was to establish the potential impact of music interventions for the management of various types of diabetic patients using available empirical evidence.

Diabetes is a chronic metabolic disorder which has become one of the most prevalent and major global health problems. Among the most notable features of diabetics are the absolute deficits in insulin secretion as well as chronic hyperglycemia and abnormalities in the metabolism of carbohydrate, lipid, and protein[11]. There are various types of diabetes described in the literature, including Type 1, Type 2 (DM2), prediabetes, gestational, monogenic, cystic fibrosis, and chemically induced diabetes[12]. A poorly managed form of diabetes can damage vital organs and tissues such as the kidneys, eyes, nerves, and heart[12]. This study deals with the utilization of music intervention in treating diabetes ailments.

The use of music intervention therapy has been found effective in treating a wide range of health issues, including diabetes. As a result, music has a significant impact on individual minds before its perceived meaning is transmitted into thoughts and feelings[13]. Since it helps create psychological wellness, increases the ability to concentrate and think critically, and enhances emotional expression and clarity of thinking, music can be used to treat psychological ailments as well as psychosomatic diseases[13]. The potential benefits of music therapy have been noted in the areas of health care, education and social welfare, as well as its artistic and cultural benefits[14]. Music therapy has been found to be the most accepted and evaluated modality of integrative medicine as well as complementary alternative medicine[14]. The major aim of this current study was to establish the potential impact of music intervention in the management of diabetic condition based on the available empirical studies.

METHODOLOGY

This study adopted a descriptive literature review approach to investigate the potential impact of music interventions on managing diabetic conditions. Since this study was based on empirical literature analysis, ethical approval was not required. Based on an extensive literature search, we identified and cited published papers in reputable journals and databases. A multiple inclusion criteria were used to select papers for this literature analysis. Firstly, only studies that examined the potential effects of music intervention on the management of diabetes were included. The study must be conducted on the human population; hence, animal studies were excluded. The music intervention must involve listening to music, either live or recorded; any intervention studies that dealt with the making of music were excluded; the study must involve two groups. Studies must include either psychological or physiological outcome variable(s); thus, studies without any of these outcome variables were excluded; intervention studies that included participants less than 18 years were excluded; and finally, studies that were not written in the English language were not included. Based on these selection criteria, a total of 6 articles met the criteria for inclusion.

The descriptive literature review approach enabled us to describe the selected literature and present their implications for research and practice. We were able to find substantial information on people with diabetes, and the potential impact of music interventions on managing diabetic conditions from several sources including Google Scholar, Directory of Open Access Journals, Dimensions, SciLit, Bielefeld Academic Search Engine, Lens, Scopus, *Reference Citation Analysis* (https://www.referencecitation-analysis.com/) and PubMed Central. Qualitative and quantitative papers in the English version were rigorously searched, evaluated, selected, and synthesized by the researchers. Search terms used include music intervention, diabetes management, music intervention and diabetes intervention, music therapy and diabetes management, and the impact of music on diabetes management.

POTENTIAL IMPACT OF MUSIC INTERVENTION IN MANAGING DIABETIC CONDITIONS

An extensive review of the medical literature has demonstrated that chronic illness associated with insulin inefficiency contributes significantly to the development of diabetes. However, the use of music interventions can greatly contribute in managing diabetes and accompanying psychological symptoms [13-19] (see Table 1). For instance, a past study[15] used an intervention program to evaluate the effects of Indian classical music on blood sugar levels of DM2 patients compared to non-diabetic participants. In all groups, a significant reduction was observed in blood glucose levels. In addition, the findings of the study indicated that no significant differences were observed in blood sugar reduction between participants in control and experimental conditions. The results of this study indicate that music intervention can reduce blood sugar levels to a certain extent, even though the effect is not statistically significant.

The effectiveness of active and silent music interventions on patients with DM2 was also examined by researchers[16] using a repeated measures study design. The results of this study revealed that the activation coefficient of DM2 patients using Gas Discharge Visualization parameters was significantly affected by both active and silent music. However, it was indicated that silent music intervention led to boredom as compared to active music. A session of active music intervention led to a significant improvement in the health condition of the DM2 patients, which could ultimately assist them in maintaining autonomous balance. The findings of this study affirmed that music intervention has the potential impact on management of diabetic conditions.

Also, a study examined the effects of Indonesian traditional music on DM2 patients using a quasi-experimental design of pre-test and post-tests[18]. It was revealed that Saluang music significantly reduced the incidence of DM2 in patients. Thus, it implies that Saluang music is effective in treating stress-related problems associated with DM2. Likewise, a study investigated the effect of combining music and exercise on elderly patients with diabetes mellitus using a quasi-experimental research approach[19]. During the following three months of intervention, it was found that music intervention improved adherence to low exercise levels significantly compared to the control group. Therefore, combining music and low exercise therapeutic intervention enhances the extent of exercise compliance in elderly patients suffering from diabetes and improves blood circulation in their feet. In addition, music therapy was used in a randomised controlled trial to treat DM2 with psychosomatic disease[13]. The study focused on two types of music that were both joyful and relaxing in reducing glucose levels. In both intervention groups, music therapy increased the psychological parameters of patients with DM2 as well as lowered their blood glucose levels.

Physiological disorders caused by stress can lead to functional abnormalities in a variety of organs, either temporarily or permanently. But, it has been shown that music therapy can reduce psychological and physiological stress, metabolic changes, and the pain experienced by diabetic patients[13]. Patients with diabetes, for example, have low hepatic carbohydrate stores due to insulin deficiency[13]. Because of this shortage, sugar cannot be transported from the blood to the liver or other cells that require it, resulting in elevated blood sugar levels. As a complex carbohydrate called glycogen, sugar is injected

Table 1 Empirical literature on potential impact of music intervention among diabetic patients

Ref.	Year	Duration	Study objectives	Method/sample	Results
Cioca[13]	2013	Not specified	To determine the impact of music intervention on reduction of glycaemia (glucose) among diabetic patients and healthy peoples	Randomised controlled experimental research design using criterion sampling to sample 120 participants	This study revealed that hypoglycemic role of classic music for DM2 patients decreased the patients' glucose levels
Pillai and Dave[15]	2018	A day	To establish the effect of Indian classical music on blood sugar level of DM2 and non-diabetic patients	Quasi-experimental controlled trial using criterion sampling technique to sample 100 participants	There was a significant reduction in the blood sugar of the selected participants, but not significant when compared to other groups
Rao and Nagendra [16]	2014	A day	The main purpose of this study was to compare the difference of the effect of active and silent music intervention on the autonomous balance of diabetic patients	Repeated measure of pre-post design was used in a sample of 42 participants	It was revealed that silent music was more bore compare to active music; active music led to significant change in the parameter towards enhancement of health status of patients which could be more helpful in achieving autonomous balance of the diabetic patients
Deshkar *et al*[17]	2022	A day	To evaluate the effect of music therapy on heart rate variability among diabetic patients	Pure experimental research using criterion sampling procedure sample 30 diabetic patients	It was revealed that music intervention lessened the heart rate. The difference was statistically significant
Sastra and Reni[18]	2022	7 d	The main purpose was to examine the effect of Salaung Indonesian music on reducing stress of DM2 patients	Quasi-experimental one-group pretest-post-test using criterion sampling procedure was used to sample 20 participants	The study revealed that Indonesian traditional music is effective in reducing patient stress level
Ji *et al*[19]	2015	6 mo	The objective was to evaluate the effectiveness of music therapy with lower exercise on elderly patient with diabetes compliance with lower exercise and blood circulation	Randomised control trial using criterion sampling procedure was adopted to sample 72 participants	The study affirmed that music intervention with lower extremity exercise can both enhance the extent of exercise compliance of elderly patients as well as improve blood circulation in their feet among elderly patients

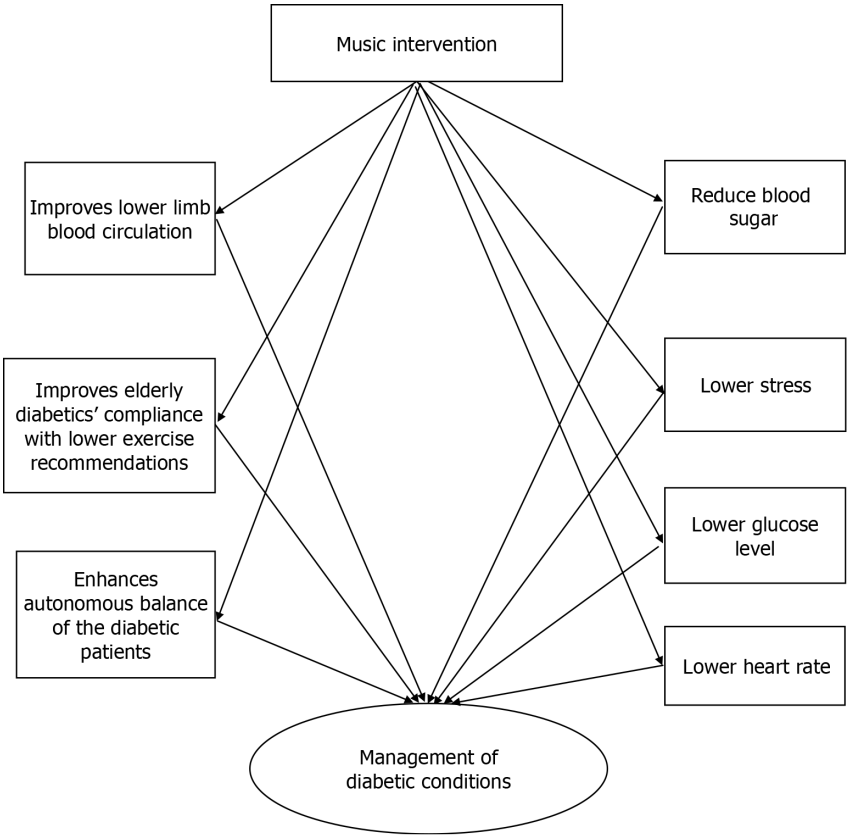
DM2: Type 2 diabetes mellitus.

into the bloodstream through epinephrine on demand. The stimulation of beta cells in the organs by classical music contributes to the maintenance of normality for a limited period of time. Emotional situations affect blood sugar levels[13]. As a result of gently altering the neurotransmitter epinephrine, classical music can assist in the promotion of relaxation.

From available literature, six studies focused on the potential impact of music intervention on the management of DM2 conditions. This indicates that there is a dearth of empirical studies on the potential impact of music intervention on the management of other types of diabetes. In other words, more studies on the impact of music intervention on the management of other diabetic conditions are required. Also, the type of music intervention adopted depends on the environment where the studies were carried out. The majority of the music used in this study were predominant Asian, involving joyful and relaxing music[13]; classical, folk instrumental, cheerful, religious, and soothing[19]; and Indonesian Salaung music[18]. There is a dearth of empirical studies in this regard in other parts of the world, especially on the African continent, where there is a high prevalence of diabetes cases.

Furthermore, two of the selected studies[13,19] used randomized controlled designs whereas other studies[15,18] used non-randomized designs. Therefore, there is a need for empirical studies with high levels of control and randomisation of participants. This will enable the establishment of the potential impact of music intervention on the management of diabetic conditions with robust design. Among the randomised groups, there was a significant reduction in the associated symptoms of diabetics in the treatment groups. But, most of the sample sizes used in the studies were small, which hinders the generalization of the findings. In some studies with larger samples, there was a substantial potential impact of music intervention on the management of diabetic patients. The period of intervention was not specified[13] while others used shorter periods, which ranged from 1-7 d. Only one study lasted for six months[19]. Hence, more studies that span a longer period of time are needed to establish the potential impact of music intervention on the management of diabetes since one time exposure to music intervention may not be sufficient to establish the potential effect of music intervention in the management of diabetic conditions.

Figure 1 show that music therapy has been found to enhance the psychological and physical health of patients with diabetes based on the four empirical evidences. First, music intervention has been found to lower the glucose level of patients with diabetes from 197.75 to 158.93, demonstrating its significant impact on managing overall diabetic conditions[13]. The efficacies of two kinds of music intervention (relaxing music and joyful music) were tested with regards to reduction in glucose levels. Specifically,



DOI: 10.12998/wjcc.v11.i13.2916

Figure 1 Potential impact of music interventions in managing diabetic conditions.

music for relaxation reduced glucose levels from 169.76 to 148.1, whereas music for joy reduced glucose levels from 197.53 to 172.83. These two types of music intervention are of considerable benefit to diabetic patients by reducing glucose levels without taking any drug such as metformin.

Second, music therapy has been found to enhance lower limb blood circulation in patients with diabetes. Specifically, music therapy enhanced the peak velocity of the dorsal artery in patients with diabetes after 6 mo, as those in the control group had a mean score of 14.5 while those in the intervention group had a mean score of 15.91[19]. This indicates that music therapy is efficacious in enhancing a patient's dorsal artery and an increase in the peak velocity of the dorsal artery translates to enhanced blood circulation in diabetics.

Third, music therapy has the potential to improve elderly patients' compliance with lower extreme exercise regimens after 6 mo of treatment[19]. The elderly diabetic patient increased their compliance with lower limb exercise from 13.56 to 21.18, indicating that music therapy had a significant impact on their health condition management. Fourth, the significant impact of music therapy in the management of diabetes has been established in lowering the heart rate of patients. For instance, music therapy reduced the elderly diabetic's heart rate from 93.9 to 84.7, demonstrating the importance of music therapy in the management of diabetic conditions[17]. Fifth, high blood sugar has been found to be one of the symptoms of diabetes. However, application of music intervention therapy has been found to lower blood sugar from 225.925 to 216.025, indicating that this therapy is efficacious in managing the symptoms of DM2[15].

Finally, diabetic patients suffer numerous pains (physical and psychological pains) that are sometimes persistent and resistant to any type of medication, which results in the patient being stressed. However, application of music intervention therapy has been found to lessen stress associated with diabetic patients, as study indicates that the stress level of patients with diabetes decreased from 22.5 to 14.5[18]. Music therapy assists by stimulating endorphin secretions or distracting them. Music can also make a diabetic patient believe that he/she is in charge, thus relaxing him/her by regulating his heartbeat and respiration. Music therapy is one of the creative and experimental forms of alternative medicine used to restore people's psychic and physical well-being[13]. Music therapy is also helpful in moderating the metabolic changes, as an increase in catecholamine levels occurs when music is complex and intense, whereas a slow and discrete piece of music lowers glycaemia levels.

Music intervention therapy was tolerated by all the patients as there was no report of any specific adverse effect in any study. Music intervention therapy has a positive in management of diabetic conditions as it plays a dual role in the management of diabetic patients. The first impactful role of

music therapy in the management of individuals with diabetes is to improve the self-care of patients as well as enhance individuals' engagement in some activities that improve their health conditions[20-22].

Music therapy intervention mostly plays the role of solidifying treatment effectiveness by enhancing exercise compliance[23]. This suggests that music therapy increases the rate at which a patient with diabetes engages in exercise. When diabetic patients exercise more regularly, the incidence of complications decreases[24,25]. Music intervention is mainly applied to patients in order to relieve pains, depression, and muscle spasms, as well as to improve neurological deficits and enhance recovery of motor function[9,26].

The use of music intervention programme designed specifically for active and silent music categories has been found to improve the autonomous balance of diabetic patients[16]. Active music has been demonstrated to be beneficial in preserving energy levels and reducing the right-side entropy which assist in sustaining left balance in the integral area. Active music has been demonstrated to impact significantly on the parameters that improve health conditions which contributes to enhancing autonomous balance among diabetic patients. Similarly, silent music has been found to be less effective in improving health conditions that translates to autonomous balance of diabetic patients.

REFLECTIONS BASED ON AVAILABLE LITERATURE

In the music literature, it has been demonstrated that listening to music and understanding it bring about an unavoidable alteration in an individual's mindset. This modification has been linked to a significant reduction in blood sugar levels in DM2 patients who listen to western classical music[13]. Furthermore, Indian music such as Raga Bageshree has been revealed to have a positive impact on the management of diabetic conditions through the reduction of blood sugar[27]. So, music therapy intervention including traditional music can help an individual with diabetes lower their blood sugar level, which is important for taking care of diabetic patients.

Music therapy has been found to be effective in managing the stress that diabetics often encounter. This assertion is strengthened by the disclosure that the Saluang form of Indonesian music positively affects the stress of patients with DM2[18]. Thus, the use of some areas of native music has had important influence on diabetics' well-being. Music therapy, including the use of classical music, exerts positive influence diabetics' mood states, stress level, heart rate, blood pressure, memory, and attention thereby leading to feelings of relaxation, calmness, and comfort[28,29]. Slow-tempo or rhythmic music has been shown to inhibit catecholamine release into blood vessels, resulting in a decrease in catecholamine concentrations in plasma. This process triggers the sympathetic nerves, which in turn stimulate the release of stress hormones that cause the body to relax[30]. Music impact in lessening stress associated diabetic condition has found to be low cost, free from side effects as well as uses indigenous approach. Diabetic patients' emotional attachment to a particular music or emotion conveyed through music tends to be affected by their cultural background[31].

In addition, a high glucose level, which is a commonly reported symptom of DM2 occur as a result of resistance to insulin, and have been found to decrease due to the impact of music therapy in the management of patients with diabetic conditions. In the music intervention literature, joyful and relaxing music therapies have been found to be impactful in reducing the level of glucose in individual patients with diabetes[32]. According to music literature, walking and jogging outside at a consistent pace while listening to favourite music lowers glucose levels in diabetics[33]. Despite the fact that music therapy has been shown to reduce glucose levels in diabetic patients, there was no significant difference in blood glucose levels before and after intervention in one study[34]. Despite this, music therapy is essential in the management of the general health condition of patients with diabetes.

The impact of music on resilience to exercise is probably attributed to its affecting sympathetic nerve excitability, slowing heart rate and breathing, and ultimately affecting the patients' nerve and muscle systems, which further improves perception and involvement with activities[35,36]. Also, different types of somatic and mental disorders can be managed through the use of music therapy in DM2 patients[37]. It is an efficient therapeutic method that modulates emotions and autonomous nervous system activity[17]. Because music intervention induces high relation and low tension subjectively in young people, it is often effective.

Additionally, ecological momentary music interventions and usual music interventions are feasible and pleasant activity-based approaches that can reduce psychological stress, chronic pains, lower voluntary mobility during pain episodes and decrease perceived stress, burnout, traumatic stress among patients[38-41]. A recent longitudinal study on management of DM2 also revealed that music with painting therapies positively lowers the level of blood glucose among individuals with DM2[42]. Another recent research revealed that music therapy remains the best way to reduce anxiety and depression among DM2 patients since it consistently reduced their mean post-test and follow-up ratings [43]. Also, spiritual music could decrease heart rate and blood pressure[44]. In comparison to DM2 patients treated without music-assisted alagliptin, music-assisted alagliptin was shown to reduce blood glucose levels and improve quality of life of DM2 patients[45]. Thus, various forms of music interventions have continued to date to demonstrate their efficacy in the management of diabetics'

mental and physical health symptoms.

IMPLICATIONS AND RECOMMENDATIONS

The results of this study have implications for future research on the effective use of music therapeutic interventions for diabetes management. Music intervention was found to be impactful in the management of diabetic conditions by improving patients' engagement in exercise, autonomous balance, and lower limb blood circulation. The number of people that are diagnosed with diabetes is increasing on a daily basis, and these cases are prevalent among the aging population. Considering the fact that music intervention is inexpensive and easy to integrate into the medical setting as well as the daily lives of these aged patients in order to enhance their lives, it is very imperative to recognize the significant impact of music intervention on the management of their mood, mental health, glycemic control and emotions[37].

Also, this study established that music intervention is impactful in the management of diabetic conditions through reduction in blood sugar, heart rate, glucose level, and stress. These symptoms have been widely recognized as the manifestation of diabetic conditions among patients. It is crucial to further investigate the significant effects of music intervention in curtailing these symptoms through the selection of specific music that reduces these specific symptoms in diabetics.

The majority of the empirical studies in the music intervention literature focused on DM2 condition. This means that the impact of music intervention in the management of diabetic conditions has not been tested on other types of diabetic conditions. Therefore, further studies should consider establishing the impact of the management of other types of diabetic conditions using music intervention therapy.

Also, most of the studies on music intervention in the management of diabetes are non-randomised controlled trials. This review suggests that future research should focus on a randomised control trial involving two or more groups in order to effectively establish the potential impact of music intervention on the management of diabetic conditions that other researchers can easily replicate. Additionally, the study revealed that the sample size of the available studies and the duration of the intervention programme were small and short. Small sample size with a short period of intervention affects the efficacy of the intervention as well as the generalizability of the findings. Thus, further studies should consider recruiting a substantial sample size as well as allocating a sufficient period for executing the programme.

Also, the majority of the available empirical literature was conducted in Asia, where Indonesian and Indian music were used in the management of DM2 conditions. Hence, further studies should consider validating the potential impact of music intervention in other regions including sub-Saharan Africa, where there is a prevalence of different categories of diabetes.

CONCLUSION

This study has demonstrated the potential impact of music intervention in the management of diabetic conditions using available empirical evidence. The evidence from music literature affirmed that music intervention is impactful in the management of diabetic conditions through enhancement of individuals with diabetes' compliance with exercise, autonomous balance and lower limb blood circulation among patients, as well as facilitation of reduction in blood sugar, heart rate, glucose level, and stress level. The potential impact of music intervention on diabetics is still a work in progress, and the available findings so far suggest the viability of conducting further research in this area.

FOOTNOTES

Author contributions: Eseadi C and Amedu AN conceived the study; Eseadi C and Amedu AN designed the study, conducted the literature review and were all responsible for the analysis, drafting, editing, and approval of the final version of this manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: South Africa

ORCID number: Chiedu Eseadi 0000-0003-1711-7558; Amos Nnaemeka Amedu 0000-0003-1072-1592.

S-Editor: Hu YR
L-Editor: A
P-Editor: Guo X

REFERENCES

1 **American Music Therapy Association**. What is music therapy. (AMTA). Available from: https://www.musictherapy.org/about/musictherapy/
2 **Kamioka H**, Tsutani K, Yamada M, Park H, Okuizumi H, Tsuruoka K, Honda T, Okada S, Park SJ, Kitayuguchi J, Abe T, Handa S, Oshio T, Mutoh Y. Effectiveness of music therapy: a summary of systematic reviews based on randomized controlled trials of music interventions. *Patient Prefer Adherence* 2014; **8**: 727-754 [PMID: 24876768 DOI: 10.2147/PPA.S61340]
3 **Leubner D**, Hinterberger T. Reviewing the Effectiveness of Music Interventions in Treating Depression. *Front Psychol* 2017; **8**: 1109 [PMID: 28736539 DOI: 10.3389/fpsyg.2017.01109]
4 **Bradt J**, Dileo C. Music interventions for mechanically ventilated patients. *Cochrane Database Syst Rev* 2014; **2014**: CD006902 [PMID: 25490233 DOI: 10.1002/14651858.CD006902.pub3]
5 **Hilz MJ**, Stadler P, Gryc T, Nath J, Habib-Romstoeck L, Stemper B, Buechner S, Wong S, Koehn J. Music induces different cardiac autonomic arousal effects in young and older persons. *Auton Neurosci* 2014; **183**: 83-93 [PMID: 24636674 DOI: 10.1016/j.autneu.2014.02.004]
6 **Nomura S**, Yoshimura K, Kurosawa Y. A pilot study on the effect of music-heart beat feedback system on human heart activity. *J Med Inform Technol* 2013; **22**: 251-256
7 **Good M**, Picot BL, Salem SG, Chin CC, Picot SF, Lane D. Cultural differences in music chosen for pain relief. *J Holist Nurs* 2000; **18**: 245-260 [PMID: 11847812 DOI: 10.1177/089801010001800306]
8 **Koelsch S**, Fuermetz J, Sack U, Bauer K, Hohenadel M, Wiegel M, Kaisers UX, Heinke W. Effects of Music Listening on Cortisol Levels and Propofol Consumption during Spinal Anesthesia. *Front Psychol* 2011; **2**: 58 [PMID: 21716581 DOI: 10.3389/fpsyg.2011.00058]
9 **Bradt J**, Dileo C, Magill L, Teague A. Music interventions for improving psychological and physical outcomes in cancer patients. *Cochrane Database Syst Rev* 2016; CD006911 [PMID: 27524661 DOI: 10.1002/14651858.CD006911.pub3]
10 **Hilliard RE**. Music Therapy in Hospice and Palliative Care: A Review of the Empirical Data. *Evid Based Complement Alternat Med* 2005; **2**: 173-178 [PMID: 15937557 DOI: 10.1093/ecam/neh076]
11 **Golbidi S**, Ebadi SA, Laher I. Antioxidants in the treatment of diabetes. *Curr Diabetes Rev* 2011; **7**: 106-125 [PMID: 21294707 DOI: 10.2174/157339911794940729]
12 **Cleveland Clinic**. Diabetes. Available from: https://my.clevelandclinic.org/health/diseases/7104-diabetes-mellitus-an-overview
13 **Cioca IE**. Type 2 diabetes – psychosomatic disease approachable through music therapy. *Proc Rom Acad Series B* 2013; **15**: 38-46
14 **Bando H**. Music therapy and internal medicine. *Asian Med J* 2001; **44**: 30-35
15 **Pillai AM**, Dave DJ. Evaluation of the effect of Indian classical music on the blood sugar level of Type-2 diabetes mellitus patients. *MMD* 2018; **10**: 175 [DOI: 10.47513/mmd.v10i4.615]
16 **Rao TI**, Nagendra HR. The effect of active and silent music interventions on patients with type 2 diabetes measured with electron photonic imaging technique. *Int J Humanit Soc Sci* 2014; **3**: 7-14
17 **Deshkar AA**, Kaur M, Kamble RL. Music Therapy Session as Stress Buster among Diabetic: An Analysis by Heart Rate Variability. *Int J Sci Stud* 2022; **10**: 69-72
18 **Sastra L**, Reni I. The effect of Indonesian traditional music on stress in type II diabetes mellitus patients. *KnE Life Sciences* 2022; **7**: 706-717 [DOI: 10.18502/kls.v7i2.10371]
19 **Ji L**, Bai JJ, Sun J, Ming Y, Chen LR. Effect of combining music media therapy with lower extremity exercise on elderly patients with diabetes mellitus. *Int J Nurs Sci* 2015; **2**: 243-247 [DOI: 10.1016/j.ijnss.2015.07.008]
20 **Colberg SR**, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, Chasan-Taber L, Albright AL, Braun B; American College of Sports Medicine; American Diabetes Association. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care* 2010; **33**: e147-e167 [PMID: 21115758 DOI: 10.2337/dc10-9990]
21 **Thomas DE**, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2006; **2006**: CD002968 [PMID: 16855995 DOI: 10.1002/14651858.CD002968.pub2]
22 **Montero D**, Walther G, Benamo E, Perez-Martin A, Vinet A. Effects of exercise training on arterial function in type 2 diabetes mellitus: a systematic review and meta-analysis. *Sports Med* 2013; **43**: 1191-1199 [PMID: 23912806 DOI: 10.1007/s40279-013-0085-2]
23 **Johnson G**, Otto D, Clair AA. The effect of instrumental and vocal music on adherence to a physical rehabilitation exercise program with persons who are elderly. *J Music Ther* 2001; **38**: 82-96 [PMID: 11469917 DOI: 10.1093/jmt/38.2.82]
24 **Lerman I**. Adherence to treatment: the key for avoiding long-term complications of diabetes. *Arch Med Res* 2005; **36**: 300-306 [PMID: 15925020 DOI: 10.1016/j.arcmed.2004.12.001]
25 **Bacus IP**, Mahomed H, Murphy AM, Connolly M, Neylon O, O'Gorman C. Play, art, music and exercise therapy impact on children with diabetes. *Ir J Med Sci* 2022; **191**: 2663-2668 [PMID: 35037160 DOI: 10.1007/s11845-021-02889-5]

26 **Kim SJ**, Koh I. The effects of music on pain perception of stroke patients during upper extremity joint exercises. *J Music Ther* 2005; **42**: 81-92 [PMID: 15839735 DOI: 10.1093/jmt/42.1.81]

27 **Sridharan A**, Moh M, Moh TS. Similarity Estimation for Classical Indian Music. 2018 17th IEEE International Conference on Machine Learning and Applications (ICMLA); Orlando, FL, USA. IEEE, 2018: 814-819 [DOI: 10.1109/ICMLA.2018.00130]

28 **Darki C**, Riley J, Dadabhoy DP, Darki A, Garetto J. The Effect of Classical Music on Heart Rate, Blood Pressure, and Mood. *Cureus* 2022; **14**: e27348 [PMID: 36046316 DOI: 10.7759/cureus.27348]

29 **Tumuluri I**, Hegde S, Nagendra HR. Effectiveness of Music Therapy on Focused Attention, Working Memory and Stress in Type 2 Diabetes: An Exploratory Study. *Int J Yoga* 2017; **10**: 167-170 [PMID: 29422748 DOI: 10.4103/0973-6131.213471]

30 **Weeks BP**, Nilsson U. Music interventions in patients during coronary angiographic procedures: a randomized controlled study of the effect on patients' anxiety and well-being. *Eur J Cardiovasc Nurs* 2011; **10**: 88-93 [PMID: 20685168 DOI: 10.1016/j.ejcnurse.2010.07.002]

31 **Argstatter H**. Perception of basic emotions in music: Culture-specific or multicultural? *Psychol Music* 2016; **44**: 674-90 [DOI: 10.1177/0305735615589214]

32 **Mukherjee O**, Mutnury SL. Management of chronic illness through music therapy: A Review. *Indian J Health Sci* 2021; **3**: 55-94

33 **Bando H**. Combined diabetic treatment with low carbohydrate diet, exercise and music therapy. *Diabetes Update* 2018; **1**: 1-2 [DOI: 10.15761/DU.1000103]

34 **Mottahedian Tabrizi E**, Sahraei H, Movahhedi Rad S, Hajizadeh E, Lak M. The effect of music on the level of cortisol, blood glucose and physiological variables in patients undergoing spinal anesthesia. *EXCLI J* 2012; **11**: 556-565 [PMID: 27350774]

35 **Im ML**, Lee JI. Effects of art and music therapy on depression and cognitive function of the elderly. *Technol Health Care* 2014; **22**: 453-458 [PMID: 24704654 DOI: 10.3233/THC-140803]

36 **Yamamoto T**, Ohkuwa T, Itoh H, Kitoh M, Terasawa J, Tsuda T, Kitagawa S, Sato Y. Effects of pre-exercise listening to slow and fast rhythm music on supramaximal cycle performance and selected metabolic variables. *Arch Physiol Biochem* 2003; **111**: 211-214 [PMID: 14972741 DOI: 10.1076/apab.111.3.211.23464]

37 **Witusik A**, Kaczmarek S, Pietras T. The role of music therapy in the treatment of patients with type 2 diabetes. *Pol Merkur Lekarski* 2022; **50**: 210-212 [PMID: 35801608]

38 **Moon JR**, Song J, Huh J, Kang IS, Kim JH, Park SW, Chang SA. The effects of music intervention on anxiety and stress responses in adults with CHD undergoing cardiac catheterisation. *Cardiol Young* 2023; **33**: 213-220 [PMID: 35285439 DOI: 10.1017/S1047951122000439]

39 **Gudi H**, Gowribhatla Y, Sharma V. Role of Music Intervention on Professional Quality of Life and Work Stress: An Experimental Investigations. *Indian J Health Sci* 2023; **5**: 106-120

40 **Du J**, Shi P, Fang F, Yu H. Effect of music intervention on subjective scores, heart rate variability, and prefrontal hemodynamics in patients with chronic pain. *Front Hum Neurosci* 2022; **16**: 1057290 [PMID: 36466624 DOI: 10.3389/fnhum.2022.1057290]

41 **Feneberg AC**, Nater UM. An ecological momentary music intervention for the reduction of acute stress in daily life: A mixed methods feasibility study. *Front Psychol* 2022; **13**: 927705 [PMID: 36248548 DOI: 10.3389/fpsyg.2022.927705]

42 **Wang X**, Jiang J, Hu Y, Qin LQ, Hao Y, Dong JY. Art Engagement and Risk of Type 2 Diabetes: Evidence From the English Longitudinal Study of Ageing. *Int J Public Health* 2023; **68**: 1605556 [PMID: 36891222 DOI: 10.3389/ijph.2023.1605556]

43 **Belmon AP**, Auxillia J. Music Therapy: A Best Way to Solve Anxiety and Depression in Diabetes Mellitus Patients. In: Biswas A, Wennekes E, Wieczorkowska A, Laskar RH. Advances in Speech and Music Technology: Computational Aspects and Applications. Springer, 2023: 237–247 [DOI: 10.1007/978-3-031-18444-4_12]

44 **Adlakha K**, Mathur MK, Datta A, Kalsi R, Bhandari B. Short-Term Effect of Spiritual Music on Heart Rate Variability in Medical Students: A Single-Group Experimental Study. *Cureus* 2023; **15**: e34833 [PMID: 36919072 DOI: 10.7759/cureus.34833]

45 **Li M**, Zheng X, Zhang X, Du X. [Effects of Music Therapy Assisted Anagliptin on Glycolipid Metabolism in Patients with Type 2 Diabetes]. *Zhongguo Quanke Yixue* 2022; 25: 3275-3280 [DOI: 10.12114/j.issn.1007-9572.2022.0271]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 2925-2933

DOI: 10.12998/wjcc.v11.i13.2925

ISSN 2307-8960 (online)

MINIREVIEWS

Implications of obesity and adiposopathy on respiratory infections; focus on emerging challenges

Ioannis G Lempesis, Vasiliki E Georgakopoulou

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Belančić A, Croatia; Said MA, Saudi Arabia

Received: January 17, 2023
Peer-review started: January 17, 2023
First decision: February 17, 2023
Revised: February 17, 2023
Accepted: March 30, 2023
Article in press: March 30, 2023
Published online: May 6, 2023

Ioannis G Lempesis, Vasiliki E Georgakopoulou, Department of Infectious Diseases-COVID-19 Unit, Laiko General Hospital, Athens 11527, Greece

Corresponding author: Vasiliki E Georgakopoulou, Doctor, MSc, Doctor, Department of Infectious Diseases-COVID-19 Unit, Laiko General Hospital, 17 Agiou Thoma Street, Athens 11527, Greece. vaso_georgakopoulou@hotmail.com

Abstract

Obesity is characterized by excessive adipose tissue accumulation, which impacts physiological, metabolic, and immune functions. Several respiratory infections, including bacterial pneumonia, influenza, and coronavirus disease 2019, appear to be linked to unfavorable results in individuals with obesity. These may be attributed to the direct mechanical/physiological effects of excess body fat on the lungs' function. Notably, adipose tissue dysfunction is associated with a low-grade chronic inflammatory status and hyperleptinemia, among other characteristics. These have all been linked to immune system dysfunction and weakened immune responses to these infections. A better understanding and clinical awareness of these risk factors are necessary for better disease outcomes.

Key Words: COVID-19; Influenza; Lung disease; Immune system; Obesity

Core Tip: Obesity influences the development and outcome of various respiratory infections. This is mediated in various ways, including through direct physiological impacts on the lungs and airways and *via* the dysfunctional adipose tissue, inducing a low-grade inflammatory status that potentially affects the immune response to certain pathogens. These include, notably, influenza and coronavirus disease 2019. Clinicians should be aware of these unique challenges in this subset of patients and take preventive and aggressive therapeutic measures as needed.

Citation: Lempesis IG, Georgakopoulou VE. Implications of obesity and adiposopathy on respiratory infections; focus on emerging challenges. *World J Clin Cases* 2023; 11(13): 2925-2933
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/2925.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.2925

INTRODUCTION

Obesity is a complex chronic disease linked to increased risk of nearly every chronic condition, including insulin resistance states, diabetes, cardiometabolic diseases, and various types of cancer, overall resulting in poor quality of life and reduced life expectancy[1-3]. Furthermore, obesity has a significant impact on respiratory health, and this has become even more apparent during the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory coronavirus 2 (SARS-CoV-2)[4,5], as obesity has been associated with an increased risk of infection and unfavorable clinical outcomes in people with obesity that encounter COVID-19[6,7]. However, the burden of obesity on various infectious diseases was already recorded before and independently of the COVID-19 pandemic[8,9].

Obesity has been linked to an increased risk of pulmonary infections, including pneumonia, bronchitis, chronic obstructive pulmonary disease (COPD) exacerbations, and various other viral infections that we will further describe here[10]. Some of the mechanisms by which obesity increases the risk of respiratory infections include changes in pulmonary function, *e.g.*, decreased lung volumes, impaired gas exchange, and secretion mobilization[10-13]. Moreover, mechanical blockage can also be caused by fat deposition in the upper airways[10,13-15]. Notable obesity appears to affect the immune system through a chronic low-grade inflammatory status[2,16]. Adipose tissue, which increases with obesity, is an active endocrine organ that secretes adipocytokines and other inflammatory mediators[2]. Such substances sustain a low-grade systemic inflammation, potentially impairing the immune system's capacity to combat infections[2,8,16,17].

In this review, we presented the numerous pathophysiological implications of obesity and dysfunctional adipose tissue on pulmonary function, the immune system, and pulmonary infections. We summarized the overall impact of obesity on disease outcome and highlighted various emerging and ongoing challenging infections, including, tuberculosis, COVID-19, influenza, and other bacterial or viral infections. Finally, we explored the impact of obesity on various vaccines and suggest strategies to prevent and treat lung infections in individuals with obesity.

EPIDEMIOLOGY OF LUNG DISEASES IN THE PRESENCE OF OBESITY

Obesity has been associated with a variety of respiratory disorders, notably COPD, asthma, obstructive sleep apnea (OSA), pulmonary embolic disease, and aspiration pneumonia[18]. Several epidemiological studies have reported a relationship between respiratory tract infections and obesity, in particular higher prevalence, disease duration, and mortality[17]. Individuals with overweight or obesity had a higher rate of outpatient visits for acute respiratory infections during influenza season than individuals with normal weight, according to a large cohort study from Canada that examined a variety of acute upper (nasopharyngitis, sinusitis, tonsillitis) and lower (bronchitis, pneumonia, influenza, and other viral infections)[19]. In the United States, comparable results were obtained for the risk of community-acquired pneumonia[20] and chronic bronchitis in children, adolescents, and adults[21,22]. More recently, obesity and diabetes were recorded among the high-risk factors for severe COVID-19[23]. Notably, even though obesity is a significant risk factor for the occurrence of acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), in a recent meta-analysis it was recorded that, as opposed to those with a normal body mass index (BMI), ARDS/ALI outcomes were more favorable in the individuals in the obesity group[24]. Overall, individuals with obesity are at increased risk of severe infections, delayed recovery, and complications like ARDS or ALI[10,25].

PATHOPHYSIOLOGICAL BACKGROUND

Although the precise mechanisms linking obesity and an increased risk of pulmonary infections remain unknown, several potential factors have been hypothesized and proposed[10,11,15,26]. These are divided into two categories: First, anatomical-functional changes caused by the mechanical impediment of excess adipose tissue, which blunts respiratory processes and contributes to respiratory diseases[11,15]. And secondly, due to the obesity-related adipose tissue dysfunction/adiposopathy resulting in low-grade inflammation, hyperinsulinemia, hyperglycemia, and hyperleptinemia, all of which contribute to a weakening of both innate and adaptive immunity[17,26] (Figure 1).

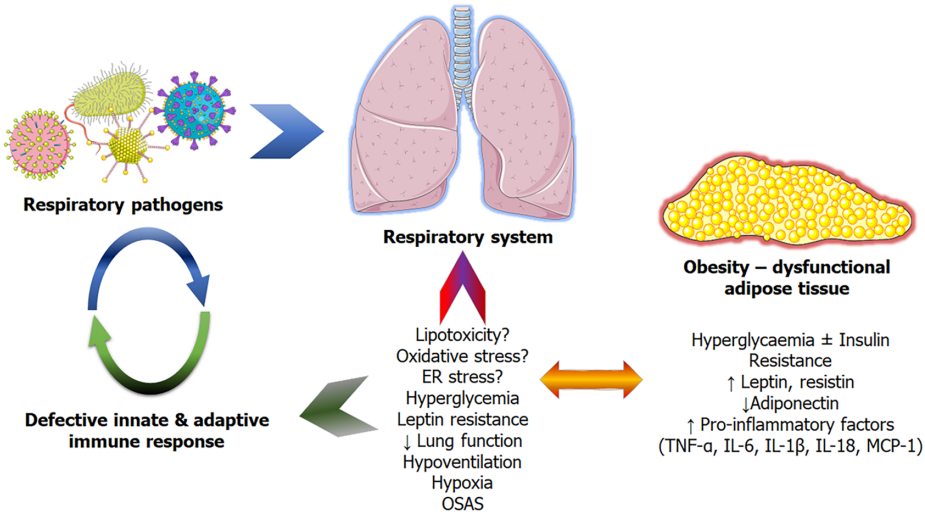


Figure 1 Obesity impacts host-defence against respiratory infections, including direct physiological/mechanical impacts on lung functions but also notably adipose tissue dysfunction, a chronic low grade inflammatory status and potentially blunted immune system responses. ER: Endoplasmic reticulum; IL: Interleukins; MCP-1: Monocyte chemoattractant protein-1; OSAS: Obstructive sleep apnoea syndrome; TNF-α: Tumour necrosis factor alpha. Parts of the figure were drawn by using pictures from Servier Medical. Smart. [cited 3 February 2023]. Available from: smart.servier.com.

Impaired lung function and related mechanisms

Obesity alters the mechanical characteristics of both the lung and thorax substantially, owing mostly to fat accumulation in the mediastinum and abdominal cavities[10]. These result in a decrease in the compliance of the lungs, thorax, and the respiratory system as a whole[10,27]. Moreover, as adipose tissue accumulates in the thoracic and abdominal cavities, the diaphragm's downward movement and the thoracic wall's outward mobility are restricted[10,28]. This affects the breathing pattern, resulting in a significant decrease in both the expiratory reserve volume and the lung's resting volume, known as functional residual capacity (FRC). The decrease in FRC is related to the degree of obesity[10,29]. Importantly, body fat distribution plays an important role, with abdominal and upper body accumulation being independent of the BMI in relation to the worsening of these parameters[12,30,31]. Obesity frequently causes increased respiratory system resistance, as well as airway restriction and closure, and airway hyperresponsiveness, resulting in unfavorable peripheral airway compression/closure results. This interferes with proper ventilation and may result in hypoxemia as a result of mismatch and trapping of airway contents such as mucus and germs, predisposing to infections[10,32-34]. Hypoxia caused by lung impairments, as discussed in the following section, may exacerbate adipose tissue dysfunction[2]. Finally, other obesity-related lung diseases, including COPD, asthma, hypoventilation syndrome, OSA, and obesity and gastroesophageal reflux disease, may further predispose to infections [26,35].

Adiposopathy, chronic low-grade inflammation, and immune system dysfunction

Excessive fat accumulation, adipose tissue (AT) malfunction (distinguished by low-grade inflammation), and ectopic fat deposition, particularly visceral, all play important roles in the pathophysiology of obesity and its comorbidities[36-40]. Adipocyte hypertrophy is characteristic of dysfunctional AT, which itself is linked to persistent low-grade inflammation. AT inflammation is partially caused by adipocytes which are secreting pro-inflammatory cytokines [including tumour necrosis factor alpha (TNF-α), and monocyte chemoattractant protein-1, and various interleukins (IL) notably IL-1β, -6], proinflammatory adipokines (leptin and resistin), and decreased levels of anti-inflammatory adipokines such as adiponectin, but also by the influx of numerous types of specialised, pro-inflammatory immune cells, such as macrophages[2,35,41,42]. Obesity may also have an imbalance in the pro- and anti-inflammatory immune cell ratio, favoring pro-inflammatory immune cell infiltration or activation and thus favoring an inflammatory state[2,16]. Moreover, adiposopathy is characterized by adipocytokine dysregulation, hormonal (insulin, catecholamines) resistance, impaired metabolism, reactive oxygen species (ROS)-induced stress and mitochondrial dysfunction, and anomalous oxygen levels, all of which pertain to ectopic fat accumulation and associated comorbidities[2,38,43,44]. Notably, in the presence of comorbidities such as OSA with hypoxic episodes of severe oxygen deprivation and acute duration, they may act negatively on the dysfunctional adipose tissue, leading to a vicious circle, as many adipocytokines appear to be oxygen-dependent, particularly in individuals with obesity[2,16]. As a result of these events, there is systemic inflammation, which may eventually compromise innate and adaptive immune function[35,45]. Confounding factors that could potentially affect immune response and infection risk independently of BMI could be comorbidities (cardiovascular disease, type 2 diabetes mellitus), altered nutrition (specific low-quality diets), and physical inactivity[9].

Increased TNF-α, IL-1, and IL-6 Levels in adipocytokine dysregulation may result in a weakened immune response[17,45,46]. Additionally, increased circulating leptin levels (a hallmark of obesity, directly proportional to AT mass) could contribute to altered immune responses as many cell types of the innate immune system express leptin receptors[17,47,48]. For instance, monocytes appear to exert a more pronounced pro-inflammatory response, and neutrophils are even more reactive to ROS once they are treated with leptin *in vitro*[17,49,50]. Leptin appears to affect various stages of B and T cell maturation and functions[17,51,52]. Moreover, hyperleptinemia was shown to impact the host defense in humans and murine models *via* effects on neutrophils[17,53]. Metabolic dysfunction associated with hyperinsulinemia may also contribute to immune system dysregulation[17]. It is crucial to highlight that these mechanisms are not necessarily exclusive and that they most likely interact to increase the overall incidence of lung infections in individuals with obesity. Furthermore, the mechanisms may differ based on the individual's underlying health problems and the kind of infection, as will be highlighted in the following sections.

COMMON INFECTIONS AND ONGOING CHALLENGSES

Obesity is associated with an increased risk of several respiratory infections, including tuberculosis, influenza, pneumococcal, staphylococcal, and more recently COVID-19-associated pneumonia[6,35,54]. Obesity and coexisting diabetes raise morbidity from pneumococcal pneumonia and influenza, and notably, diabetes influences tuberculosis control and increases drug resistance as well as mortality[35,55].

Bacterial infections

As the innate immune response, which is the first line of defense against pathogenic bacteria, is likely suppressed because of the persistent low-grade inflammatory status[26], obesity has been shown to have an impact on the outcome of severe bacterial infections[56]. Obesity appears to influence and increase the risk of Streptococcus pneumoniae in a variety of populations, particularly the elderly[57]. It has also been proposed that hyperleptinemia, which is commonly associated with obesity, affects host defense against S. pneumoniae in humans[58]. Obesity is associated with unfavorable clinical outcomes in adults with community-acquired pneumonia of various etiologies[59]. Moreover, a link between BMI and mortality in hospitalized patients with community-acquired pneumonia has been recorded[60]. Finally, diet-induced models of obesity have shown that excess adiposity affects the *in vivo* host defense against *Klebsiella pneumonia*[61].

Viruses of emerging interest

Obesity has been linked to an increased risk of several viral respiratory infections, including the notably recurrent influenza and ongoing COVID-19 pandemics, but also respiratory syncytial virus infection in children[6,62-64].

When it comes to influenza, especially influenza A viral infections, obesity appears to negatively impact humoral immunity[65] and the combined innate and adaptive responses already at the respiratory epithelium level[66-68]. Adiposity may also have a negative impact on influenza virus-related critical illnesses[69]. Immunomodulatory approaches to T cell metabolism have been explored to improve host immunity against influenza-related infections[70].

The potential negative impacts of obesity on COVID-19 have been largely described already[71,72]. Several studies have shown a direct link between obesity and COVID-19's severity and mortality[73,74]. Among other cardiometabolic risk factors, obesity appears to be a significant independent factor [75]. This appears to be the case for unfavorable outcomes in critically ill patients with COVID-19[76].

The COVID-19-associated pathophysiological response is associated with the expression of the angiotensin converting enzyme 2 (ACE2) receptors in target tissues[5,77-79]. Many organ systems, including the lungs, adipose tissue, and blood vessels, express ACE2 receptors[80]. Notably, higher levels of ACE2 have been hypothesized and demonstrated in the adipose tissue of individuals with obesity, suggesting that adipose tissue may play a role in acting as a "reservoir" for SARS-CoV-2[81,82]. The S protein of SARS-CoV-2 is responsible for significant immune response induction in the host and, *via* binding to ACE2 receptors on the target cells, mediates cellular invasion[83]. Likely to influenza viral infections, the role of hyperleptinemia in obesity has been speculated for COVID-19[84]. Finally, obesity-related low-grade chronic inflammation may be directly related to higher expression of ACE2 and pathway-associated components, as well as decreased vitamin D bioavailability, and gut microbiome dysbiosis[85-87].

Vaccinations in individuals with obesity

As demonstrated, obesity has a negative impact on the immune system, and these implications raise concerns about the absence of vaccine-induced immunity in these patients, necessitating a consideration of how this subpopulation might be better protected[88,89]. Cohort studies have shown that, particularly for influenza vaccination, individuals with obesity may have a lower immune response than

those of normal weight[90,91]. Several degrees of evidence also suggest the importance of vaccination against COVID-19 and obesity, also from real-world data[92]. However, overall, the vaccination of individuals with obesity is of paramount importance and should not be avoided, even if reduced responsiveness is suspected.

CONCLUSION

In conclusion, obesity is a major risk factor for several respiratory infections and their severity. Changes in lung function, adipose tissue accumulation and dysfunction, and immune system dysfunction all contribute to the higher risk. It is important for individuals with overweight or obesity to undertake preventive steps to maintain their weight. These include dietary and habitual patterns that can lead and maintain weight loss and if necessary, following failure of these steps to implement medicinal avenues [93-95]. Preventive measures to lower the risk of lung infections including face covering and meticulous vaccinations against respiratory pathogens and frequent medical evaluations. Furthermore, healthcare practitioners should be aware of the increased risk of lung infections in these individuals and act in preventive ways and escalate treatment measures if necessary.

FOOTNOTES

Author contributions: Lempesis IG and Georgakopoulou VE designed research; Lempesis IG and Georgakopoulou VE performed research; Lempesis IG wrote the article; Georgakopoulou VE revised the article.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Greece

ORCID number: Vasiliki E Georgakopoulou 0000-0003-0772-811X.

S-Editor: Li L
L-Editor: A
P-Editor: Chen YX

REFERENCES

1 **Lempesis IG**, Tsilingiris D, Liu J, Dalamaga M. Of mice and men: Considerations on adipose tissue physiology in animal models of obesity and human studies. *Metabol Open* 2022; **15**: 100208 [PMID: 36092796 DOI: 10.1016/j.metop.2022.100208]
2 **Lempesis IG**, van Meijel RLJ, Manolopoulos KN, Goossens GH. Oxygenation of adipose tissue: A human perspective. *Acta Physiol (Oxf)* 2020; **228**: e13298 [PMID: 31077538 DOI: 10.1111/apha.13298]
3 **Hruby A**, Hu FB. The Epidemiology of Obesity: A Big Picture. *Pharmacoeconomics* 2015; **33**: 673-689 [PMID: 25471927 DOI: 10.1007/s40273-014-0243-x]
4 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]
5 **Georgakopoulou VE**, Makrodimitri S, Triantafyllou M, Samara S, Voutsinas PM, Anastasopoulou A, Papageorgiou CV, Spandidos DA, Gkoufa A, Papalexis P, Xenou E, Chelidonis G, Sklapani P, Trakas N, Sipsas NV. Immature granulocytes: Innovative biomarker for SARSCoV2 infection. *Mol Med Rep* 2022; **26** [PMID: 35551416 DOI: 10.3892/mmr.2022.12733]
6 **Goossens GH**, Dicker D, Farpour-Lambert NJ, Frühbeck G, Mullerova D, Woodward E, Holm JC. Obesity and COVID-19: A Perspective from the European Association for the Study of Obesity on Immunological Perturbations, Therapeutic Challenges, and Opportunities in Obesity. *Obes Facts* 2020; **13**: 439-452 [PMID: 32791497 DOI: 10.1159/000510719]
7 **Frühbeck G**, Baker JL, Busetto L, Dicker D, Goossens GH, Halford JCG, Handjieva-Darlenska T, Hassapidou M, Holm JC, Lehtinen-Jacks S, Mullerova D, O'Malley G, Sagen JV, Rutter H, Salas XR, Woodward E, Yumuk V, Farpour-Lambert NJ. European Association for the Study of Obesity Position Statement on the Global COVID-19 Pandemic. *Obes Facts* 2020; **13**: 292-296 [PMID: 32340020 DOI: 10.1159/000508082]
8 **Karlsson EA**, Beck MA. The burden of obesity on infectious disease. *Exp Biol Med (Maywood)* 2010; **235**: 1412-1424

[PMID: 21127339 DOI: 10.1258/ebm.2010.010227]
9 **Dobner J**, Kaser S. Body mass index and the risk of infection - from underweight to obesity. *Clin Microbiol Infect* 2018; **24**: 24-28 [PMID: 28232162 DOI: 10.1016/j.cmi.2017.02.013]
10 **Dixon AE**, Peters U. The effect of obesity on lung function. *Expert Rev Respir Med* 2018; **12**: 755-767 [PMID: 30056777 DOI: 10.1080/17476348.2018.1506331]
11 **Hegewald MJ**. Impact of obesity on pulmonary function: current understanding and knowledge gaps. *Curr Opin Pulm Med* 2021; **27**: 132-140 [PMID: 33394747 DOI: 10.1097/MCP.0000000000000754]
12 **Molani Gol R**, Rafraf M. Association between abdominal obesity and pulmonary function in apparently healthy adults: A systematic review. *Obes Res Clin Pract* 2021; **15**: 415-424 [PMID: 34261619 DOI: 10.1016/j.orcp.2021.06.011]
13 **Brock JM**, Billeter A, Müller-Stich BP, Herth F. Obesity and the Lung: What We Know Today. *Respiration* 2020; **99**: 856-866 [PMID: 33242862 DOI: 10.1159/000509735]
14 **Schwartz AR**, Patil SP, Squier S, Schneider H, Kirkness JP, Smith PL. Obesity and upper airway control during sleep. *J Appl Physiol (1985)* 2010; **108**: 430-435 [PMID: 19875707 DOI: 10.1152/japplphysiol.00919.2009]
15 **Kaw R**, Wong J, Mokhlesi B. Obesity and Obesity Hypoventilation, Sleep Hypoventilation, and Postoperative Respiratory Failure. *Anesth Analg* 2021; **132**: 1265-1273 [PMID: 33857968 DOI: 10.1213/ANE.0000000000005352]
16 **Lempesis IG**, Hoebers N, Essers Y, Jocken JWE, Rouschop KMA, Blaak EE, Manolopoulos KN, Goossens GH. Physiological Oxygen Levels Differentially Regulate Adipokine Production in Abdominal and Femoral Adipocytes from Individuals with Obesity Versus Normal Weight. *Cells* 2022; **11** [PMID: 36428961 DOI: 10.3390/cells11223532]
17 **Pugliese G**, Liccardi A, Graziadio C, Barrea L, Muscogiuri G, Colao A. Obesity and infectious diseases: pathophysiology and epidemiology of a double pandemic condition. *Int J Obes (Lond)* 2022; **46**: 449-465 [PMID: 35058571 DOI: 10.1038/s41366-021-01035-6]
18 **McClean KM**, Kee F, Young IS, Elborn JS. Obesity and the lung: 1. Epidemiology. *Thorax* 2008; **63**: 649-654 [PMID: 18587034 DOI: 10.1136/thx.2007.086801]
19 **Campitelli MA**, Rosella LC, Kwong JC. The association between obesity and outpatient visits for acute respiratory infections in Ontario, Canada. *Int J Obes (Lond)* 2014; **38**: 113-119 [PMID: 23670219 DOI: 10.1038/ijo.2013.57]
20 **Baik I**, Curhan GC, Rimm EB, Bendich A, Willett WC, Fawzi WW. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. *Arch Intern Med* 2000; **160**: 3082-3088 [PMID: 11074737 DOI: 10.1001/archinte.160.20.3082]
21 **Lee YL**, Chen YC, Chen YA. Obesity and the occurrence of bronchitis in adolescents. *Obesity (Silver Spring)* 2013; **21**: E149-E153 [PMID: 23505197 DOI: 10.1002/oby.20262]
22 **Maccioni L**, Weber S, Elgizouli M, Stoehlker AS, Geist I, Peter HH, Vach W, Nieters A. Obesity and risk of respiratory tract infections: results of an infection-diary based cohort study. *BMC Public Health* 2018; **18**: 271 [PMID: 29458350 DOI: 10.1186/s12889-018-5172-8]
23 **Zhou Y**, Chi J, Lv W, Wang Y. Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19). *Diabetes Metab Res Rev* 2021; **37**: e3377 [PMID: 32588943 DOI: 10.1002/dmrr.3377]
24 **Zhi G**, Xin W, Ying W, Guohong X, Shuying L. "Obesity Paradox" in Acute Respiratory Distress Syndrome: Asystematic Review and Meta-Analysis. *PLoS One* 2016; **11**: e0163677 [PMID: 27684705 DOI: 10.1371/journal.pone.0163677]
25 **Huttunen R**, Syrjänen J. Obesity and the risk and outcome of infection. *Int J Obes (Lond)* 2013; **37**: 333-340 [PMID: 22546772 DOI: 10.1038/ijo.2012.62]
26 **Muscogiuri G**, Pugliese G, Laudisio D, Castellucci B, Barrea L, Savastano S, Colao A. The impact of obesity on immune response to infection: Plausible mechanisms and outcomes. *Obes Rev* 2021; **22**: e13216 [PMID: 33719175 DOI: 10.1111/obr.13216]
27 **Pelosi P**, Croci M, Ravagnan I, Tredici S, Pedoto A, Lissoni A, Gattinoni L. The effects of body mass on lung volumes, respiratory mechanics, and gas exchange during general anesthesia. *Anesth Analg* 1998; **87**: 654-660 [PMID: 9728848 DOI: 10.1097/00000539-199809000-00031]
28 **Sugerman H**, Windsor A, Bessos M, Wolfe L. Intra-abdominal pressure, sagittal abdominal diameter and obesity comorbidity. *J Intern Med* 1997; **241**: 71-79 [PMID: 9042096 DOI: 10.1046/j.1365-2796.1997.89104000.x]
29 **Jones RL**, Nzekwu MM. The effects of body mass index on lung volumes. *Chest* 2006; **130**: 827-833 [PMID: 16963682 DOI: 10.1378/chest.130.3.827]
30 **Ochs-Balcom HM**, Grant BJ, Muti P, Sempos CT, Freudenheim JL, Trevisan M, Cassano PA, Iacoviello L, Schünemann HJ. Pulmonary function and abdominal adiposity in the general population. *Chest* 2006; **129**: 853-862 [PMID: 16608930 DOI: 10.1378/chest.129.4.853]
31 **Leone N**, Courbon D, Thomas F, Bean K, Jégo B, Leynaert B, Guize L, Zureik M. Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *Am J Respir Crit Care Med* 2009; **179**: 509-516 [PMID: 19136371 DOI: 10.1164/rccm.200807-1195OC]
32 **Chapman DG**, Berend N, King GG, Salome CM. Increased airway closure is a determinant of airway hyperresponsiveness. *Eur Respir J* 2008; **32**: 1563-1569 [PMID: 18653648 DOI: 10.1183/09031936.00114007]
33 **Pellegrino R**, Gobbi A, Antonelli A, Torchio R, Gulotta C, Pellegrino GM, Dellacà R, Hyatt RE, Brusasco V. Ventilation heterogeneity in obesity. *J Appl Physiol (1985)* 2014; **116**: 1175-1181 [PMID: 24651986 DOI: 10.1152/japplphysiol.01339.2013]
34 **Hedenstierna G**, Santesson J, Norlander O. Airway closure and distribution of inspired gas in the extremely obese, breathing spontaneously and during anaesthesia with intermittent positive pressure ventilation. *Acta Anaesthesiol Scand* 1976; **20**: 334-342 [PMID: 793285 DOI: 10.1111/j.1399-6576.1976.tb05047.x]
35 **Mancuso P**. Obesity and respiratory infections: does excess adiposity weigh down host defense? *Pulm Pharmacol Ther* 2013; **26**: 412-419 [PMID: 22634305 DOI: 10.1016/j.pupt.2012.04.006]
36 **Goossens GH**. The role of adipose tissue dysfunction in the pathogenesis of obesity-related insulin resistance. *Physiol Behav* 2008; **94**: 206-218 [PMID: 18037457 DOI: 10.1016/j.physbeh.2007.10.010]
37 **Blüher M**. Adipose tissue dysfunction contributes to obesity related metabolic diseases. *Best Pract Res Clin Endocrinol*

Metab 2013; **27**: 163-177 [PMID: 23731879 DOI: 10.1016/j.beem.2013.02.005]
38 **Goossens GH**, Blaak EE. Adipose tissue dysfunction and impaired metabolic health in human obesity: a matter of oxygen? *Front Endocrinol (Lausanne)* 2015; **6**: 55 [PMID: 25964776 DOI: 10.3389/fendo.2015.00055]
39 **Goossens GH**. The Metabolic Phenotype in Obesity: Fat Mass, Body Fat Distribution, and Adipose Tissue Function. *Obes Facts* 2017; **10**: 207-215 [PMID: 28564650 DOI: 10.1159/000471488]
40 **Frühbeck G**, Busetto L, Dicker D, Yumuk V, Goossens GH, Hebebrand J, Halford JGC, Farpour-Lambert NJ, Blaak EE, Woodward E, Toplak H. The ABCD of Obesity: An EASO Position Statement on a Diagnostic Term with Clinical and Scientific Implications. *Obes Facts* 2019; **12**: 131-136 [PMID: 30844811 DOI: 10.1159/000497124]
41 **Lee BC**, Lee J. Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance. *Biochim Biophys Acta* 2014; **1842**: 446-462 [PMID: 23707515 DOI: 10.1016/j.bbadis.2013.05.017]
42 **Medzhitov R**. Origin and physiological roles of inflammation. *Nature* 2008; **454**: 428-435 [PMID: 18650913 DOI: 10.1038/nature07201]
43 **Shulman GI**. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N Engl J Med* 2014; **371**: 1131-1141 [PMID: 25229917 DOI: 10.1056/NEJMra1011035]
44 **Frayn KN**, Karpe F. Regulation of human subcutaneous adipose tissue blood flow. *Int J Obes (Lond)* 2014; **38**: 1019-1026 [PMID: 24166067 DOI: 10.1038/ijo.2013.200]
45 **Tilg H**, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006; **6**: 772-783 [PMID: 16998510 DOI: 10.1038/nri1937]
46 **Hornung F**, Rogal J, Loskill P, Löffler B, Deinhardt-Emmer S. The Inflammatory Profile of Obesity and the Role on Pulmonary Bacterial and Viral Infections. *Int J Mol Sci* 2021; **22** [PMID: 33810619 DOI: 10.3390/ijms22073456]
47 **Kalaitzopoulos DR**, Lempesis IG, Samartzis N, Kolovos G, Dedes I, Daniilidis A, Nirgianakis K, Leeners B, Goulis DG, Samartzis EP. Leptin concentrations in endometriosis: A systematic review and meta-analysis. *J Reprod Immunol* 2021; **146**: 103338 [PMID: 34126469 DOI: 10.1016/j.jri.2021.103338]
48 **La Cava A**, Matarese G. The weight of leptin in immunity. *Nat Rev Immunol* 2004; **4**: 371-379 [PMID: 15122202 DOI: 10.1038/nri1350]
49 **Papathanassoglou E**, El-Haschimi K, Li XC, Matarese G, Strom T, Mantzoros C. Leptin receptor expression and signaling in lymphocytes: kinetics during lymphocyte activation, role in lymphocyte survival, and response to high fat diet in mice. *J Immunol* 2006; **176**: 7745-7752 [PMID: 16751422 DOI: 10.4049/jimmunol.176.12.7745]
50 **Caldefie-Chezet F**, Poulin A, Tridon A, Sion B, Vasson MP. Leptin: a potential regulator of polymorphonuclear neutrophil bactericidal action? *J Leukoc Biol* 2001; **69**: 414-418 [PMID: 11261788 DOI: 10.1189/jlb.69.3.414]
51 **Claycombe K**, King LE, Fraker PJ. A role for leptin in sustaining lymphopoiesis and myelopoiesis. *Proc Natl Acad Sci U S A* 2008; **105**: 2017-2021 [PMID: 18250302 DOI: 10.1073/pnas.0712053105]
52 **Martín-Romero C**, Santos-Alvarez J, Goberna R, Sánchez-Margalet V. Human leptin enhances activation and proliferation of human circulating T lymphocytes. *Cell Immunol* 2000; **199**: 15-24 [PMID: 10675271 DOI: 10.1006/cimm.1999.1594]
53 **Ubags ND**, Stapleton RD, Vernooy JH, Burg E, Bement J, Hayes CM, Ventrone S, Zabeau L, Tavernier J, Poynter ME, Parsons PE, Dixon AE, Wargo MJ, Littenberg B, Wouters EF, Suratt BT. Hyperleptinemia is associated with impaired pulmonary host defense. *JCI Insight* 2016; **1** [PMID: 27347561 DOI: 10.1172/jci.insight.82101]
54 **Fisher-Hoch SP**, Mathews CE, McCormick JB. Obesity, diabetes and pneumonia: the menacing interface of non-communicable and infectious diseases. *Trop Med Int Health* 2013; **18**: 1510-1519 [PMID: 24237786 DOI: 10.1111/tmi.12206]
55 **Badawi A**, Gregg B, Vasileva D. Systematic analysis for the relationship between obesity and tuberculosis. *Public Health* 2020; **186**: 246-256 [PMID: 32866737 DOI: 10.1016/j.puhe.2020.06.054]
56 **Alsiö Å**, Nasic S, Ljungström L, Jacobsson G. Impact of obesity on outcome of severe bacterial infections. *PLoS One* 2021; **16**: e0251887 [PMID: 34010307 DOI: 10.1371/journal.pone.0251887]
57 **Frasca D**, McElhaney J. Influence of Obesity on Pneumococcus Infection Risk in the Elderly. *Front Endocrinol (Lausanne)* 2019; **10**: 71 [PMID: 30814978 DOI: 10.3389/fendo.2019.00071]
58 **Hales C**, Burnet L, Coombs M, Collins AM, Ferreira DM. Obesity, leptin and host defence of Streptococcus pneumoniae: the case for more human research. *Eur Respir Rev* 2022; **31** [PMID: 36002169 DOI: 10.1183/16000617.0055-2022]
59 **Viasus D**, Pérez-Vergara V, Carratalà J. Effect of Undernutrition and Obesity on Clinical Outcomes in Adults with Community-Acquired Pneumonia. *Nutrients* 2022; **14** [PMID: 35956411 DOI: 10.3390/nu14153235]
60 **Kim RY**, Glick C, Furmanek S, Ramirez JA, Cavallazzi R. Association between body mass index and mortality in hospitalised patients with community-acquired pneumonia. *ERJ Open Res* 2021; **7** [PMID: 33778059 DOI: 10.1183/23120541.00736-2020]
61 **Mancuso P**, Curtis JL, Weitzel AM, Griffin CA, Bouchard B, Freeman CM, Bridges D, Singer K. Diet-induced obesity in mice impairs host defense against Klebsiella pneumonia in vivo and glucose transport and bactericidal functions in neutrophils in vitro. *Am J Physiol Lung Cell Mol Physiol* 2022; **322**: L116-L128 [PMID: 34850640 DOI: 10.1152/ajplung.00008.2021]
62 **Akiyama N**, Segawa T, Ida H, Mezawa H, Noya M, Tamez S, Urashima M. Bimodal effects of obesity ratio on disease duration of respiratory syncytial virus infection in children. *Allergol Int* 2011; **60**: 305-308 [PMID: 21430434 DOI: 10.2332/allergolint.10-OA-0252]
63 **Moser JS**, Galindo-Fraga A, Ortiz-Hernández AA, Gu W, Hunsberger S, Galán-Herrera JF, Guerrero ML, Ruiz-Palacios GM, Beigel JH; La Red ILI 002 Study Group. Underweight, overweight, and obesity as independent risk factors for hospitalization in adults and children from influenza and other respiratory viruses. *Influenza Other Respir Viruses* 2019; **13**: 3-9 [PMID: 30515985 DOI: 10.1111/irv.12618]
64 **Bhattacharya I**, Ghayor C, Pérez Dominguez A, Weber FE. From Influenza Virus to Novel Corona Virus (SARS-CoV-2)-The Contribution of Obesity. *Front Endocrinol (Lausanne)* 2020; **11**: 556962 [PMID: 33123087 DOI: 10.3389/fendo.2020.556962]
65 **Rojas-Osornio SA**, Cruz-Hernández TR, Drago-Serrano ME, Campos-Rodríguez R. Immunity to influenza: Impact of

obesity. *Obes Res Clin Pract* 2019; **13**: 419-429 [PMID: 31542241 DOI: 10.1016/j.orcp.2019.05.003]

66 **Honce R**, Schultz-Cherry S. Impact of Obesity on Influenza A Virus Pathogenesis, Immune Response, and Evolution. *Front Immunol* 2019; **10**: 1071 [PMID: 31134099 DOI: 10.3389/fimmu.2019.01071]

67 **Green WD**, Beck MA. Obesity Impairs the Adaptive Immune Response to Influenza Virus. *Ann Am Thorac Soc* 2017; **14**: S406-S409 [PMID: 29161078 DOI: 10.1513/AnnalsATS.201706-447AW]

68 **Paich HA**, Sheridan PA, Handy J, Karlsson EA, Schultz-Cherry S, Hudgens MG, Noah TL, Weir SS, Beck MA. Overweight and obese adult humans have a defective cellular immune response to pandemic H1N1 influenza A virus. *Obesity (Silver Spring)* 2013; **21**: 2377-2386 [PMID: 23512822 DOI: 10.1002/oby.20383]

69 **Kalil AC**, Thomas PG. Influenza virus-related critical illness: pathophysiology and epidemiology. *Crit Care* 2019; **23**: 258 [PMID: 31324202 DOI: 10.1186/s13054-019-2539-x]

70 **Greene E**, MacIver NJ. Targeting T cell (oxidative) metabolism to improve immunity to viral infection in the context of obesity. *Front Immunol* 2022; **13**: 1025495 [PMID: 36275776 DOI: 10.3389/fimmu.2022.1025495]

71 **Albashir AAD**. The potential impacts of obesity on COVID-19. *Clin Med (Lond)* 2020; **20**: e109-e113 [PMID: 32571783 DOI: 10.7861/clinmed.2020-0239]

72 **Yu W**, Rohli KE, Yang S, Jia P. Impact of obesity on COVID-19 patients. *J Diabetes Complications* 2021; **35**: 107817 [PMID: 33358523 DOI: 10.1016/j.jdiacomp.2020.107817]

73 **Abumweis S**, Alrefai W, Alzoughool F. Association of obesity with COVID-19 diseases severity and mortality: A meta-analysis of studies. *Obes Med* 2022; **33**: 100431 [PMID: 35702736 DOI: 10.1016/j.obmed.2022.100431]

74 **Sjögren L**, Stenberg E, Thuccani M, Martikainen J, Rylander C, Wallenius V, Olbers T, Kindblom JM. Impact of obesity on intensive care outcomes in patients with COVID-19 in Sweden-A cohort study. *PLoS One* 2021; **16**: e0257891 [PMID: 34644316 DOI: 10.1371/journal.pone.0257891]

75 **Fayol A**, Livrozet M, Pereira H, Diehl JL, Lebeaux D, Arlet JB, Cholley B, Carette C, Carves JB, Czernichow S, Hauw C, Hamada SR, Jannot AS, Volle G, Masurkar N, Mirault T, Planquette B, Sanchez O, Châtellier G, Azizi M, Hulot JS. Cardiometabolic Disorders and the Risk of Critical COVID-19 as Compared to Influenza Pneumonia. *J Clin Med* 2021; **10** [PMID: 34640638 DOI: 10.3390/jcm10194618]

76 **Rossi AP**, Gottin L, Donadello K, Schweiger V, Nocini R, Taiana M, Zamboni M, Polati E. Obesity as a risk factor for unfavourable outcomes in critically ill patients affected by Covid 19. *Nutr Metab Cardiovasc Dis* 2021; **31**: 762-768 [PMID: 33549439 DOI: 10.1016/j.numecd.2020.11.012]

77 **Georgakopoulou VE**, Gkoufa A, Damaskos C, Papalexis P, Pierrakou A, Makrodimitri S, Sypsa G, Apostolou A, Asimakopoulou S, Chlapoutakis S, Sklapani P, Trakas N, Spandidos DA. COVID-19-associated acute appendicitis in adults. A report of five cases and a review of the literature. *Exp Ther Med* 2022; **24**: 482 [PMID: 35761802 DOI: 10.3892/etm.2022.11409]

78 **Georgakopoulou VE**, Avramopoulos P, Papalexis P, Bitsani A, Damaskos C, Garmpi A, Venetikou MS, Paramythiotis D, Karlafti E, Sklapani P, Trakas N, Spandidos DA. COVID-19 induced hypoparathyroidism: A case report. *Exp Ther Med* 2022; **23**: 346 [PMID: 35401797 DOI: 10.3892/etm.2022.11276]

79 **Georgakopoulou VE**, Lembessis P, Skarlis C, Gkoufa A, Sipsas NV, Mavragani CP. Hematological Abnormalities in COVID-19 Disease: Association With Type I Interferon Pathway Activation and Disease Outcomes. *Front Med (Lausanne)* 2022; **9**: 850472 [PMID: 35372456 DOI: 10.3389/fmed.2022.850472]

80 **Ozkurt Z**, Çınar Tanrıverdi E. COVID-19: Gastrointestinal manifestations, liver injury and recommendations. *World J Clin Cases* 2022; **10**: 1140-1163 [PMID: 35211548 DOI: 10.12998/wjcc.v10.i4.1140]

81 **Herta T**, Berg T. COVID-19 and the liver - Lessons learned. *Liver Int* 2021; **41** Suppl 1: 1-8 [PMID: 34155789 DOI: 10.1111/liv.14854]

82 **Pasquarelli-do-Nascimento G**, Braz-de-Melo HA, Faria SS, Santos IO, Kobinger GP, Magalhães KG. Hypercoagulopathy and Adipose Tissue Exacerbated Inflammation May Explain Higher Mortality in COVID-19 Patients With Obesity. *Front Endocrinol (Lausanne)* 2020; **11**: 530 [PMID: 32849309 DOI: 10.3389/fendo.2020.00530]

83 **Georgakopoulou VE**, Gkoufa A, Garmpis N, Makrodimitri S, Papageorgiou CV, Barlampa D, Garmpi A, Chiapoutakis S, Sklapani P, Trakas N, Damaskos C. COVID-19 and Acute Pancreatitis: A Systematic Review of Case Reports and Case Series. *Ann Saudi Med* 2022; **42**: 276-287 [PMID: 35933608 DOI: 10.5144/0256-4947.2022.276]

84 **Guglielmi V**, Colangeli L, D'Adamo M, Sbraccia P. Susceptibility and Severity of Viral Infections in Obesity: Lessons from Influenza to COVID-19. Does Leptin Play a Role? *Int J Mol Sci* 2021; **22** [PMID: 33804765 DOI: 10.3390/ijms22063183]

85 **Belančić A**, Kresović A, Rački V. Potential pathophysiological mechanisms leading to increased COVID-19 susceptibility and severity in obesity. *Obes Med* 2020; **19**: 100259 [PMID: 32501427 DOI: 10.1016/j.obmed.2020.100259]

86 **Belančić A**. Gut microbiome dysbiosis and endotoxemia - Additional pathophysiological explanation for increased COVID-19 severity in obesity. *Obes Med* 2020; **20**: 100302 [PMID: 32984641 DOI: 10.1016/j.obmed.2020.100302]

87 **Lempesis IG**, Karlafti E, Papalexis P, Fotakopoulos G, Tarantinos K, Lekakis V, Papadakos SP, Cholongitas E, Georgakopoulou VE. COVID-19 and liver injury in individuals with obesity. *World J Gastroenterol* 2023; **29**: 908-916 [PMID: 36844135 DOI: 10.3748/wjg.v29.i6.908]

88 **Painter SD**, Ovsyannikova IG, Poland GA. The weight of obesity on the human immune response to vaccination. *Vaccine* 2015; **33**: 4422-4429 [PMID: 26163925 DOI: 10.1016/j.vaccine.2015.06.101]

89 **Tagliabue C**, Principi N, Giavoli C, Esposito S. Obesity: impact of infections and response to vaccines. *Eur J Clin Microbiol Infect Dis* 2016; **35**: 325-331 [PMID: 26718941 DOI: 10.1007/s10096-015-2558-8]

90 **Clarke M**, Mathew SM, Giles LC, Pena AS, Barr IG, Richmond PC, Marshall HS. A Prospective Study Investigating the Impact of Obesity on the Immune Response to the Quadrivalent Influenza Vaccine in Children and Adolescents. *Vaccines (Basel)* 2022; **10** [PMID: 35632458 DOI: 10.3390/vaccines10050699]

91 **Jagielska AM**, Brydak LB, Nitsch-Osuch AS. Immunogenicity of Split Inactivated Quadrivalent Influenza Vaccine in Adults with Obesity in the 2017/2018 Season. *Med Sci Monit* 2021; **27**: e929572 [PMID: 33994536 DOI: 10.12659/MSM.929572]

92 **Piernas C**, Patone M, Astbury NM, Gao M, Sheikh A, Khunti K, Shankar-Hari M, Dixon S, Coupland C, Aveyard P, Hippisley-Cox J, Jebb SA. Associations of BMI with COVID-19 vaccine uptake, vaccine effectiveness, and risk of severe COVID-19 outcomes after vaccination in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2022; **10**: 571-580 [PMID: 35780805 DOI: 10.1016/S2213-8587(22)00158-9]

93 **Sagris M**, Kokkinidis DG, Lempesis IG, Giannopoulos S, Rallidis L, Mena-Hurtado C, Bakoyiannis C. Nutrition, dietary habits, and weight management to prevent and treat patients with peripheral artery disease. *Rev Cardiovasc Med* 2020; **21**: 565-575 [PMID: 33388001 DOI: 10.31083/j.rcm.2020.04.202]

94 **Lempesis IG**, Liu J, Dalamaga M. The catcher in the gut: Tirzepatide, a dual incretin analog for the treatment of type 2 diabetes mellitus and obesity. *Metabol Open* 2022; **16**: 100220 [PMID: 36530219 DOI: 10.1016/j.metop.2022.100220]

95 **Vallianou NG**, Tsilingiris D, Kounatidis D, Lempesis IG, Karampela I, Dalamaga M. Sodiumglucose cotransporter2 inhibitors in obesity and associated cardiometabolic disorders: where do we stand? *Pol Arch Intern Med* 2022; **132** [PMID: 36094176 DOI: 10.20452/pamw.16342]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 2934-2944

DOI: 10.12998/wjcc.v11.i13.2934

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Case Control Study

Association of C-reactive protein and complement factor H gene polymorphisms with risk of lupus nephritis in Chinese population

Qiu-Yu Li, Jian-Min Lv, Xiao-Ling Liu, Hai-Yun Li, Feng Yu

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Reda R, Italy; Tanaka H, Japan

Received: September 16, 2022
Peer-review started: September 16, 2022
First decision: October 11, 2022
Revised: October 25, 2023
Accepted: February 21, 2023
Article in press: February 21, 2023
Published online: May 6, 2023

Qiu-Yu Li, Department of Respiratory and Critical Care Medicine, Peking University Third Hospital, Beijing 100191, China

Jian-Min Lv, School of Basic Medical Sciences, Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China

Xiao-Ling Liu, School of Life Sciences, Lanzhou University, Lanzhou 730000, Gansu Province, China

Hai-Yun Li, School of Basic Medical Sciences, Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China

Feng Yu, Department of Medicine, Peking University First Hospital, Beijing 100034, China

Corresponding author: Hai-Yun Li, PhD, Assistant Professor, School of Basic Medical Sciences, Xi'an Jiaotong University, No. 76 Yanta West Road, Xi'an 710061, Shaanxi Province, China. lihaiy@xjtu.edu.cn

Abstract

BACKGROUND

Complement overactivation is a major driver of lupus nephritis (LN). Impaired interactions of C-reactive protein (CRP) with complement factor H (CFH) have been shown as a pathogenic mechanism that contributes to the overactivation of complement in LN. However, genetic variations of neither CRP nor CFH show consistent influences on the risk of LN.

AIM

To examine whether genetic variations of CRP and CFH in combination can improve the risk stratification in Chinese population.

METHODS

We genotyped six CRP single nucleotide polymorphisms (SNPs) (rs1205, rs3093062, rs2794521, rs1800947, rs3093077, and rs1130864) and three CFH SNPs (rs482934, rs1061170, and rs1061147) in 270 LN patients and 303 healthy subjects.

RESULTS

No linkage was found among CRP and CFH SNPs, indicating lack of genetic interactions between the two genes. Moreover, CRP and CFH SNPs, neither individually nor in combination, are associated with the risk or clinical manifest-

ations of LN. Given the unambiguous pathogenic roles of the two genes.

CONCLUSION
These findings suggest that the biological effects of most genetic variations of CRP and CFH on their expressions or activities are not sufficient to influence the disease course of LN.

Key Words: Systemic lupus erythematosus; Lupus nephritis; C-reactive protein; Complement factor H; Single nucleotide polymorphism.

Core Tip: In spite of the unambiguous pathogenic roles of C-reactive protein (CRP)and complement factor H (CFH) in lupus nephritis (LN), our present study involving a Chinese population has failed to reveal any significant associations of their genetic variations with LN risk. These findings suggest that most genetic variations of CRP and CFH might possess limited biological effects on their expressions or activities and are thus not sufficient to influence the disease course of LN. Overall, we concluded that genetic variations of CRP and CFH could not be used to improve the risk stratification of LN in Chinese population.

Citation: Li QY, Lv JM, Liu XL, Li HY, Yu F. Association of C-reactive protein and complement factor H gene polymorphisms with risk of lupus nephritis in Chinese population. *World J Clin Cases* 2023; 11(13): 2934-2944
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/2934.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.2934

INTRODUCTION

As an autoimmune disease, the pathogenesis of systemic lupus erythematosus (SLE) involves clearance defect of apoptotic cells, uncontrolled activation of complement and massive production of autoantibodies[1,2].Previously studies have shown that 40% of SLE patients have clinical manifestations of renal dysfunction and that about 80% of SLE patients have different degrees of pathological renal damage, including lupus nephritis (LN), a common and severe complication of SLE, which is regarded as the main factor for the poor prognosis of patients[3-5].

reactive protein (CRP) is an acute phase reactant and a commonly used clinical marker of inflammation[6-10]. Besides, CRP could promote the elimination of damaged cells or pathogens by activating and regulating the complement system. Previous clinical studies suggest that CRP and SLE/LN have certain correlations. Firstly, CRP gene locates in the chromosome 1q23, an SLE linkage region[11,12]. Secondly, elevation of CRP levels is generally impaired in SLE patients especially those with kidney and skin involvement[13]. Thirdly, CRP autoantibodies can be detected in a considerable number of patients, which may relate to abnormal plasma levels in SLE[14-16]. Lastly, several animal studies on lupus-prone mouse strain (NZB/NZW) revealed that human CRP could help to produce less proteinuria and prolonged survival[17-19]. In the past decades, studies have been made to clarify the associations of CRP Single Nucleotide Polymorphisms (SNPs) with SLE susceptibility, while conclusions remained inconsistent[20-24]. Moreover, no CRP SNPs studies have been performed in the Chinese population.

In addition to CRP, complement factor H (CFH), a factor that negatively regulates alternative complement pathway, is another candidate associated with SLE. Firstly, CFH deficiency has been proven to accelerate the development of LN[25], and serum CFH level was observed to be associated with clinical and pathological activities of SLE patients with LN[26]. Secondly, several families suffering from SLE were reported to possess CFH deficiency or mutations[27,28]. Genetic variations of CFH can sometimes affect its bioactivities, in which several exotic SNPs were found to be related to various human diseases[29]. Among CFH SNPs, rs1061170 corresponds to a CFH variant Tyr402His, which exhibits impaired CFH-CRP binding efficiency. Because CRP could inhibit the complement overactivation by recruiting CFH, so Tyr402His theoretically results in dysregulated complement activation[30].

Despite that LN is a complement-related disease, and that both CRP and CFH are involved in complement regulation, it remains unclear whether CRP and CFH SNPs directly impact the pathogenesis of LN. In this scenario, we carried out the present study, in which six CRP SNPs and three CFH SNPs were genotyped in 270 LN patients and 303 healthy controls of a Chinese cohort. Association analysis was subsequently performed for these SNPs and LN risk from the perspectives of allele, genotype, combined SNPs and haplotype. As far as we know, this is the first study to consider SNPs of CRP and CFH together when evaluating their relationship with LN risk in the Chinese population. Our data show that SNPs of both genes have no significant association with LN risk. Given the

unambiguous pathogenic role of the two genes, these findings suggest that the biological effects of genetic variations of CRP and CFH on their expression or activities are not sufficient to influence the disease course of LN in the Chinese population.

MATERIALS AND METHODS

Participators

Renal histopathological data of 270 patients with renal biopsy-proven LN, diagnosed between January 2000 and July 2017 in Peking University First Hospital, were reviewed and reclassified according to the International Society of Nephrology and Renal Pathology Society (ISN/RPS) 2003 classification[31]. 303 age and gender matched healthy controls were collected. The work was approved by the Ethics Committee of Peking University First Hospital [Approval No. 2017(1333)].

DNA Preparation and SNP Genotyping.

Blood samples of the 270 SLE patients and 303 healthy controls of Chinese Han individuals were collected with the approval of the Ethics Committee of Peking University First Hospital. Human genomic DNA was extracted using Qiagen Blood DNA Kit (QIAGEN China, Shanghai) according to the manufacturer's instructions. Subsequently, the CRP SNPs (rs1205, rs3093077, rs3091244, rs1130864, rs1800947, rs2794521), and CFH SNPs (rs1061170, rs482934 and rs1061147) was genotyped by SNaPshot (ABI PRISM® SNaPshot™ Multiplex Kit, ABI) with specific primers.

Evaluation of Clinical, Laboratory and Renal Pathological Indexes of LN Patients

For clinical evaluation, the disease activities of all patients were assessed by the SLE Disease Activity Index[32,33]. Briefly, the following items were collected and analyzed: Sex, fever, malar rash, photosensitivity, oral ulcer, alopecia, arthritis, serositis, neurologic disorder, anemia, leukocytopenia, thrombocytopenia, hematuria, and leukocyturia. For laboratory assessment, the following items were collected as we previously reported[34]: Complete blood count, plasma lactate dehydrogenase, liver enzymes, peripheral blood smear, urine analysis, serum creatinine, serum antinuclear antibodies, anti-double-stranded DNA antibodies, anti-extractable nuclear antigen antibodies, anti-cardiolipin antibodies and C3. For renal histopathology, all renal biopsy specimens were examined by light microscopy, direct immunofluorescence, and electron microscopy techniques as our previous reports [35]. All samples were double-blind reviewed by two experienced pathologists based on the 2003 ISN/RPS recommendation on LN classification[36]. The pathologists classified and scored the biopsies separately, especially for the activity indices, chronicity indices. Differences in scoring between pathologists were resolved by re-reviewing the biopsies and thus reaching a consensus. Renal histopathological data of 270 LN patients was classified according to the ISN/RPS 2003 classification, which was an improved version of World Health Organization (WHO)[37].

Statistical Analysis

Hardy-Weinberg equilibrium testing was performed for all healthy controls using a chi-squared test. Distributions of genotype, allele and haplotype were compared between control and case groups using Pearson's chi-squared test or Fisher's exact test. For comparison of clinical, laboratory and pathological features of patients, student's *t*-test and one way analysis of variance (ANOVA) were used. A P value less than 0.05 was considered to be significant. Pairwise Linkage Disequilibrium (LD) and haplotype analysis were both conducted using the SHEs is platform[38]. SNP pairs with D' value great than 0.8 and r^2 value great than 0.33 were considered to be in significant LD. Meta-analysis was performed by using Stata 15 software. Relative risks of SLE/LN were estimated according to ORs with 95% CIs. The inconsistency index I^2 was calculated to quantify the heterogeneity: If $I^2 < 50\%$, suggesting that the degree of heterogeneity was low, and the meta-analysis was performed using the fixed effect model; otherwise, the random effects model was used. $P > 0.05$ means no statistical significance.

RESULTS

Association of CRP SNPs and haplotypes with LN risk

Six CRP SNPs (rs1205, rs3093077, rs3091244, rs1130864, rs1800947 and rs2794521) were genotyped in 270 LN patients and 303 healthy controls (Figure 1). Chi-squared test showed that genotype frequency distributions of CRP SNPs in all healthy controls were all in Hardy-Weinberg equilibrium (Supplementary Table 1). In subsequent comparisons of case and control groups (Table 1), none of the alleles or genotypes was observed to be significantly associated with the SLE risk ($P > 0.05$). In further analysis, we examined the effects of CRP SNP combinations, and again failed to observe any significant difference in genotype distributions of LN patients and healthy controls (Supplementary Table 2).

Table 1 Genotype and allele frequencies of C-reactive protein single nucleotide polymorphisms, *n* (%)

Genotype	LN	Normal	*P* value	Allele	LN	Normal	*P* value
rs1205 (C>T)							
CC	53 (19.63)	49 (16.17)	0.469	C	245 (45.37)	254 (41.91)	0.239
CT	139 (51.48)	156 (51.49)		T	295 (54.63)	352 (58.09)	
TT	78 (28.89)	98 (32.34)					
rs3093077 (A>C)							
AA	173 (64.07)	208 (68.65)	0.436	A	436 (80.74)	502 (82.84)	0.358
AC	90 (33.33)	86 (28.38)		C	104 (19.26)	104 (17.16)	
CC	7 (2.59)	9 (2.97)					
rs3091244 (C>T>A)							
CC	153 (56.67)	180 (59.41)	0.935[1]	C	410 (75.93)	467 (77.06)	0.712
CT	23 (8.52)	28 (9.24)		T	29 (5.37)	36 (5.94)	
CA	81 (30.00)	79 (26.07)		A	101 (18.70)	103 (17.00)	
TT	1 (0.37)	1 (0.33)					
TA	4 (1.48)	6 (1.98)					
AA	8 (2.96)	9 (2.97)					
rs1130864 (G>A)							
GG	241 (89.26)	270 (89.11)	0.797[1]	G	509 (94.26)	572 (94.39)	0.924
GA	27 (10.00)	32 (10.56)		A	31 (5.74)	34 (5.61)	
AA	2 (0.74)	1 (0.33)					
rs1800947 (C>G)							
CC	245 (90.74)	273 (90.10)	1.000[1]	C	515 (95.37)	575 (94.88)	0.703
CG	25 (9.26)	29 (9.57)		G	25 (4.63)	31 (5.12)	
GG	0 (0.00)	1 (0.33)					
rs2794521 (T>C)							
TT	187 (69.26)	222 (73.27)	0.177	T	446 (82.59)	520 (85.81)	0.135
TC	72 (26.67)	76 (25.08)		C	94 (17.41)	86 (14.19)	
CC	11 (4.07)	5 (1.65)					

[1]Fisher's exact test; unmarked, Pearson's chi-squared test.
LN: Lupus nephritis.

Subsequently, pairwise LD analysis was conducted for CRP SNPs in healthy controls. Of all SNP pairs, rs3091244/rs3093077 and rs3091244/rs1205 pairs were found to be in significant LD (Table 2). Considering that SNP haplotype may provide more informative details, CRP haplotypes were thus included for further investigation. Given the acceptable number, we included all 6 CRP SNPs in the haplotype analysis. Finally, 6 CRP haplotypes were observed at frequencies greater than 3.0% in both healthy controls and LN patients. However, no significant differences were found in the distribution frequencies of those haplotypes between the two groups (Table 3).

To further confirm whether these CRP SNPs are indeed unrelated to LN in the present population, we thus further checked the association of these SNPs with clinical, laboratory and pathological features of all patients (Supplementary Tables 3-6). In line with the conclusions above, most indexes exhibited no significant differences between genotypes of these SNPs. Notably, WHO classification for all LN patients was performed and association between pathological subclass and SNPs were further analyzed, whereas no significant differences were observed. However, several items showed differences, which might imply potential relevance of these SNPs with LN to some extent, suggesting that conclusion should cautiously draw.

Table 2 Pairwise linkage disequilibrium analysis of C-reactive protein single nucleotide polymorphisms in healthy controls

r^2\D'	rs3093077	rs1205	rs1130864	rs1800947	rs3091244	rs2794521
rs3093077		1.000	0.990	0.985	**0.979**	0.748
rs1205	0.278		0.999	0.999	**0.984**	1.000
rs1130864	0.012	0.082		0.986	1.000	0.974
rs1800947	0.011	0.039	0.003		0.993	0.986
rs3091244	**0.675**	**0.360**	0.212	0.014		0.996
rs2794521	0.019	0.229	0.009	0.009	0.044	

D′ and r^2 are listed on the top right and lower left, respectively. Bold represents pairs with D′ values great than 0.8 and r^2 values great than 0.33.

Table 3 Association of C-reactive protein haplotypes with risk of lupus nephritis

CRP haplotype		SLE-freq (%, *n* = 270)	Normal-freq (%, *n* = 303)	χ^2	Overall *P* value
H1	G G G G T A	17.8	16.7	3.293	0.655
H2	T A G C G A	4.3	5.1		
H3	T A G G G A	50.2	52.8		
H4	T G A G A A	5.4	5.6		
H5	T G G G G A	4.1	5.1		
H6	T G G G G G	16.6	13.7		

Single nucleotide polymorphism order in the haplotypes is arranged according to their positions in the chromosome (rs3093077, rs1205, rs1130864, rs1800947, rs3091244, rs2794521). Only the significant haplotypes (frequency > 3.0%) are shown. CRP: C-reactive protein; SLE: Systemic lupus erythematosus.

Association of CFH SNPs and haplotypes with LN risk

Similarly, we subsequently genotyped 3 CFH SNPs, namely rs1061170, rs482934 and rs1061147, in 270 LN patients and 303 healthy controls (Figure 1). After Hardy-Weinberg equilibrium was checked for all genotype frequencies of controls (Supplementary Table 7), association of CFH polymorphism with LN risk were examined. Of note, no significant enrichment or depletion of allele and genotype distribution has been observed in LN patients (Table 4). In further exploration, pairwise LD for those CFH SNPs was examined as before. Dramatically, all three SNP pairs were found to be in strong LD (Table 5). Based on this, haplotype analysis was conducted, in which two CFH haplotypes were observed at frequencies greater than 3.0% in both healthy controls and LN patients. However, no significant associations were found between those two haplotypes and LN risk (Table 6).

In further analysis, we checked the association of rs1061170 with clinical, laboratory and pathological features of all LN patients (Supplementary Table 8). Similar to CRP SNPs, except for a few items, most indexes exhibited no significant differences between genotypes of these SNPs.

Association of CRP-CFH SNP combinations with LN risk

Given the key roles of complement overactivation in SLE pathogenesis and the capacity of CRP to inhibit this process *via* interaction with CFH, we next asked whether any potential associations could be found in SNP combinations of CRP and CFH. Specifically, CFH SNP rs1061170, which corresponds to a variant Tyr402His with impaired capacity to bind CRP[39,40], was combined with 6 CRP SNPs and evaluated individually. However, we failed to observe any significant associations in all SNP combinations included (Table 7). Besides, cross pairs of the CRP and CFH SNPs were further included for pairwise LD evaluation, in which no significant LD was observed (Supplementary Table 9).

DISCUSSION

In the past decades, studies have been focused on revealing the associations of CRP/CFH genetic variations with SLE/LN[41]. However, those studies were mainly based on the European or American populations, and often gained inconsistent conclusions. Moreover, although CRP/CFH interaction

Table 4 Genotype and allele frequencies of complement factor H single nucleotide polymorphisms, *n* (%)

Genotype	LN	Normal	*P* value	Allele	LN	Normal	*P* value
rs1061170 (T>C)							
TT	235 (87.04)	258 (85.15)	0.220[1]	T	503 (93.15)	561 (92.57)	0.707
TC	33 (12.22)	45 (14.85)		C	37 (6.85)	45 (7.43)	
CC	2 (0.74)	0 (0.00)					
rs482934 (A>C)							
AA	236 (87.41)	258 (85.15)	0.189[1]	A	504 (0.93)	561 (0.93)	0.617
AC	32 (11.85)	45 (14.85)		C	36 (0.07)	45 (0.07)	
CC	2 (0.74)	0 (0.00)					
rs1061147 (C>A)							
CC	235 (87.04)	257 (84.82)	0.194[1]	C	503 (0.93)	560 (0.92)	0.63
CA	33 (12.22)	46 (15.18)		A	37 (0.07)	46 (0.08)	
AA	2 (0.74)	0 (0.00)					

[1]Fisher's exact test; unmarked, Pearson's chi-squared test.
LN: Lupus nephritis.

Table 5 Pairwise linkage disequilibrium analysis of complement factor H single nucleotide polymorphisms in healthy controls

r^2\D'	rs1061147	rs482934	rs1061170
rs1061147		**0.976**	**1.000**
rs482934	**0.930**		**0.976**
rs1061170	**0.977**	**0.952**	

D′ and r^2 are listed on the top right and lower left, respectively. Bold represents pairs with D′ values great than 0.8 and r^2 values great than 0.33.

Table 6 Association of complement factor H haplotypes with risk of lupus nephritis

CRP Haplotype		LN-freq (%, *n* = 270)	Normal-freq (% *n* = 303)	χ^2	Overall *P* value
H1	A C G	6.3	7.3	0.426	0.514
H2	C A A	93.3	92.2		

SNP order in the haplotypes is arranged according to their positions in the chromosome.
CRP: C-reactive protein; LN: Lupus nephritis.

theoretically plays a role in LN pathogenesis, they have not been considered together when evaluating the association of their genetic variations with the LN risk.

In this study, we enrolled 6 CRP SNPs and 3 CFH SNPs of a Chinese cohort, and studied their relationship with LN risk, which has not yet been systematically reported. Our study revealed that there were no significant associations between these SNPs and LN susceptibility in the Chinese population. All patients in this study were selected from the same center and their diagnosis were all confirmed by renal biopsy. Moreover, the complete clinical, laboratory and pathological indexes were also included to test the results. Therefore, although no statistical associations were observed in our study, valid and useful information could still be revealed.

In addition, these negative results are generally consistent with the conclusions of previous researches to a large extent. Among the 6 CRP SNPs, rs1800947[20,24-26] and rs2794521[23,25] were included in several studies, which were repeatedly reported to be unrelated to SLE in various populations, consistent with our results. For rs1205[20,21,24-26], rs3091244[20,21,24,25] and rs1130864 [20-22], conclusions remained inconsistent among these studies, which might rationalize the existence of our negative results to some extent. For the CFH SNPs, Zhao *et al*[29]evaluated an Asian group

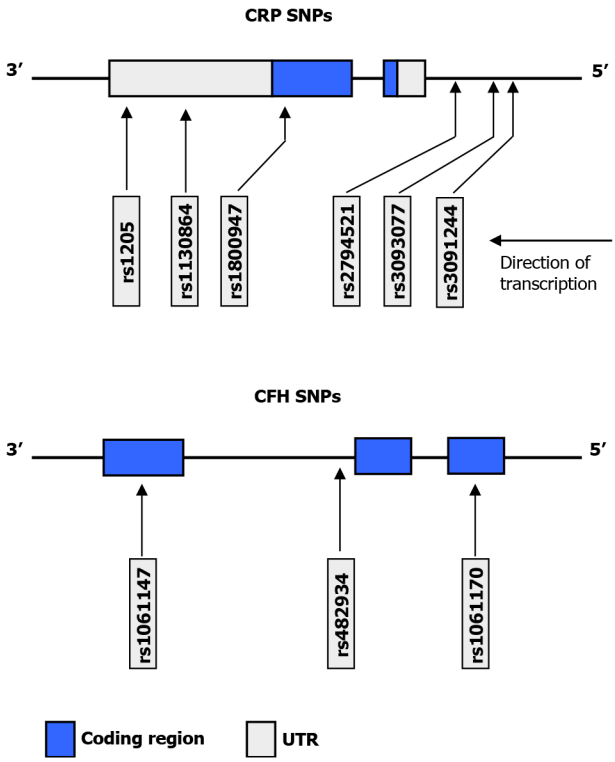
Table 7 Genotype frequencies of combined single nucleotide polymorphisms of C-reactive protein and complement factor H, *n* (%)

CRP-CFH genotype combination	LN	Normal	*P* value
rs1205 + rs1061170			
CCTT	46 (17.10)	45 (14.85)	0.105
CCTC	7 (2.60)	4 (1.32)	
CTTT	124 (46.10)	125 (41.25)	
CTTC	14 (5.20)	31 (10.23)	
TTTT	65 (24.16)	88 (29.04)	
TTTC	13 (4.83)	10 (3.30)	
rs3093077 + rs1061170			
AATT	150 (56.39)	180 (59.80)	0.322
AATC	23 (8.65)	28 (9.30)	
ACTT	81 (30.45)	71 (23.59)	
ACTC	8 (3.01)	15 (4.98)	
CCTT	4 (1.50)	7 (2.33)	
rs3091244 + rs1061170			
CCTT	133 (50.57)	155 (52.19)	0.756
CCTC	21 (7.98)	25 (8.42)	
CTTT	21 (7.98)	25 (8.42)	
CATT	71 (27.00)	64 (21.55)	
CATC	9 (3.42)	15 (5.05)	
TATT	4 (1.52)	6 (2.02)	
AATT	4 (1.52)	7 (2.36)	
rs1130864 + rs1061170			
GGTT	208 (78.49)	228 (76.25)	0.772
GGTC	32 (12.08)	42 (14.05)	
GATT	25 (9.43)	29 (9.70)	
rs1800947 + rs1061170			
CCTT	214 (80.75)	232 (77.85)	0.655
CCTC	30 (11.32)	41 (13.76)	
CGTT	21 (7.92)	25 (8.39)	
rs2794521 + rs1061170			
TTTT	160 (59.93)	187 (61.92)	0.431
TTTC	26 (9.74)	35 (11.59)	
TCTT	66 (24.72)	67 (22.19)	
TCTC	6 (2.25)	9 (2.98)	
CCTT	9 (3.37)	4 (1.32)	

Pearson's chi-squared test.
CRP: C-reactive protein; CFH: Complement factor H; LN: Lupus nephritis.

involving 200 Chinese SLE cases and found no significant association between rs1061147 and SLE (without LN). Tan *et al*[41] enrolled 334 LN patients, 269 SLE patients without LN and 350 healthy controls from China, but failed to observe any significant differences in allele and genotype frequencies of rs1061170 among groups. Both conclusions were consistent with our present findings.

A



B

Characteristics	Value
Clinical evaluation	
Number of patient	241
Gender (male/female)	40/201
Age (mean ± SD) (years)	32 ± 12.04
Follow-up time (months, median, range)	38 (18-38)
Fever (non-infectious) No. (%)	52 (21.58)
Acute renal failure No. (%)	27 (11.20)
Nephrotic syndrome No. (%)	116(48.13)
SLEDAI	16 (14-21)
Laboratory assessment	
Urine protein (mean ± SD) (g/24 hours)	3.45 (1.82-6.38)
Serum creatinine (median, range) (μmol/l)	80 (63.5-114.5)
C3 (mean ± SD) (g/l)	0.44 (0.31-0.60)
Anti-nuclear antibody (+) No. (%)	231(95.85)
Anti-SSA antibody (+) No. (%)	96 (39.83)
Anti-SSB antibody (+) No. (%)	26 (10.79)
C1q(ug/mL) (median; interquartile range)	23.32 (17.50-46.89)
C3a(ng/mL) (median; interquartile range)	1210.07 (529.36-2049.23)
C5a(ng/mL) (median; interquartile range)	17.19 (10.03-27.43)
C4d(ug/mL) (median; interquartile range)	2.49 (0.67-1.40)
Mac(ng/mL) (median; interquartile range	1042.76 (727.24-1340.94)
Bb(ug/mL) (median; interquartile range)	0.79 (0.66-1.40)
FH(ug/mL) (median; interquartile range)	254.30 (163.8-372.8)
Renal histopathology indices	
Activity indices (AI) score	7 (6-9)
Endocapillary hypercellualrity	2 (1-3)

DOI: 10.12998/wjcc.v11.i13.2934

Figure 1 Polymorphisms schematic diagram and the clinical characteristics of patients with lupus nephritis. A: Polymorphisms in the C-reactive protein (CRP) and complement factor H (CFH) gene, six single nucleotide polymorphisms (SNPs) in CRP and three SNPs in CFH were selected; B: Clinical characteristics of patients with lupus nephritis. CRP: C-reactive protein; CFH: Complement factor H; SNP: Single nucleotide polymorphisms; UTR: Untranslated regions.

Given that interaction of CRP and CFH would theoretically help to regulate complement and therefore play roles in SLE/LN pathogenesis, we combined 6 CRP SNPs individually with CFH SNP rs1061170, which corresponds to a CFH variant with impaired capacity in CRP binding. To our knowledge, this is the first study to combine these two genes when performing a correlation analysis with LN risk. However, we still failed to observe any significant associations from this perspective.

Overall, our results suggest that CRP and CFH genetic variation and interaction do not affect the occurrence of LN at the gene level in a Chinese population. In future studies, multiple-center sampling is needed to expand the study scale, whereas SLE patients without LN from other rheumatism departments should also be included. Moreover, more SNPs should be examined for these two genes, while other molecules along the pathogenesis pathway of CRP and CFH should be involved for a joint analysis.

CONCLUSION

In spite of the unambiguous pathogenic roles of CRP and CFH in LN, our present study involving a Chinese population has failed to reveal any significant associations of their genetic variations with LN risk. These findings suggest that most genetic variations of CRP and CFH might possess limited biological effects on their expressions or activities, and are thus not sufficient to influence the disease course of LN. Overall, we concluded that genetic variations of CRP and CFH could not be used to improve the risk stratification of LN in Chinese population.

ARTICLE HIGHLIGHTS

Research background

Both C-reactive protein (CRP) and complement factor H (CFH) play roles in pathogenesis of lupus

nephritis (LN).

Research motivation
It still keeps unclear whether genetic variations of CRP and CFH are involved in risk of LN.

Research objectives
To examine whether genetic variations of CRP and CFH are associated with the susceptibility to LN in the Chinese population.

Research methods
A case control study was conducted, in which six CRP Single Nucleotide Polymorphisms (SNPs) and three CFH SNPs were genotyped and analysed in 270 LN patients and 303 healthy subjects.

Research results
CRP and CFH SNPs, neither individually nor in combination, are associated with the risk or clinical manifestations of LN. Moreover, no linkage was found among CRP and CFH SNPs, indicating lack of genetic interactions between the two genes.

Research conclusions
Biological effects of most genetic variations of CRP and CFH on their expressions or activities are not sufficient to influence the disease course of LN.

Research perspectives
Future studies involving multiple-center sampling are needed to expand the study scale. Moreover, more SNPs should be examined for these two genes, while other molecules along the pathogenesis pathway of CRP and CFH should be involved for a joint analysis.

FOOTNOTES

Author contributions: Yu F and Li HY designed the research. Li QY, Lv JM, and Liu XL performed the experiments. Lv JM and Li HY analyzed the data and wrote the paper. All authors reviewed and approved the final version of the manuscript.

Institutional review board statement: The work was approved by the Ethics Committee of Peking University First Hospital [Approval No. 2017(1333)].

Informed consent statement: Informed written consent was obtained from the patient and her family for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest with the contents of this article.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: China

ORCID number: Qiu-Yu Li 0000-0002-8707-5229; Jian-Min Lv 0000-0001-9693-4200; Hai-Yun Li 0000-0002-7458-7399; Feng Yu 0000-0003-3060-6233.

S-Editor: Liu GL
L-Editor: A
P-Editor: Liu GL

REFERENCES

1 **Rahman A**, Isenberg DA. Systemic lupus erythematosus. *N Engl J Med* 2008; **358**: 929-939 [PMID: 18305268 DOI: 10.1056/NEJMra071297]

2 **Almaani S**, Meara A, Rovin BH. Update on Lupus Nephritis. *Clin J Am Soc Nephrol* 2017; **12**: 825-835 [PMID: 27821390 DOI: 10.2215/CJN.05780616]

3 **Johanneson B**, Lima G, von Salomé J, Alarcón-Segovia D, Alarcón-Riquelme ME; Collaborative Group on the Genetics of SLE, The BIOMED II Collaboration on the Genetics of SLE and Sjögrens syndrome. A major susceptibility locus for systemic lupus erythemathosus maps to chromosome 1q31. *Am J Hum Genet* 2002; **71**: 1060-1071 [PMID: 12373647 DOI: 10.1086/344289]

4 **Tsao BP**, Cantor RM, Grossman JM, Kim SK, Strong N, Lau CS, Chen CJ, Shen N, Ginzler EM, Goldstein R, Kalunian KC, Arnett FC, Wallace DJ, Hahn BH. Linkage and interaction of loci on 1q23 and 16q12 may contribute to susceptibility to systemic lupus erythematosus. *Arthritis Rheum* 2002; **46**: 2928-2936 [PMID: 12428234 DOI: 10.1002/art.10590]

5 **Tsao BP**. Update on human systemic lupus erythematosus genetics. *Curr Opin Rheumatol* 2004; **16**: 513-521 [PMID: 15314487 DOI: 10.1097/01.bor.0000132648.62680.81]

6 **Caprio V**, Badimon L, Di Napoli M, Fang WH, Ferris GR, Guo B, Iemma RS, Liu D, Zeinolabediny Y, Slevin M. pCRP-mCRP Dissociation Mechanisms as Potential Targets for the Development of Small-Molecule Anti-Inflammatory Chemotherapeutics. *Front Immunol* 2018; **9**: 1089 [PMID: 29892284 DOI: 10.3389/fimmu.2018.01089]

7 **Jimenez RV**, Wright TT, Jones NR, Wu J, Gibson AW, Szalai AJ. C-Reactive Protein Impairs Dendritic Cell Development, Maturation, and Function: Implications for Peripheral Tolerance. *Front Immunol* 2018; **9**: 372 [PMID: 29556231 DOI: 10.3389/fimmu.2018.00372]

8 **Molins B**, Romero-Vázquez S, Fuentes-Prior P, Adan A, Dick AD. C-Reactive Protein as a Therapeutic Target in Age-Related Macular Degeneration. *Front Immunol* 2018; **9**: 808 [PMID: 29725335 DOI: 10.3389/fimmu.2018.00808]

9 **Romero-Vázquez S**, Adán A, Figueras-Roca M, Llorenç V, Slevin M, Vilahur G, Badimon L, Dick AD, Molins B. Activation of C-reactive protein proinflammatory phenotype in the blood retinal barrier in vitro: implications for age-related macular degeneration. *Aging (Albany NY)* 2020; **12**: 13905-13923 [PMID: 32673285 DOI: 10.18632/aging.103655]

10 **Zeinolabediny Y**, Kumar S, Slevin M. Monomeric C-Reactive Protein - A Feature of Inflammatory Disease Associated With Cardiovascular Pathophysiological Complications? *In Vivo* 2021; **35**: 693-697 [PMID: 33622861 DOI: 10.21873/invivo.12309]

11 **Moser KL**, Neas BR, Salmon JE, Yu H, Gray-McGuire C, Asundi N, Bruner GR, Fox J, Kelly J, Henshall S, Bacino D, Dietz M, Hogue R, Koelsch G, Nightingale L, Shaver T, Abdou NI, Albert DA, Carson C, Petri M, Treadwell EL, James JA, Harley JB. Genome scan of human systemic lupus erythematosus: evidence for linkage on chromosome 1q in African-American pedigrees. *Proc Natl Acad Sci U S A* 1998; **95**: 14869-14874 [PMID: 9843982 DOI: 10.1073/pnas.95.25.14869]

12 **Cantor RM**, Yuan J, Napier S, Kono N, Grossman JM, Hahn BH, Tsao BP. Systemic lupus erythematosus genome scan: support for linkage at 1q23, 2q33, 16q12-13, and 17q21-23 and novel evidence at 3p24, 10q23-24, 13q32, and 18q22-23. *Arthritis Rheum* 2004; **50**: 3203-3210 [PMID: 15476245 DOI: 10.1002/art.20511]

13 **Pereira Da Silva JA**, Elkon KB, Hughes GR, Dyck RF, Pepys MB. C-reactive protein levels in systemic lupus erythematosus: a classification criterion? *Arthritis Rheum* 1980; **23**: 770-771 [PMID: 7387742 DOI: 10.1002/art.1780230609]

14 **Li QY**, Li HY, Fu G, Yu F, Wu Y, Zhao MH. Autoantibodies against C-Reactive Protein Influence Complement Activation and Clinical Course in Lupus Nephritis. *J Am Soc Nephrol* 2017; **28**: 3044-3054 [PMID: 28566480 DOI: 10.1681/ASN.2016070735]

15 **Bell SA**, Faust H, Schmid A, Meurer M. Autoantibodies to C-reactive protein (CRP) and other acute-phase proteins in systemic autoimmune diseases. *Clin Exp Immunol* 1998; **113**: 327-332 [PMID: 9737658 DOI: 10.1046/j.1365-2249.1998.00655.x]

16 **Sjöwall C**, Eriksson P, Almer S, Skogh T. Autoantibodies to C-reactive protein is a common finding in SLE, but not in primary Sjögren's syndrome, rheumatoid arthritis or inflammatory bowel disease. *J Autoimmun* 2002; **19**: 155-160 [PMID: 12419286 DOI: 10.1006/jaut.2002.0608]

17 **Rodriguez W**, Mold C, Kataranovski M, Hutt J, Marnell LL, Du Clos TW. Reversal of ongoing proteinuria in autoimmune mice by treatment with C-reactive protein. *Arthritis Rheum* 2005; **52**: 642-650 [PMID: 15692982 DOI: 10.1002/art.20846]

18 **Szalai AJ**, Weaver CT, McCrory MA, van Ginkel FW, Reiman RM, Kearney JF, Marion TN, Volanakis JE. Delayed lupus onset in (NZB x NZW)F1 mice expressing a human C-reactive protein transgene. *Arthritis Rheum* 2003; **48**: 1602-1611 [PMID: 12794828 DOI: 10.1002/art.11026]

19 **Szalai AJ**, Wu J, Lange EM, McCrory MA, Langefeld CD, Williams A, Zakharkin SO, George V, Allison DB, Cooper GS, Xie F, Fan Z, Edberg JC, Kimberly RP. Single-nucleotide polymorphisms in the C-reactive protein (CRP) gene promoter that affect transcription factor binding, alter transcriptional activity, and associate with differences in baseline serum CRP level. *J Mol Med (Berl)* 2005; **83**: 440-447 [PMID: 15778807 DOI: 10.1007/s00109-005-0658-0]

20 **Russell AI**, Cunninghame Graham DS, Shepherd C, Roberton CA, Whittaker J, Meeks J, Powell RJ, Isenberg DA, Walport MJ, Vyse TJ. Polymorphism at the C-reactive protein locus influences gene expression and predisposes to systemic lupus erythematosus. *Hum Mol Genet* 2004; **13**: 137-147 [PMID: 14645206 DOI: 10.1093/hmg/ddh021]

21 **Atisha-Fregoso Y**, Lima G, Carrillo-Maravilla E, Posadas-Sánchez R, Pérez-Hernández N, Baños-Peláez M, Iturralde-Chávez A, Hernández-Díaz N, Jakez-Ocampo J, Rodríguez-Pérez JM, Vargas-Alarcón G, Llorente L, Romero-Díaz J. C-reactive protein (CRP) polymorphisms and haplotypes are associated with SLE susceptibility and activity but not with serum CRP levels in Mexican population. *Clin Rheumatol* 2018; **37**: 1817-1824 [PMID: 29556849 DOI: 10.1007/s10067-018-4059-5]

22 **Delongui F**, Lozovoy MAB, Iriyoda TMV, Costa NT, Stadtlober NP, Alfieri DF, Flauzino T, Dichi I, Simão ANC, Reiche EMV. C-reactive protein +1444CT (rs1130864) genetic polymorphism is associated with the susceptibility to systemic lupus erythematosus and C-reactive protein levels. *Clin Rheumatol* 2017; **36**: 1779-1788 [PMID: 28567557 DOI:

10.1007/s10067-017-3695-5]
23 **Kim HA**, Chun HY, Kim SH, Park HS, Suh CH. C-reactive protein gene polymorphisms in disease susceptibility and clinical manifestations of Korean systemic lupus erythematosus. *J Rheumatol* 2009; **36**: 2238-2243 [PMID: 19755616 DOI: 10.3899/jrheum.090243]
24 **Shih PB**, Manzi S, Shaw P, Kenney M, Kao AH, Bontempo F, Barmada MM, Kammerer C, Kamboh MI. Genetic variation in C-reactive protein (CRP) gene may be associated with risk of systemic lupus erythematosus and CRP concentrations. *J Rheumatol* 2008; **35**: 2171-2178 [PMID: 18793001 DOI: 10.3899/jrheum.080262]
25 **Wang FM**, Yu F, Tan Y, Song D, Zhao MH. Serum complement factor H is associated with clinical and pathological activities of patients with lupus nephritis. *Rheumatology (Oxford)* 2012; **51**: 2269-2277 [PMID: 22956549 DOI: 10.1093/rheumatology/kes218]
26 **Fijen CA**, Kuijper EJ, Te Bulte M, van de Heuvel MM, Holdrinet AC, Sim RB, Daha MR, Dankert J. Heterozygous and homozygous factor H deficiency states in a Dutch family. *Clin Exp Immunol* 1996; **105**: 511-516 [PMID: 8809142 DOI: 10.1046/j.1365-2249.1996.d01-777.x]
27 **Sánchez-Corral P**, Bellavia D, Amico L, Brai M, Rodríguez de Córdoba S. Molecular basis for factor H and FHL-1 deficiency in an Italian family. *Immunogenetics* 2000; **51**: 366-369 [PMID: 10803850 DOI: 10.1007/s002510050631]
28 **Rodríguez de Córdoba S**, Esparza-Gordillo J, Goicoechea de Jorge E, Lopez-Trascasa M, Sánchez-Corral P. The human complement factor H: functional roles, genetic variations and disease associations. *Mol Immunol* 2004; **41**: 355-367 [PMID: 15163532 DOI: 10.1016/j.molimm.2004.02.005]
29 **Zhao J**, Wu H, Khosravi M, Cui H, Qian X, Kelly JA, Kaufman KM, Langefeld CD, Williams AH, Comeau ME, Ziegler JT, Marion MC, Adler A, Glenn SB, Alarcón-Riquelme ME; BIOLUPUS Network; GENLES Network, Pons-Estel BA, Harley JB, Bae SC, Bang SY, Cho SK, Jacob CO, Vyse TJ, Niewold TB, Gaffney PM, Moser KL, Kimberly RP, Edberg JC, Brown EE, Alarcon GS, Petri MA, Ramsey-Goldman R, Vilá LM, Reveille JD, James JA, Gilkeson GS, Kamen DL, Freedman BI, Anaya JM, Merrill JT, Criswell LA, Scofield RH, Stevens AM, Guthridge JM, Chang DM, Song YW, Park JA, Lee EY, Boackle SA, Grossman JM, Hahn BH, Goodship TH, Cantor RM, Yu CY, Shen N, Tsao BP. Association of genetic variants in complement factor H and factor H-related genes with systemic lupus erythematosus susceptibility. *PLoS Genet* 2011; **7**: e1002079 [PMID: 21637784 DOI: 10.1371/journal.pgen.1002079]
30 **Li Q**, Song D, Wang F, Tan Y, Yu F, Zhao M. Clinicopathological characteristics and outcomes of Chinese patients with scanty immune deposits lupus nephritis: a large cohort study from a single center. *ScientificWorldJournal* 2014; 212597 [PMID: 24672300 DOI: 10.1155/2014/212597]
31 **Liang MH**, Socher SA, Larson MG, Schur PH. Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. *Arthritis Rheum* 1989; **32**: 1107-1118 [PMID: 2775320 DOI: 10.1002/anr.1780320909]
32 **Bombardier C**, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992; **35**: 630-640 [PMID: 1599520 DOI: 10.1002/art.1780350606]
33 **Huang J**, Han SS, Qin DD, Wu LH, Song Y, Yu F, Wang SX, Liu G, Zhao MH. Renal Interstitial Arteriosclerotic Lesions in Lupus Nephritis Patients: A Cohort Study from China. *PLoS One* 2015; **10**: e0141547 [PMID: 26544865 DOI: 10.1371/journal.pone.0141547]
34 **Song D**, Wu LH, Wang FM, Yang XW, Zhu D, Chen M, Yu F, Liu G, Zhao MH. The spectrum of renal thrombotic microangiopathy in lupus nephritis. *Arthritis Res Ther* 2013; **15**: R12 [PMID: 23320601 DOI: 10.1186/ar4142]
35 **Weening JJ**, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, Balow JE, Bruijn JA, Cook T, Ferrario F, Fogo AB, Ginzler EM, Hebert L, Hill G, Hill P, Jennette JC, Kong NC, Lesavre P, Lockshin M, Looi LM, Makino H, Moura LA, Nagata M; International Society of Nephrology Working Group on the Classification of Lupus Nephritis; Renal Pathology Society Working Group on the Classification of Lupus Nephritis. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int* 2004; **65**: 521-530 [PMID: 14717922 DOI: 10.1111/j.1523-1755.2004.00443.x]
36 **Shi YY**, He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. *Cell Res* 2005; **15**: 97-98 [PMID: 15740637 DOI: 10.1038/sj.cr.7290272]
37 **Schaumberg DA**, Christen WG, Kozlowski P, Miller DT, Ridker PM, Zee RY. A prospective assessment of the Y402H variant in complement factor H, genetic variants in C-reactive protein, and risk of age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2006; **47**: 2336-2340 [PMID: 16723442 DOI: 10.1167/iovs.05-1456]
38 **Molins B**, Fuentes-Prior P, Adán A, Antón R, Arostegui JI, Yagüe J, Dick AD. Complement factor H binding of monomeric C-reactive protein downregulates proinflammatory activity and is impaired with at risk polymorphic CFH variants. *Sci Rep* 2016; **6**: 22889 [PMID: 26961257 DOI: 10.1038/srep22889]
39 **Rhodes B**, Fürnrohr BG, Vyse TJ. C-reactive protein in rheumatology: biology and genetics. *Nat Rev Rheumatol* 2011; **7**: 282-289 [PMID: 21468143 DOI: 10.1038/nrrheum.2011.37]
40 **Rhodes B**, Wong A, Navarra SV, Villamin C, Vyse TJ. Genetic determinants of basal C-reactive protein expression in Filipino systemic lupus erythematosus families. *Genes Immun* 2008; **9**: 153-160 [PMID: 18216863 DOI: 10.1038/sj.gene.6364459]
41 **Tan M**, Hao JB, Chu H, Wang FM, Song D, Zhu L, Yu F, Li YZ, Song Y, Zhao MH. Genetic variants in FH are associated with renal histopathologic subtypes of lupus nephritis: a large cohort study from China. *Lupus* 2017; **26**: 1309-1317 [PMID: 28403670 DOI: 10.1177/0961203317702254]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 2945-2955

DOI: 10.12998/wjcc.v11.i13.2945

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Comparison of the application value of transvaginal ultrasound and transabdominal ultrasound in the diagnosis of ectopic pregnancy

Hui-Juan Hu, Juan Sun, Rui Feng, Liang Yu

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Berardi R, Italy; Dong-Wook K, South Korea

Received: February 27, 2023
Peer-review started: February 27, 2023
First decision: March 10, 2023
Revised: March 19, 2023
Accepted: March 24, 2023
Article in press: March 24, 2023
Published online: May 6, 2023

Hui-Juan Hu, Department of Ultrasonic, Hangzhou Red Cross Hospital, Affiliated Hangzhou Chest Hospital, Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang Province, China

Juan Sun, Department of Ultrasonic, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310000, Zhejiang Province, China

Rui Feng, Department of Interventional Medicine, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310000, Zhejiang Province, China

Liang Yu, Department of Radiology, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310000, Zhejiang Province, China

Corresponding author: Liang Yu, MM, Associate Chief Physician, Department of Radiology, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, 158 Shangtang Road, Hangzhou 310000, Zhejiang Province, China. 422086056@qq.com

Abstract

BACKGROUND

Ectopic pregnancy (EP) is one of the most common acute abdominal diseases in gynecology. Once the condition of EP is delayed, it may lead to massive hemorrhage, shock, and even death in a short time, seriously threatening the patient's life. Early diagnosis is the key to preventing and improving the prognosis of EP. Transabdominal ultrasound (TAS) and transvaginal ultrasound (TVS) are the main diagnostic methods for abdominal diseases. The purpose of this study is to explore the application value and effect of TAS and TVS in the diagnosis of EP, hoping to provide more valuable references for the diagnosis of EP.

AIM

To explore the application value of TAS and TVS in the diagnosis of EP and to improve the level of clinical diagnosis.

METHODS

A total of 140 patients with EP admitted to our hospital from July 2018 to July 2020 were selected for this study. All patients were divided into two groups according to the examination methods. 63 patients who underwent abdominal ultrasound examination were set as the TAS group, while 77 patients who underwent TVS examination were set as the TVS group. We compared the

diagnostic accuracy and misdiagnosis rates between the two types of ultrasound examinations, as well as the postoperative pathological results of the two diagnostic methods for different types of ectopic pregnancies. We also analyzed the sonograms for the presence of mixed ectopic masses, adnexal masses, ectopic gestational sacs, the presence or absence of visible embryo and fetal heart in the ectopic sac shadow, and the detection of fluid in the rectal fossa of the uterus, such as the adnexal area, yolk sac, and embryo, *etc.* In addition, the diagnosis time, days of gestational sac appearance, operation time, endometrial thickness, and blood flow resistance index were compared as well.

RESULTS

After performing both types of ultrasound examinations in 140 patients with EP, we found that the diagnostic accuracy of TVS was significantly higher than that of TAS, and the misdiagnosis rate was significantly lower than that of TAS. The differences were statistically significant ($P < 0.05$). In addition, the detection rate of TVS was better than that of TAS for the presence of mixed masses, adnexal masses, ectopic gestational sacs, the presence or absence of visible embryo and fetal heart in the shadow of the ectopic sac, and sonograms such as the adnexal area, yolk sac, and embryo, *etc.* The coincidence rate of its postoperative pathological examination results was significantly higher than those of TAS. The diagnosis time and the days of gestational sac appearance by TVS were significantly shorter than that by TAS, and the operation time was earlier than that by TAS. What's more, the detection rates of the endometrial thickness £ 1.5 mm and blood flow resistance £ 0.5 were significantly higher in TVS diagnosis of EP than in TAS. All differences were statistically significant ($P < 0.05$).

CONCLUSION

Compared with TAS, TVS has the advantages of high detection accuracy and good sonogram performance.

Key Words: Transvaginal ultrasound; Transabdominal ultrasound; Ectopic pregnancy; Application value

Core Tip: Transabdominal ultrasound (TAS) is the primary method for early detection of ectopic pregnancy (EP). However, because of the low frequency of the TAS probe and the certain distance between it and the gestational sacs, it is susceptible to interference of the probe acquisition data by factors such as the filling bladder, abdominal fat, abdominal wall trabecular contents, and intestinal wall, which further reduces the accuracy of diagnosis. With the development of clinical diagnostic technology and the improvement of the medical level, transvaginal ultrasound (TVS) is gradually applied in the diagnosis of various clinical fields. Based on this, this study aims to compare and analyze the application value of TAS and TVS in the diagnosis of EP, hoping to provide some help for the early diagnosis and treatment of EP.

Citation: Hu HJ, Sun J, Feng R, Yu L. Comparison of the application value of transvaginal ultrasound and transabdominal ultrasound in the diagnosis of ectopic pregnancy. *World J Clin Cases* 2023; 11(13): 2945-2955
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/2945.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.2945

INTRODUCTION

Ectopic pregnancy (EP) is one of the common acute abdominal diseases in gynecology, which mainly refers to the implantation of fertilized eggs outside the uterine cavity[1,2]. There are many causes of EP, such as pelvic inflammation, pelvic effusion, fallopian tube abnormalities, *etc*[3]. EP can be divided into tubal pregnancy, ovarian pregnancy, and cervical pregnancy according to the different locations of fertilized eggs implanted outside the uterine cavity, among which EP accounts for more than 95%[4]. Menopause, abdominal pain, and vaginal bleeding are the typical clinical manifestations of EP, especially tubal pregnancy. As a result of acute intra-abdominal bleeding and severe abdominal pain, mild cases of fainting can lead to shock and even death in severe cases, seriously threatening the lives of patients[5,6]. Therefore, improving the diagnostic accuracy of EP can help patients get timely treatment and effectively guarantee their prognosis.

At present, there are many methods to diagnose EP, such as pregnancy test, ultrasound diagnosis, posterior fornix puncture, laparoscopy, endometrial pathology examination, *etc.*[7], among which

transabdominal ultrasound (TAS) has become a common clinical examination method because of its convenience and quick operation. However, due to factors such as the thickness of human abdominal sebum and the low frequency of the probe, misdiagnosis and missed diagnosis of abdominal ultrasound is inevitable. Therefore, it is very important to find a more efficient and accurate method for the diagnosis of EP. Transvaginal ultrasound (TVS) is a kind of intracavitary ultrasound, which requires a special vaginal probe to be placed directly in the vagina for an ultrasound examination. As a technological breakthrough in the application of obstetrical and gynecological ultrasound in recent years, compared with traditional TAS, it can clearly show the internal organ and tissue structure of the female pelvic cavity without filling the bladder. It has early and accurate characteristics for the diagnosis of normal and abnormal pregnancies and gynecological diseases[8]. Previous studies have found that TVS examination of EP can improve diagnostic accuracy and ensure the timely treatment of patients[9]. In addition, studies by Mei *et al*[10] have shown that TAS and TVS are the main diagnostic methods for abdominal diseases, especially in the early diagnosis of EP[11-12].

Based on this, this study aims to explore the application value and effect of TAS and TVS in the diagnosis of EP through retrospective analysis of clinical data of patients with EP, hoping to provide more valuable references for the diagnosis of EP.

MATERIALS AND METHODS

General data

In this study, 140 patients with EP admitted to our hospital from July 2018 to July 2020 were selected. All patients ranged in age from 21 to 39 years, among which 82 were primiparas, and 58 were multiparas. All patients understood the content of the study and voluntarily signed the informed consent form. According to different examination methods, we divided the 140 patients into two groups: 63 patients in the TAS group were diagnosed with TAS and 77 patients in the TVS group were diagnosed with transvaginal color Doppler ultrasound. The general data of all patients were compared and the differences were not statistically significant ($P > 0.05$), as shown in Table 1.

Inclusion and exclusion criteria

Inclusion criteria: All patients were tested for β-humanchorionic gonadotrophin, and the results were positive or weakly positive. Patients were diagnosed with EP according to the clinical symptoms and pathological features; patients had no history of EP and no other gynecological diseases.

Exclusion criteria: Patients with intrauterine abortion, ovarian cyst torsion, and acute tubal infection [13]; patients with vaginal inflammation or other contraindications to vaginal examination; patients with severe mental illness or communication disorders; patients who do not actively cooperate with the examination.

Methods

In the TAS Group, we adopted the Philips HD7 ultrasound diagnostic instrument. Before the operation, the patients were instructed to drink more water to make the bladder fill properly. Patients were placed in a supine position. The probe frequency was 3.5-5 MHz. Patients were then scanned from the pubic bone to the upper abdomen at multiple angles after applying a coupling agent on the probe tip. The focus was placed on uterine volume, uterine cavity, endometrial thickness, bilateral adnexa, and other pelvic organs[14].

In the TVS group, a Voluson 730 expert color Doppler ultrasound instrument from GE company was used, and the TVS probe frequency was 3.0-10.0 MHz. The patients were instructed to perform a vaginal ultrasound examination after complete urination and they were placed in a lithotomy position. The probe tip was coated with a coupling agent and then wrapped in a condom and slowly placed into the vagina and tightly pressed against the posterior vaginal fornix. The probe handle was slowly rotated, and a multi-directional and multi-sectional scan was performed with a focus on uterine volume, uterine cavity, endometrial thickness, bilateral adnexa, and other pelvic organs[15].

Two diagnostic methods were used to observe the presence of uterine gestational sac, adnexal gestational sac mass, extrauterine gestational sac, and cardiovascular pulsation, the presence of visible embryo and fetal heart in the external gestational sac shadow, and fluid accumulation in the rectal fossa of the uterus. In addition, the endometrial shape and blood flow were also focused on. Continuous scanning was performed to clearly show the shape of the uterine orifice to the endometrial fundus. The thickest part of the endometrial thickness was measured in a longitudinal section, and pulsed Doppler was performed at the most brightly colored areas of color Doppler flow imaging to record the endometrial thickness and blood flow resistance, and the results of TAS and vaginal ultrasound were compared and analyzed.

Table 1 Comparison of general data in each group, *n* (%)

Group	Age (years), mean ± SD	Multiparas	Primipara	Urine HCG (weak) positive	Blood HCG (weak) positive
TAS group (n = 63)	35.57 ± 3.65	24 (38.10)	39 (61.90)	58 (92.06)	60 (95.23)
TVS group (n = 77)	35.56 ± 3.78	34 (44.16)	43 (55.84)	72 (93.51)	75 (97.40)
T/χ^2	0.017	0.581		0.399	
P value	0.987	0.469		0.310	

SD: Standard deviation; HCG: Humanchorionic gonadotrophin; TAS: Transabdominal ultrasound; TVS: Transvaginal ultrasound.

Observational index

Analysis of the testing accuracy of TAS and TVS: Ultrasound diagnostic criteria for EP[16-18]: (1) Tubal pregnancy: During the examination, there are no gestational sacs in the uterus, a hypoechoic area appears next to the uterus, and cardiovascular pulsations and embryo can be detected inside it; (2) Ovarian pregnancy: No gestational sac in the uterus, enlarged ovaries, hypoechoic area inside, and gestational sac can be detected inside; (3) Cervical pregnancy: No gestational sacs in the uterus, enlarged cervix, gestational sac can be detected inside; (4) Cornual pregnancy: No gestational signs in the uterine cavity, and the horn of the uterus is protruding, there is a muscle wall outside the gestational sac, and cardiovascular pulsation and embryo can be detected inside; (5) Uterine stump pregnancy: There is no gestational sac in the uterus, but there is a hypoechoic area outside the uterus where the gestational sac can be detected and the placental echo can be seen and fetal activity can be detected; and (6) Abdominal pregnancy: The uterine body is enlarged and cardiovascular pulsations and embryo can be detected in the upper uterus. Diagnostic accuracy = (tubal pregnancy + ovarian pregnancy + cervical pregnancy + abdominal pregnancy + uterine stump pregnancy) / total number of cases.

Analysis of the coincidence rate of TAS and TVS on the pathological findings of EP after surgery: The laparoscopic surgery can effectively magnify the fallopian tube under the video screen to quickly locate the pregnancy location. Using laparoscopic findings as the gold standard for the diagnosis of EP, we compared the coincidence rate between TAS and TVS for postoperative pathological findings of EP in different pregnancy types, including tubal pregnancy, ovarian pregnancy, cervical pregnancy, scarred uterine pregnancy, abdominal pregnancy, and uterine stump pregnancy.

Observation of ultrasound sonographic performance in the diagnosis of EP in two groups of patients: According to the characteristics of the ultrasound image, it can be divided into the following types: (1) Mixed mass: The mixed echogenic mass with uneven density can be seen in the pelvic cavity, mainly cystic, with irregular solid echogenicity and coarse septum; (2) Gestational sac-viable type: A ring-like hyperechoic mass similar to the gestational sac can be seen in the adnexal area, which is a small fluid hyperechoic area, and yolk sac, embryo bud, and original cardiac pulsation can be seen in some types of the gestational sac; (3) Adnexal mass: Solid masses with blurred contours and varying intensity of internal echogenicity can be seen in the parametrium due to clotting plan and adhesion to surrounding tissues, which may be accompanied by a small amount of pelvic fluid; and (4) Utero-rectal fossa fluid: The utero-rectal fossa is the space between the uterus and the rectum, the lowest position in the female pelvis. When there is a small amount of exudate from the pelvic viscera and the patient has ruptured bleeding or pelvic inflammatory disease, the fluid will first accumulate in the pelvic cavity, thus forming pelvic fluid. The sonographic presentation of the different types of EP described above was compared by observing ultrasound image analysis of TAS and TVS.

Comparison of the accuracy of TAS and TVS in the diagnosis of EP: The accuracy of TAS and TVS in diagnosing EP was compared by analyzing the diagnosis time of EP, the days of the gestational sac appearance, and the operation time using an ultrasound diagnostic device.

Comparison of endometrial thickness and blood flow resistance detection in patients with EP: The patients were examined by abdominal b-mode ultrasound and transvaginal b-mode ultrasound respectively using B-mode ultrasound diagnostic instrument. The endometrial thickness and the blood flow resistance index in the mass were measured accurately, and the diagnostic accuracy of TAS and TVS in EP was analyzed.

Statistical analysis

In this study, we adopted IBM SPSS 21.0 software (SPSS Inc., Chicago, IL, USA) to process and analyze all the data. The measurement data were expressed as mean ± SD and a t-test was used for comparison between groups. The count data were expressed as n (%) and the χ^2 test was used for comparison. All the differences were statistically significant at $P < 0.05$.

RESULTS

Comparison of the diagnostic accuracy of patients with EP

We observed the detection rate of positive EP in the two groups after different ultrasound diagnoses and found that the accuracy rate of transvaginal color Doppler ultrasound was significantly higher (97.40%) than that of TAS (88.89%), and its misdiagnosis rate (2.60%) was significantly lower than that of TAS (11.11%), which was statistically significant ($P < 0.05$). This indicates that the accuracy of transvaginal color Doppler ultrasound in the diagnosis of EP is better (Table 2).

Coincidence rate of postoperative pathological examination results

We further compared and analyzed the coincidence rate between TAS and TVS on the postoperative pathological results of ectopic pregnancies of different pregnancy types, such as tubal pregnancy, ovarian pregnancy, cervical pregnancy, scarred uterine pregnancy, abdominal pregnancy, and uterine stump pregnancy. It was found that the coincidence rate of postoperative pathological examination by transvaginal B-mode ultrasound was better than that by TAS, and the difference was statistically significant ($P < 0.05$), especially in the diagnosis of postoperative pathological examination results of a tubal pregnancy (Table 3).

Sonographic performance in the diagnosis of EP in both groups

In an EP, the uterus is significantly enlarged on ultrasound, but the uterine cavity is empty, and a hypoechoic area next to the uterus or a gestational sac or fetal heart, or embryo can be seen. The EP can also be determined by the protrusion of the uterine horn on one side of the uterus, localized thickening of the muscular layer, and the presence of a visible gestational sac. To further investigate the value of vaginal ultrasound and TAS in the diagnosis of EP, we compared the sonograms of the two kinds of ultrasound diagnosis and found that compared with TAS, transvaginal color Doppler ultrasound could more clearly observe the ectopic gestational sac shadow, the presence of mixed masses, and the presence of fetal heart and embryo, the adnexal area, and the yolk sac. The difference between the two groups was statistically significant ($P < 0.05$), (Table 4, Figure 1).

Comparison of diagnosis time and days of gestational sac appearance

It was found that the diagnosis time of EP and the days of gestational sac appearance in the transvaginal B-mode ultrasound group were shorter than those in the control group. At the same time, the operation time of the transvaginal B-mode ultrasound group was earlier than that of the transabdominal B-mode ultrasound group ($P < 0.05$). The results showed that TVS could diagnose EP earlier and the operation could be performed earlier to enhance the therapeutic effect (Table 5).

Comparison of endometrial thickness and blood flow resistance in patients with EP

It was found that the detection rate of endometrial thickness ≤ 1.5 mm and blood flow resistance ≤ 0.5 in TVS diagnosis of EP was significantly higher than that in TAS diagnosis, and the difference was statistically significant ($P < 0.05$). This indicated that TVS could more accurately predict the site of pregnancy, identify the blood flow resistance index, and improve the diagnosis rate of EP (Table 6).

DISCUSSION

In normal pregnancy, the fertilized eggs are deposited in the uterine cavity, whereas in EP, the fertilized eggs are deposited outside the uterine cavity and grow and develop[19-21]. In the early stage of EP, there is no obvious clinical manifestation, some patients present with menopause, abdominal pain, and a small amount of vaginal bleeding. Patients often suffer from acute severe abdominal pain, and recurrent episodes, and are more painful at the onset. However, there are still some patients with EP who do not have typical clinical symptoms, and the diagnosis rate is low at the early stage, which undoubtedly increases the difficulty of clinical diagnosis. And once the condition is delayed, it may lead to hemorrhage, even shock, and death in a short period[22-24]. Therefore, the principle of treatment for EP is early diagnosis and early treatment.

At present, EP is mainly treated clinically by surgery, which presupposes scientific and accurate clinical judgment[25,26]. It has been reported that ultrasound diagnosis has become the main method for early diagnosis of patients with EP because of its convenience, noninvasiveness, and freedom from the pain of diagnostic curettage and fornix puncture[27]. TAS was an earlier method of clinical diagnosis. EP is diagnosed when the diagnostic TAS image shows an increase in the thickness of the endometrium, the absence of a gestational sac in the uterine cavity, a mixed mass with uneven echogenic borders on the side of the uterus, or even a mass of gestational sac, embryo or even primitive ventricular pulsation on the side of the uterine cavity in some patients[28,29]. But TAS requires the patient to have a full bladder, and it is far away from the uterus and fallopian tube, which makes lesion detection unclear or incomplete and also prone to misdiagnosis. As a result, the application of TAS is

Table 2 Comparison of the accuracy and misdiagnosis rate of the two methods

Group	Consistent with the diagnosis	Misdiagnosis	Accuracy rate
TAS group (n = 63)	56	7	88.89
TVS group (n = 77)	75	2	97.40
χ^2	0.090		0.036
P value	0.041		0.017

TAS: Transabdominal ultrasound; TVS: Transvaginal ultrasound.

Table 3 Comparison of the coincidence rate between the results of different examination methods and postoperative pathological examination

Type	Consistent with the diagnosis	TAS group	TVS group	χ^2	P
Ovarian pregnancy	58	54 (93.10)	56 (96.55)	-	-
Tubal pregnancy	20	7 (35.00)	16 (80.00)	0.011	0.004
Cervical pregnancy	15	13 (86.67)	13 (86.67)	-	-
Scarred uterine pregnancy	12	10 (83.33)	11 (91.67)	-	-
Abdominal pregnancy	11	10 (90.91)	11 (100.00)	-	-
Uterine stump pregnancy	9	8 (88.89)	8 (88.89)	-	-
Cornual pregnancy	15	13 (86.67)	14 (93.33)	-	-
Total	140	115 (82.14)	129 (92.14)	0.020	0.012

TAS: Transabdominal ultrasound; TVS: Transvaginal ultrasound.

Table 4 Comparison of sonographic performance differences between two types of ultrasounds for the diagnosis of ectopic pregnancy

	TAS group (n = 63)	TVS group (n = 77)	χ^2	P
Extrauterine mixed mass	17 (26.98)	34 (44.16)	0.054	0.036
Ectopic gestational sac shadow	43 (68.25)	65 (84.42)	0.039	0.023
Uterine rectal fossa fluid	15 (23.81)	8 (10.39)	0.057	0.033
Fetal heart and embryo in the shadow of ectopic gestational sac	45 (71.43)	66 (85.71)	0.062	0.038
Adnexal area	12 (19.05)	27 (35.06)	0.056	0.035
Yolk sac	52 (82.54)	73 (94.81)	0.039	0.020
Consistent with the diagnosis	152 (82.61)	231 (84.62)	0.062	0.045

TAS: Transabdominal ultrasound; TVS: Transvaginal ultrasound.

not very ideal, and cannot improve the detection rate of clinical diagnosis.

With the development of clinical diagnosis technology and the improvement of the medical level, ultrasonic equipment and examination technology have also developed. Transvaginal ultrasonography is gradually being used in the diagnosis of various clinical fields[30,31]. Studies have shown that TVS has a higher sensitivity in the diagnosis of EP (especially in the early stage of tubal pregnancy, where there is little internal bleeding and the non-echogenic area is confined to the rectum fossa and around the uterus)[32]. TVS allows the probe to be placed into the vagina, which is closer to the pelvic tissues and organs, and can significantly reduce the interference of gas and fatty tissue in the abdominal cavity, making the uterus and ovaries appear clearer[33,34]. Calì *et al*[35] also found that TVS does not require the patient to have a full bladder during the diagnosis, which is suitable for the examination of gynecological emergencies, thus saving time for patients with ruptured EP-type hemorrhage. Based on this, this study aimed to compare the value of TAS and TVS in the diagnosis of EP, hoping to provide some help for the early diagnosis and treatment of EP.

Table 5 Comparison of diagnosis time and days of gestational sac appearance (mean ± SD)

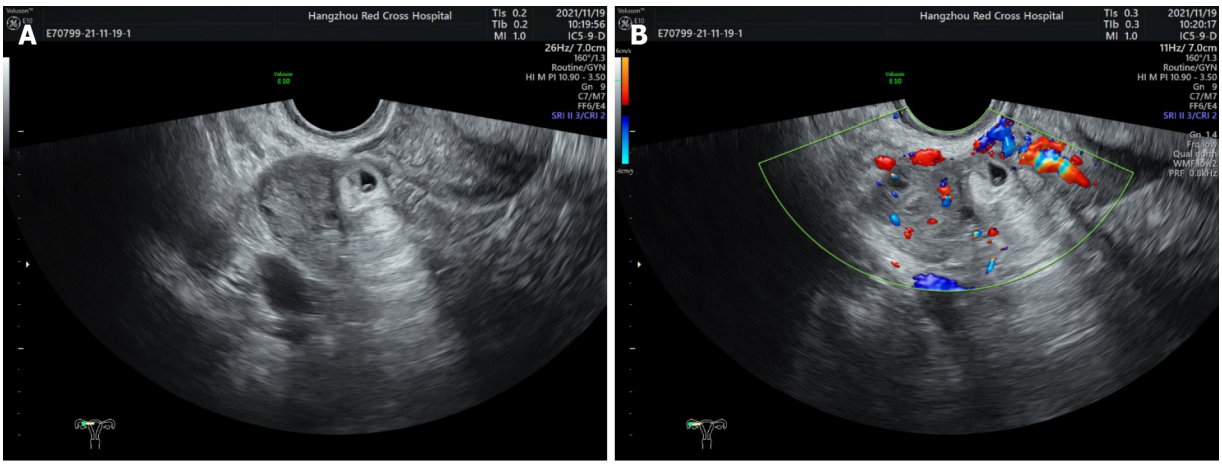
Group	Diagnosis time	Days of gestational sac appearance	Operation time
TAS group (n = 63)	38.24 ± 6.27	32.56 ± 5.35	42.33 ± 4.65
TVS group (n = 77)	34.56 ± 6.21	28.67 ± 5.54	32.59 ± 4.31
T	3.473	4.197	12.838
P value	< 0.001	< 0.001	< 0.001

TAS: Transabdominal ultrasound; TVS: Transvaginal ultrasound.

Table 6 Comparison of endometrial thickness and blood flow resistance

Detection Method	Endometrial thickness		Blood flow resistance in the endometrium	
	≤ 1.5 mm	≥ 1.5 mm	≤ 0.5	≥ 0.5
TAS group (n = 63)	36 (57.14)	27 (42.86)	24 (38.10)	39 (61.90)
TVS group (n = 77)	46 (59.74)	31 (40.26)	43 (55.84)	34 (44.16)
χ^2	1.096		4.374	
P value	0.019		0.036	

TAS: Transabdominal ultrasound; TVS: Transvaginal ultrasound.



DOI: 10.12998/wjcc.v11.i13.2945

Figure 1 Color Doppler sonogram of the uterus in a patient with ectopic pregnancy. A: Color Doppler sonogram suggesting that the patient has a right fallopian tube pregnancy; and B: Color Doppler sonogram suggesting abundant blood flow around the pregnancy.

In this study, TAS and TVS were performed on 140 patients with EP. The diagnostic accuracy of TVS was 97.40%, which was significantly higher than the 88.89% accuracy of TAS, and its misdiagnosis rate was significantly lower than that of TAS. In addition, a comparative sonogram analysis revealed that a transvaginal Doppler sonography was able to show more clearly the ectopic gestational sac shadow, mixed masses, and the presence of fetal heart and embryo in the ectopic sac shadow. The main reason may be that the resolution of the TVS probe is higher than that of TAS, and the penetration of the probe is stronger, which can clearly show the changes in the uterine cavity and endometrium, and accurately reflect the situation of adnexal masses. In addition, the TVS probe is directly placed into the patient's vagina and is closer to the uterus, which is less likely to be affected by other factors[36]. In contrast, the abdominal ultrasound probe has a lower frequency and is at a certain distance from the gestational sac, so it is easy to be interfered with by factors such as the filling bladder, abdominal fat, abdominal wall invasive bowel contents, and the bowel wall, *etc*., thus reducing the accuracy of diagnosis[37,38].

Previous studies have shown that when there is no specificity in the sonogram of adnexal masses, special trophoblast blood flow can be formed after implantation with the help of color Doppler flow imaging, and low resistance flow can be detected in nonspecific adnexal masses that separate from the

ovary, thus improving the sensitivity and specificity of EP diagnosis[39,40]. In this study, by comparing and analyzing the diagnostic time and the days of gestational sac appearance between TAS and vaginal ultrasound, it was also found that the diagnostic time of TVS for EP and the days of showing the gestational sac were significantly shorter than that of TAS, and the operation time was significantly earlier than that of TAS. This may be related to the fact that TAS requires more than 5 wk of menopause for detection, whereas TVS can detect the gestational sac within 3-30 d of menopause[41]. This suggests that TVS is more accurate and sensitive in detecting EP compared to TAS, which is consistent with the study by Ramanan *et al*[42]. That is to say, TVS can detect EP more accurately and its diagnostic time and days of gestational sac appearance are shorter, allowing for earlier surgical treatment options. Timely diagnosis and surgery can enhance the outcome of treatment and reduce the risk of postoperative hemorrhage, which undoubtedly increases the value of TVS and makes it more suitable for use in the diagnosis of gynecologic emergencies. In addition, our results showed that the postoperative pathological findings are more consistent with TVS than with TAS and that its postoperative diagnosis of tubal pregnancy is particularly typical, which may be related to the fact that tubal pregnancy accounts for more than 95% of ectopic pregnancies[43].

It has been found that ultrasound sonograms can reflect cyclic changes in the thickness of endometrial morphology from linear and progressive thickening in the early stages of hyperplasia to 7-10 mm in the late stages of secretion. Since the blood supply and chorionic villus development vary depending on the location of the implanted egg, making differences in the corresponding hormones and the thickness of the endometrium which directly influenced by them. Thus, a combination of endometrial thickness detection can predict the site of pregnancy and improve the accuracy of EP[44,45]. The resistance encountered by blood as it flows through the blood vessels is called blood flow resistance. Blood flow resistance is reported to be caused by energy consumption due to friction during blood flow, and increased blood flow resistance is mainly due to the influence of blood viscosity. Any factor that increases the viscosity of blood has a high potential to increase peripheral resistance and increase blood pressure, thus increasing cardiac burden. Therefore, monitoring the mass flow resistance index may improve diagnostic rates[46,47]. Based on this, we compared the endometrial thickness and blood flow resistance under two different ultrasound diagnoses. It was found that the detection rates of endometrial thickness ≤ 1.5 mm and blood flow resistance ≤ 0.5 were significantly higher in TVS diagnosis of EP than in TAS diagnosis, which is also consistent with previous studies[48]. That is to say, TVS can more accurately predict the location of the pregnancy, identify the blood flow resistance index, and improve the diagnostic rate of EP. This is related to the higher resolution and better penetration of the TVS probe, which allows for clearer visualization of the uterine cavity, endometrial changes, and blood flow. Our research also has certain limitations, the included sample size was limited, and the findings still need more multicentered studies with large samples for further confirmation. In addition, this is a retrospective study, a prospective study using these two scans for pregnant women is the next step to be undertaken.

CONCLUSION

To sum up, compared with TAS, TVS has higher diagnostic accuracy, clearer image quality, higher accuracy, and specificity in the diagnosis of EP, and is worthy of widespread promotion in the clinical setting. Of course, abdominal ultrasound also has its advantages, but it should be avoided especially for clinical use in patients with combined vaginal and intrauterine inflammation to further avoid infection aggravation. Therefore, the clinical diagnosis of EP needs to be tailored to the patient's actual situation so that the most suitable detection method can be adopted. As for the effect of combined treatment on the positive diagnosis rate, we will further explore this in the follow-up study.

ARTICLE HIGHLIGHTS

Research background

Ectopic pregnancy (EP) is the leading cause of pregnancy related deaths in the first trimester. Transvaginal ultrasound (TVS) is the key to diagnosis of EP.

Research motivation

140 patients with EP who underwent transabdominal ultrasound (TAS) and TVS were reviewed. The application value of TAS and TVS in the diagnosis of EP was discussed, and the difference between TAS and TVS was compared.

Research objectives

To explore the application value of TAS and TVS in the diagnosis of EP and improve the clinical diagnosis level of EP.

Research methods

140 patients with EP who received TAS and TVS were analyzed retrospectively. The diagnostic accuracy and misdiagnosis rate of the two kinds of ultrasound examination were compared.

Research results

The results showed that the diagnostic accuracy of TVS was significantly higher than that of TAS, and the misdiagnosis rate of TVS was lower than that of TAS, the difference was statistically significant ($P < 0.05$).

Research conclusions

For the diagnosis of EP, TVS is more accurate than TAS.

Research perspectives

Compared with TAS, TVS has higher accuracy in the diagnosis of EP, and is more safe and accurate in clinical practice, which is worthy of extensive clinical promotion.

FOOTNOTES

Author contributions: Hu HJ and Yu L designed the study; Hu HJ wrote the manuscript; Hu HJ, Sun J, and Feng R collected and analyzed the data; Feng R and Yu L revised and reviewed the manuscript; and all authors have read and approved the final manuscript.

Institutional review board statement: The study was approved by Ethics Committee of Affiliated Hangzhou Chest Hospital, Zhejiang University School of Medicine.

Informed consent statement: All study participants, or their family members, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Hui-Juan Hu 0000-0002-1694-1679; Liang Yu 0000-0002-3087-7335.

S-Editor: Liu XF
L-Editor: A
P-Editor: Yuan YY

REFERENCES

1 **Tonick S**, Conageski C. Ectopic Pregnancy. *Obstet Gynecol Clin North Am* 2022; **49**: 537-549 [PMID: 36122984 DOI: 10.1016/j.ogc.2022.02.018]

2 **Committee on Practice Bulletins—Gynecology**. ACOG Practice Bulletin No. 191: Tubal Ectopic Pregnancy. *Obstet Gynecol* 2018; **131**: e65-e77 [PMID: 29232273 DOI: 10.1097/AOG.0000000000002464]

3 **Yoder N**, Tal R, Martin JR. Abdominal ectopic pregnancy after *in vitro* fertilization and single embryo transfer: a case report and systematic review. *Reprod Biol Endocrinol* 2016; **14**: 69 [PMID: 27760569 DOI: 10.1186/s12958-016-0201-x]

4 **Belics Z**, Gérecz B, Csákány MG. Early diagnosis of ectopic pregnancy. *Orv Hetil* 2014; **155**: 1158-1166 [PMID: 25016448 DOI: 10.1556/OH.2014.29933]

5 **Lipscomb GH**. Ectopic pregnancy. Foreword. *Clin Obstet Gynecol* 2012; **55**: 375 [PMID: 22510617 DOI: 10.1097/GRF.0b013e318252c80b]

6 **Rana P**, Kazmi I, Singh R, Afzal M, Al-Abbasi FA, Aseeri A, Khan R, Anwar F. Ectopic pregnancy: a review. *Arch Gynecol Obstet* 2013; **288**: 747-757 [PMID: 23793551 DOI: 10.1007/s00404-013-2929-2]

7 **Shen Z**, Liu C, Zhao L, Xu L, Peng B, Chen Z, Li X, Zhou J. Minimally-invasive management of intramural ectopic pregnancy: an eight-case series and literature review. *Eur J Obstet Gynecol Reprod Biol* 2020; **253**: 180-186 [PMID: 32871441 DOI: 10.1016/j.ejogrb.2020.08.021]

8 **Shi L**, Huang L, Liu L, Yang X, Yao D, Chen D, Xiong J, Duan J. Diagnostic value of transvaginal three-dimensional ultrasound combined with color Doppler ultrasound for early cesarean scar pregnancy. *Ann Palliat Med* 2021; **10**: 10486-10494 [PMID: 34763495 DOI: 10.21037/apm-21-2208]

9 **Dal Moro F**, De Gobbi A, Crestani A. Transvaginal ultrasound and ureteral stones. *Ultrasound Obstet Gynecol* 2013; **42**: 244 [PMID: 23893602 DOI: 10.1002/uog.12544]

10 **Mei JY**, Afshar Y, Platt LD. First-Trimester Ultrasound. *Obstet Gynecol Clin North Am* 2019; **46**: 829-852 [PMID: 31677757 DOI: 10.1016/j.ogc.2019.07.011]

11 **Scibetta EW**, Han CS. Ultrasound in Early Pregnancy: Viability, Unknown Locations, and Ectopic Pregnancies. *Obstet Gynecol Clin North Am* 2019; **46**: 783-795 [PMID: 31677754 DOI: 10.1016/j.ogc.2019.07.013]

12 **Stamilio D**, Carlson LM. Transabdominal ultrasound is appropriate. *Am J Obstet Gynecol* 2016; **215**: 739-743.e1 [PMID: 27888999 DOI: 10.1016/j.ajog.2016.07.020]

13 **Plett SK**, Poder L, Brooks RA, Morgan TA. Transvaginal Ultrasound-Guided Biopsy of Deep Pelvic Masses: How We Do It. *J Ultrasound Med* 2016; **35**: 1113-1122 [PMID: 27091918 DOI: 10.7863/ultra.15.08002]

14 **Pedersen JK**, Sira C, Trovik J. Handheld transabdominal ultrasound, after limited training, may confirm first trimester viable intrauterine pregnancy: a prospective cohort study. *Scand J Prim Health Care* 2021; **39**: 123-130 [PMID: 33853486 DOI: 10.1080/02813432.2021.1910643]

15 **Liu JX**, Li JY, Zhao XY, Zhang QH, Cao Y, Huang XJ, Sun XF, Xie YL, Zhang ST, Yang SS. Transvaginal ultrasound- and laparoscopy-guided percutaneous microwave ablation for adenomyosis: preliminary results. *Int J Hyperthermia* 2019; **36**: 1233-1238 [PMID: 31818163 DOI: 10.1080/02656736.2019.1690169]

16 **Duchatel FC**. Ectopic pregnancy. *Curr Opin Obstet Gynecol* 1995; **7**: 472-476 [PMID: 8620082 DOI: 10.1097/00001703-199512000-00013]

17 **Naveed AK**, Anjum MU, Hassan A, Mahmood SN. Methotrexate *vs* expectant management in ectopic pregnancy: a meta-analysis. *Arch Gynecol Obstet* 2022; **305**: 547-553 [PMID: 34524502 DOI: 10.1007/s00404-021-06236-y]

18 **Moore L**. Ectopic pregnancy. *Nurs Stand* 1998; **12**: 48-53; quiz 54 [PMID: 9775912 DOI: 10.7748/ns.12.38.48.s58]

19 **Solima E**, Luciano AA. Ectopic pregnancy. *Ann N Y Acad Sci* 1997; **828**: 300-315 [PMID: 9329851 DOI: 10.1111/j.1749-6632.1997.tb48551.x]

20 **Carson SA**, Buster JE. Ectopic pregnancy. *N Engl J Med* 1993; **329**: 1174-1181 [PMID: 8377783 DOI: 10.1056/NEJM199310143291608]

21 **Shaw JL**, Diamandis EP, Horne AW, Barnhart K, Bourne T, Messinis IE. Ectopic pregnancy. *Clin Chem* 2012; **58**: 1278-1285 [PMID: 22389311 DOI: 10.1373/clinchem.2012.184168]

22 **Walker JJ**. Ectopic pregnancy. *Clin Obstet Gynecol* 2007; **50**: 89-99 [PMID: 17304026 DOI: 10.1097/GRF.0b013e31802f4f79]

23 **Al-Jabri S**, Malus M, Tulandi T. Ectopic pregnancy. *BMJ* 2010; **341**: c3770 [PMID: 20675392 DOI: 10.1136/bmj.c3770]

24 **Islam A**, Fawad A, Shah AA, Jadoon H, Sarwar I, Abbasi AU. Analysis Of Two Years Cases Of Ectopic Pregnancy. *J Ayub Med Coll Abbottabad* 2017; **29**: 65-67 [PMID: 28712177]

25 **Hendriks E**, Rosenberg R, Prine L. Ectopic Pregnancy: Diagnosis and Management. *Am Fam Physician* 2020; **101**: 599-606 [PMID: 32412215]

26 **Marion LL**, Meeks GR. Ectopic pregnancy: History, incidence, epidemiology, and risk factors. *Clin Obstet Gynecol* 2012; **55**: 376-386 [PMID: 22510618 DOI: 10.1097/GRF.0b013e3182516d7b]

27 **Richardson A**, Gallos I, Dobson S, Campbell BK, Coomarasamy A, Raine-Fenning N. Accuracy of first-trimester ultrasound in diagnosis of tubal ectopic pregnancy in the absence of an obvious extrauterine embryo: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2016; **47**: 28-37 [PMID: 25766776 DOI: 10.1002/uog.14844]

28 **Bobdiwala S**, Saso S, Verbakel JY, Al-Memar M, Van Calster B, Timmerman D, Bourne T. Diagnostic protocols for the management of pregnancy of unknown location: a systematic review and meta-analysis. *BJOG* 2019; **126**: 190-198 [PMID: 30129999 DOI: 10.1111/1471-0528.15442]

29 **Hsu S**, Euerle BD. Ultrasound in pregnancy. *Emerg Med Clin North Am* 2012; **30**: 849-867 [PMID: 23137399 DOI: 10.1016/j.emc.2012.08.001]

30 **Andres MP**, Borrelli GM, Ribeiro J, Baracat EC, Abrão MS, Kho RM. Transvaginal Ultrasound for the Diagnosis of Adenomyosis: Systematic Review and Meta-Analysis. *J Minim Invasive Gynecol* 2018; **25**: 257-264 [PMID: 28864044 DOI: 10.1016/j.jmig.2017.08.653]

31 **Dueholm M**, Lundorf E. Transvaginal ultrasound or MRI for diagnosis of adenomyosis. *Curr Opin Obstet Gynecol* 2007; **19**: 505-512 [PMID: 18007126 DOI: 10.1097/GCO.0b013e3282f1bf00]

32 **Liu L**, Li W, Leonardi M, Condous G, Da Silva Costa F, Mol BW, Wong L. Diagnostic Accuracy of Transvaginal Ultrasound and Magnetic Resonance Imaging for Adenomyosis: Systematic Review and Meta-Analysis and Review of Sonographic Diagnostic Criteria. *J Ultrasound Med* 2021; **40**: 2289-2306 [PMID: 33502767 DOI: 10.1002/jum.15635]

33 **Kirk E**. Ultrasound in the diagnosis of ectopic pregnancy. *Clin Obstet Gynecol* 2012; **55**: 395-401 [PMID: 22510620 DOI: 10.1097/GRF.0b013e31824e35fe]

34 **Casikar I**, Reid S, Condous G. Ectopic pregnancy: Ultrasound diagnosis in modern management. *Clin Obstet Gynecol* 2012; **55**: 402-409 [PMID: 22510621 DOI: 10.1097/GRF.0b013e31825109bd]

35 **Calì G**, Timor-Tritsch IE, Palacios-Jaraquemada J, Monteaugudo A, Buca D, Forlani F, Familiari A, Scambia G, Acharya G, D'Antonio F. Outcome of Cesarean scar pregnancy managed expectantly: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2018; **51**: 169-175 [PMID: 28661021 DOI: 10.1002/uog.17568]

36 **Bignardi T**, Alhamdan D, Condous G. Is ultrasound the new gold standard for the diagnosis of ectopic pregnancy? *Semin Ultrasound CT MR* 2008; **29**: 114-120 [PMID: 18450136 DOI: 10.1053/j.sult.2008.01.001]

37 **Yang H**, Wang R, Zhao L, Ye J, Li N, Kong L. Diagnosis and Analysis of Transabdominal and Intracavitary Ultrasound in Gynecological Acute Abdomen. *Comput Math Methods Med* 2021; **2021**: 9508838 [PMID: 35003327 DOI: 10.1155/2021/9508838]

38 **Flisser E**, Grifo JA, Krey LC, Noyes N. Transabdominal ultrasound-assisted embryo transfer and pregnancy outcome.

Fertil Steril 2006; **85**: 353-357 [PMID: 16595211 DOI: 10.1016/j.fertnstert.2005.08.015]

39 **Derbak A**. Ectopic pregnancy in the ultrasound. Case reports. Retrospektive analysis. *Ceska Gynekol* 2016; **81**: 63-70 [PMID: 26982068]

40 **Brady PC**. New Evidence to Guide Ectopic Pregnancy Diagnosis and Management. *Obstet Gynecol Surv* 2017; **72**: 618-625 [PMID: 29059454 DOI: 10.1097/OGX.0000000000000492]

41 **Zahálková L**, Kacerovský M. Cesarean scar ectopic pregnancy. *Ceska Gynekol* 2016; **81**: 414-419 [PMID: 27918158]

42 **Ramanan RV**, Gajaraj J. Ectopic pregnancy--the leash sign. A new sign on transvaginal Doppler ultrasound. *Acta Radiol* 2006; **47**: 529-535 [PMID: 16796320 DOI: 10.1080/02841850600644782]

43 **Shaw JL**, Horne AW. The paracrinology of tubal ectopic pregnancy. *Mol Cell Endocrinol* 2012; **358**: 216-222 [PMID: 21827822 DOI: 10.1016/j.mce.2011.07.037]

44 **Levine Y**, Yahav L, Schwarzman P, Yohai D, Hershkovitz R, Weintraub AY. The correlation between endometrial thickness and the criteria for MTX treatment for ectopic pregnancy. *J Obstet Gynaecol* 2021; **41**: 1230-1233 [PMID: 33616483 DOI: 10.1080/01443615.2020.1849068]

45 **Babayev E**, Robins JC. Endometrial thickness as an independent risk factor for ectopic pregnancy in in vitro fertilization: should we change our counseling and practice? *Fertil Steril* 2020; **113**: 78-79 [PMID: 32033730 DOI: 10.1016/j.fertnstert.2019.10.033]

46 **Marossy A**, Svorc P, Kron I, Gresová S. Hemorheology and circulation. *Clin Hemorheol Microcirc* 2009; **42**: 239-258 [PMID: 19628890 DOI: 10.3233/CH-2009-1192]

47 **Hale SA**, Schonberg A, Badger GJ, Bernstein IM. Relationship between prepregnancy and early pregnancy uterine blood flow and resistance index. *Reprod Sci* 2009; **16**: 1091-1096 [PMID: 19657141 DOI: 10.1177/1933719109341843]

48 **Fang T**, Chen M, Yu W, Ma T, Su Z, Chan DYL, Zhao M, Zheng Q, Wang W. The predictive value of endometrial thickness in 3117 fresh IVF/ICSI cycles for ectopic pregnancy. *J Gynecol Obstet Hum Reprod* 2021; **50**: 102072 [PMID: 33508484 DOI: 10.1016/j.jogoh.2021.102072]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 2956-2965

DOI: 10.12998/wjcc.v11.i13.2956

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Assessment of knowledge, cultural beliefs, and behavior regarding medication safety among residents in Harbin, China

Xuan-Tong Liu, Na Wang, Li-Qiu Zhu, Yu-Bo Wu

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Capparè P, Italy; Chakrabarti S, India; Zhang Y, China

Received: August 1, 2022
Peer-review started: August 1, 2022
First decision: October 24, 2022
Revised: November 9, 2022
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 6, 2023

Xuan-Tong Liu, Yu-Bo Wu, Department of Pharmacy, The Fourth Hospital of Harbin Medical University, Harbin 150001, Heilongjiang Province, China

Na Wang, Department of Pharmacy, Heilongjiang Provincial Hospital, Harbin 150001, Heilongjiang Province, China

Li-Qiu Zhu, Ge Xin Community Health Service Center, Harbin 150001, Heilongjiang Province, China

Corresponding author: Xuan-Tong Liu, MD, Doctor, Department of Pharmacy, The Fourth Hospital of Harbin Medical University, No. 37 Yiyuan Street, Harbin 150001, Heilongjiang Province, China. liuxuantong1986@126.com

Abstract

BACKGROUND

Medication misuse or overuse is significantly associated with poor health outcomes. Information regarding the knowledge, cultural beliefs, and behavior about medication safety in the general population is important.

AIM

To conduct a survey on medication habits and explored the potential factors impacting medication safety.

METHODS

The current survey included adults from 18 districts and counties in Harbin, China. A questionnaire on medication safety was designed based on knowledge, cultural beliefs, and behavior. Both univariate and multivariate analyses were used to explore the factors that impacted medication safety.

RESULTS

A total of 394 respondents completed the questionnaires on medication safety. The mean scores for knowledge, cultural beliefs, and behavior about medication safety were 59.41 ± 19.33, 40.66 ± 9.24, and 60.97 ± 13.69, respectively. The medication knowledge score was affected by age (P = 0.044), education (P < 0.001), and working status (P = 0.015). Moreover, the cultural beliefs score was significantly affected by education (P < 0.001). Finally, education (P = 0.003) and working status (P = 0.011) significantly affected the behavior score.

CONCLUSION

The knowledge, cultural beliefs, and behavior about medication safety among the general population was moderate. Health education should be provisioned for the elderly, individuals with a low education level, and the unemployed to improve medication safety in Harbin, China.

Key Words: Knowledge; Cultural beliefs; Behavior; Medication safety; Cross-sectional study

Core Tip: Despite its importance, little work has been done to understand the knowledge, cultural beliefs, and behavior around medication safety among the public. To conduct a survey on medication habits and explored the potential factors impacting medication safety. This study described the knowledge, cultural beliefs, and behavior around medication safety in the general population of Harbin, China, and identified factors that impact these aspects.

Citation: Liu XT, Wang N, Zhu LQ, Wu YB. Assessment of knowledge, cultural beliefs, and behavior regarding medication safety among residents in Harbin, China. *World J Clin Cases* 2023; 11(13): 2956-2965
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/2956.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.2956

INTRODUCTION

Inappropriate medication use and adverse drug events can cause adverse health outcomes. Thus the provision of safe medications is a priority for health care[1]. Medication safety and pharmacovigilance are essential for healthcare systems to ensure patient safety. It has been demonstrated that medication safety is significantly related to preventable hospitalization and increased economic burden[2]. The medication treatment process includes the doctor's prescription, pharmacist's check-ups, and administration to the patient; medication safety is important at all three stages.

Medication-related problems have become an important cause of patient injury in China. The Global Burden of Disease Study indicated that drug abuse was China's 18th most common reason for disability-adjusted life years in China[3]. Moreover, the incidence of drug-induced liver injury in China was 23.90 per 100000 people annually, as reported in 2019, which was higher than that in Western countries[4]. Furthermore, medication-derived acute kidney injuries (AKIs) account for 37.50% of hospital-acquired AKIs[5]. Given that the high incidence of medication-related problems is significantly associated with increased risks of morbidity and mortality and that the coronavirus disease 2019 pandemic has already disrupted the daily work of clinicians, the general population needs to be attentive to medication safety [6-10].

A prior study found that only 49.47% of the respondents answered correctly about antibiotic use and drug resistance, and 19.96% answered that they did not know how to use their medicines[11]. These results suggest that popular science books and public lectures on medication should be introduced for local residents. Currently, self-administrated, over-the-counter (OTC) medications are used for disease symptoms identified through self-diagnosis, by choice, and for medical use[12,13]. Moreover, high literacy rates in elderly populations provide the best conditions for the use of OTC medications[14]. They are associated with a lower economic burden and are fully accessible at pharmacies[15,16]. However, the wide use of OTC medications could cause more medication safety events[12,15]. Considering that poor medication safety in the general population is related to a lack of medication knowledge, poor safety awareness, and incorrect medication behavior, this study investigated the knowledge, cultural beliefs, behavior, and factors impacting those aspects of medication safety in the general population of Harbin, China.

MATERIALS AND METHODS

Study design and setting

This cross-sectional study included 552 Chinese citizens aged > 18.0 years from 18 districts and counties in Harbin, China, between April and June 2021. This study was approved by the ethics committee of the Fourth Hospital of Harbin Medical University. An approaching sampling approach was adopted, and the adult residents of Harbin were the survey objects. The sample size in our study was calculated using the following formula: $n\ (\text{required sample size}) = \frac{(\frac{Z_{\alpha/2} \times \text{variance}}{\delta})^2 \times \text{N}}{\text{N} + (\frac{Z_{\alpha/2} \times \text{variance}}{\delta})^2}$, N: Total population in Harbin (10009854); δ

(allowable error): 0.20; variance: 1.58; $Z_{\alpha/2}$: 1.96. This indicated that at least 240 individuals should be recruited. The questionnaire was distributed using both online and offline methods. The online questionnaire relied on the WeChat application, and the Wenjuanxing platform was the data collection carrier. To eliminate responses from those who did not fill in the answers carefully, online responses to back-end statistics completed in less than 180 s were eliminated from the analysis. Subsequently, an objective test was conducted based on the same questions, and those with inconsistent answers to these questions were also eliminated.

The offline survey was carried out as follows: The investigator issued the questionnaire and allowed the respondents to complete it independently, after which the investigator captured the data onto a database. This all took place on-site. Elderly adults completed the paper questionnaire with the help of the investigators. Data from the offline survey were entered in Epi Info (CDC, Atlanta, Georgia, United States). Investigators were trained at a community health service center, and experiences were shared to assist in dealing with problems that may arise during the investigation process. In the end, 394 questionnaires were used for further analyses.

Questionnaire design

The questionnaire was developed based on the knowledge, cultural beliefs, behavior, and medication safety items in the Science and Technology Development Center of the Chinese Pharmaceutical Association (Supplementary material)[17]. The reliability of the questionnaire was assessed; Cronbach's α was 0.883[18]. It contained questions regarding gender, age, income, medical insurance, education level, working status, occupation, drug and medication knowledge, cultural beliefs toward the exposure to and treatment of medication knowledge *via* lectures or education, and behaviors related to the medication process. A six-level score system was applied for each question in the questionnaire, which was quantified using the Likert Scale, and scored as follows: (1) Strongly disagree; (2) Disagree; (3) General; (4) Agree; (5) Strongly agree; and (6) Unclear. High scores in each item indicated patients at high risk. The knowledge domain included 27 questions, and the scoring system ranged from 27 to 162; a score of 27-54 was defined as excellent, 55-82 as good, and > 82 as to be improved. The cultural beliefs domain included 11 questions, and the scoring system ranged from 11 to 66; a score of 11-22 was defined as excellent, 23-33 as good, and > 33 as to be improved. The behavior domain included 24 questions, and the scoring system ranged from 24 to 144; a score of 24-48 was defined as excellent, 49-72 as good, and > 72 as to be improved.

Statistical analysis

The knowledge, cultural beliefs, and behavior scores were presented as means ± SD, and the scores according to individuals' characteristics were compared using independent *t*-tests or one-way ANOVA. The Bonferroni method was applied to assess differences between groups where the one-way ANOVA indicated significant differences. Categorical variables were presented as frequencies and proportions. Multivariate linear regression was applied to explore the impact factors of knowledge, cultural beliefs, and behavior. Variable screening was performed using the step-by-step entry method, and the regression coefficient of the multivariate linear regression model was used to estimate the parameters (α = 0.05, β = 0.10). All reported *P* values were two-sided, and the inspection level was 0.05. All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0 (SPSS 26.0).

RESULTS

Knowledge, cultural beliefs, and behavior scores for medication risk in Harbin residents

The total score for knowledge, cultural beliefs, and behavior was 161.23 ± 33.05, and the mean scores for knowledge, cultural beliefs, and behavior were 59.41 ± 19.33, 40.66 ± 9.24, and 60.97 ± 13.69, respectively (Table 1). The scoring rate was defined as mean score/total score and was considered high at < 20%, medium at 20%-49%, and low at > 50%. The scoring rates for medication knowledge, cultural beliefs, and behavior were 36.67%, 61.61%, and 42.34%, respectively. Therefore, the medication knowledge and behavior scoring rates were medium and for cultural beliefs it was low. We noted that the scoring rate for knowledge of antibacterial drugs was the lowest (35.75%), and that of drug stores was the highest (39.25%). Moreover, the scoring rate for medication purchase behavior (59.39%) and expired medication management (54.89%) were both low in the behavior domain.

Knowledge, cultural beliefs, and behavior scores according to demographic characteristics

The knowledge, cultural beliefs, and behavior scores of medication risk according to demographic characteristics are shown in Table 2. We noted significant differences in knowledge scores when stratified by age ($P < 0.001$), income ($P = 0.035$), education level ($P < 0.001$), working status ($P < 0.001$), and occupation ($P = 0.043$). Moreover, the cultural beliefs scores were statistically significant when stratified by medical insurance ($P = 0.007$), education level ($P = 0.002$), working status ($P = 0.047$), and occupation ($P = 0.041$). Finally, the behavior scores differed significantly when stratified by age ($P =$

Table 1 The scores for each dimensions in KAP model

Domain	Total level/factor	Number of items	Range	mean ± SD	Scoring rate, %
Knowledge	Medicine tips	13	13-78	28.08 ± 9.70	35.9
	Antibacterial drugs	6	6-36	12.87 ± 5.56	35.75
	Drug withdrawal	4	4-24	9.22 ± 3.69	38.42
	Drug store	2	2-12	4.71 ± 1.99	39.25
	Drug selection	2	2-12	4.54 ± 1.98	37.83
	Total scores	27	27-162	59.41 ± 19.33	36.67
Cultural beliefs	Cultural beliefs 1	6	6-36	26.90 ± 5.57	74.72
	Cultural beliefs 2	5	5-30	13.76 ± 6.22	45.87
	Total scores	11	14-66	40.66 ± 9.24	61.61
Behavior	Premeditation behavior	8	9-48	22.24 ± 6.24	46.33
	Behavior in medication	3	3-18	4.91 ± 2.48	27.28
	Medication compliance	6	6-36	11.31 ± 4.50	31.42
	Medication storage behavior	3	3-18	8.53 ± 3.11	47.39
	Medication purchasing behavior	3	4-18	10.69 ± 2.33	59.39
	Expired medication management	1	1-6	3.29 ± 1.52	54.83
	Total scores	24	35-144	60.97 ± 13.69	42.34

0.049), education level (P = 0.024), and working status (P = 0.007).

Impact factors on knowledge, cultural beliefs, and behavior scores

Table 3 presents the results of the multivariate linear regression of knowledge, cultural beliefs, and behavior scores. We noted that knowledge scores could be affected by age (P = 0.044), education level (P < 0.001), and working status (P = 0.015) but not by salary (P = 0.317) and occupation (P = 0.411). Moreover, the cultural beliefs score was affected by education level (P < 0.001) but not by medical insurance (P = 0.153) and working status (P = 0.514) after adjusting potential confounders. Finally, education level (P = 0.003) and working status (P = 0.011) were significantly associated with the behavior score, while age was not (P = 0.054).

DISCUSSION

This cross-sectional study aimed to assess the knowledge, cultural beliefs, and behavior around medication safety in the general population of Harbin, China. We noted that the knowledge, cultural beliefs, and behavior for medication safety in the general population were relatively good. Moreover, we noted that increased age could affect medication safety knowledge, education level could affect knowledge, cultural beliefs, and behavior scores, and working status could affect knowledge and behavior scores.

Several studies have addressed people's knowledge, attitude, and behavior around medication safety [19-21]. One cross-sectional study included healthcare practitioners from a tertiary care setting in Saudi Arabia and found that their staff had sufficient knowledge regarding medication error reporting. However, medication errors are generally under-reported in practice[19]. Al-Mutairi *et al*[20] suggested that educational programs should be applied to improve adverse drug reaction reporting rates after reporting positive attitudes and satisfactory practices relating to medication safety knowledge, attitude, and behavior among hospital pharmacists. Lee *et al*[21] surveyed the knowledge, attitude, and behavior of elderly Korean adults and found that knowledge regarding medication use was positively related to their attitudes and practices. However, no study to date has focused on the knowledge, cultural beliefs, and behavior of the general population in China. Therefore, the current study was carried out to describe these aspects and the factors affecting them in the general population.

Our study found that the knowledge, cultural beliefs, and behavior scores for medication safety in the general population were 59.41, 40.66, and 60.97, respectively, and the total score was 161.23. For the knowledge domain category, we noted that understanding related to the application of antibacterial drugs was relatively acceptable, and the level of rational knowledge of drug stores needed to be strengthened. However, we noted that behaviors related to purchasing medication and management of

Table 2 The knowledge, cultural beliefs, and behavior scores of medication risk according to demographic characteristics

Variable	Number	Knowledge			Cultural beliefs			Behavior		
		Scores	*t*/*F* value	*P* value	Scores	*t*/*F* value	*P* value	Scores	*t*/*F* value	*P* value
Gender										
Male	116	57.38 ± 17.26	-1.349	0.178	41.74 ± 9.35	1.262	0.208	60.19 ± 11.10	-0.73	0.466
Female	278	60.26 ± 20.10			40.47 ± 9.00			61.29 ± 14.64		
Age (yr)										
19-34	135	54.52 ± 22.70	8.047	< 0.001	40.81 ± 9.71	0.03	0.993	62.47 ± 15.95	2.644	0.049
35-49	158	58.97 ± 16.45			40.89 ± 9.14			59.69 ± 11.96		
50-64	67	66.24 ± 18.03			40.64 ± 9.02			58.84 ± 12.94		
Over 65	34	67.41 ± 12.68			41.21 ± 6.79			65.18 ± 11.80		
Salary (RMB)										
< 1000	19	54.95 ± 11.91	2.606	0.035	42.53 ± 8.93	0.776	0.542	63.47 ± 10.41	0.654	0.624
1000-2000	50	64.12 ± 22.38			42.22 ± 9.11			60.94 ± 13.61		
2000-4000	158	61.63 ± 20.31			40.68 ± 9.32			61.71 ± 14.67		
4000-6000	93	56.94 ± 18.78			40.99 ± 9.38			60.77 ± 15.10		
> 6000	74	55.74 ± 16.01			39.66 ± 8.38			59.01 ± 10.06		
Medical insurance										
Social basic	309	58.54 ± 18.74	2.021	0.091	40.34 ± 9.08	3.544	0.007	60.58 ± 13.54	0.996	0.409
Commercial	14	66.86 ± 14.60			43.29 ± 7.43			62.14 ± 10.90		
Self-funded	23	56.87 ± 13.67			44.30 ± 8.86			66.13 ± 13.89		
Free	16	58.38 ± 15.49			36.44 ± 6.68			59.06 ± 9.13		
Others	32	66.94 ± 28.50			44.38 ± 9.83			61.50 ± 17.40		
Education level										
Postgraduates	22	48.00 ± 18.84	11.661	< 0.001	36.82 ± 9.61	3.804	0.002	56.64 ± 9.33	2.628	0.024
Undergraduates	141	53.35 ± 13.39			39.19 ± 9.39			59.20 ± 11.32		
College students	125	60.82 ± 19.13			41.30 ± 8.76			61.78 ± 16.32		
Secondary or senior high	62	64.31 ± 18.70			42.89 ± 9.33			61.02 ± 13.69		

Junior high school	41	74.56 ± 26.50			43.68 ± 7.04			65.95 ± 13.23		
Primary school	3	61.00 ± 12.77			48.33 ± 1.53			73.33 ± 2.31		
Working status										
On-the-job	285	56.58 ± 19.07	12.137	< 0.001	40.45 ± 9.43	3.072	0.047	59.86 ± 13.59	5.027	0.007
Retired	63	65.35 ± 14.05			40.35 ± 7.89			61.90 ± 13.09		
Unemployed	46	68.83 ± 22.47			43.96 ± 8.20			66.57 ± 13.92		
Occupation										
Enterprise workers	58	60.86 ± 16.57	2.025	0.043	59.41 ± 19.33	2.038	0.041	60.45 ± 11.54	1.242	0.273
Company employees	76	56.25 ± 17.60			41.67 ± 10.58			61.41 ± 13.23		
Cadres	25	60.52 ± 16.95			41.53 ± 8.07			58.84 ± 9.86		
Medical institution	98	55.01 ± 18.81			39.20 ± 7.83			58.27 ± 12.49		
Teachers	8	61.50 ± 18.68			38.52 ± 9.58			60.88 ± 6.69		
Enterprise management	15	68.93 ± 23.21			37.75 ± 7.78			63.87 ± 24.99		
Freelanced	47	64.57 ± 21.90			39.40 ± 8.98			64.00 ± 10.95		
Students	11	64.55 ± 30.39			41.98 ± 7.55			66.64 ± 25.47		
Others	56	60.86 ± 16.57			40.64 ± 12.67			62.18 ± 15.12		

expired medication were poor. There could be several reasons for this. Harbin residents do not frequently participate in lectures or educational activities on medication knowledge, and only 40.03% of the respondents supported the idea that these educational activities should be carried out in various ways. The low participation rate may be because such activities do not attract all audiences; young people prefer internet-based science education, and the elderly prefer one-on-one learning within their communities. In addition, the sick and the healthy have different concerns regarding medications, and media coverage of this is very limited. Unfortunately, certain healthcare companies have deceived the public in the name of "health lectures" and "free physical examinations". This has affected the public's enthusiasm and willingness to participate in knowledge-seeking educational activities on medication carried out by hospitals and pharmacists.

Our study found that the elderly had less knowledge of medication safety. This may be because the elderly use more medication than any other group. Physically, the elderly are in a degraded state of function, and multiple integrated diseases are more common among them. Therefore, there are more varieties of medications for the elderly, which are associated with an increased risk of medication error [21]. Moreover, knowledge, cultural beliefs, and behavior scores were significantly related to education levels. In our study, the literacy rate among the 3 (0.76%) individuals with a primary school level education was 100%, which was higher than the literacy rate in the elderly population. Low education levels are significantly related to low medication knowledge levels, leading to an increased risk of

Table 3 Multivariate linear regression of knowledge, cultural beliefs, and behavior scores

Domain	Factors	Non-standardized coefficients		Standardized coefficients	*t*	*P* value	95.0% confidence interval for B	
		B	SE	Beta			LL	UL
Knowledge	Constant	30.764	5.402	-	5.695	< 0.001	20.143	41.385
	Age	2.242	1.109	0.108	2.022	0.044	0.062	4.422
	Salary	0.947	0.946	0.053	1.002	0.317	-0.912	2.807
	Education	4.926	0.948	0.281	5.196	< 0.001	3.062	6.79
	Working status	3.775	1.542	0.134	2.447	0.015	0.742	6.807
	Occupation	0.3	0.365	0.042	0.823	0.411	-0.417	1.017
Cultural beliefs	Constant	34.41	1.51	-	22.795	< 0.001	31.442	37.378
	Medical insurance	0.524	0.366	0.072	1.432	0.153	-0.195	1.244
	Education	1.585	0.427	0.192	3.711	< 0.001	0.745	2.424
	Working status	0.466	0.713	0.035	0.653	0.514	-0.935	1.866
Behavior	Constant	54.513	2.23	-	24.44	< 0.001	50.128	58.898
	Age	-1.53	0.793	-0.104	-1.929	0.054	-3.09	0.029
	Education	1.988	0.674	0.16	2.948	0.003	0.662	3.313
	Working status	2.666	1.042	0.134	2.558	0.011	0.617	4.716

LL: Low level; UL: Upper level.

medication error. People with low education levels develop their knowledge of medication use through experience and intuition, and their awareness of the risks associated with medication error is insufficient[22]. Comparatively, highly educated people have a greater desire for knowledge of medication safety, and medication guidance is sought to understand safety issues better[23]. Furthermore, knowledge and behavior scores could be affected by work status; unemployment was linked with high scores for the risks associated with medication safety. A reason for this could be that the unemployed are less aware of the importance of obtaining knowledge on medication safety. Therefore, to improve residents' literacy on medication safety, the elderly, less educated, and unemployed should seek rational knowledge of medications and enhance their awareness of medication safety. Therefore, some interventions should be applied to improve medication safety, including: (1) Outpatient pharmacy services and drug consultation offices should be provided for patients (especially high-risk patients) to improve medication safety; (2) Health education should be introduced for medication used according to the patients' characteristics and should encompass both an online and offline approach; and (3) Medication follow-up visits and management should be monitored by an online platform, like WeChat official.

Several limitations of the current study should be acknowledged. First, this study was cross-sectional, and the causalities associated with the impact factors of knowledge, cultural beliefs, and behavior could not be obtained. Second, the survey was conducted using both online and offline methods, and the quality of the completed questionnaires differed between the two, which could induce uncontrolled information bias. Third, some of the questionnaires completed online within 180 s were ruled out, and this potential selection bias could affect the analysis outcomes. Finally, we recruited individuals from 18 districts using an approaching sampling approach, and the difference in districts might affect knowledge, cultural beliefs, and behavior.

CONCLUSION

This study found that the knowledge, cultural beliefs, and behavior associated with medication safety in the general population of Harbin, China was moderate, and the main factors impacting them included age, education level, and working status. Therefore, health education should be applied to improve medication safety for the elderly, individuals with low levels of education, and the unemployed.

ARTICLE HIGHLIGHTS

Research background

The Global Burden of Disease Study indicated that drug abuse was China's 18th most common reason for disability-adjusted life years. Moreover, the incidence of drug-induced liver injury in China was 23.90 per 100000 people annually, as reported in 2019, which was higher than that in Western countries. The high incidence of medication errors and adverse events is significantly associated with an increased risk of morbidity, mortality, prolonged hospitalization, and increased economic burden.

Research motivation

The knowledge, cultural beliefs, and behavior around medication safety in the general population are important, and no study to date has focused on the general population in China.

Research objectives

The knowledge, cultural beliefs, and behavior regarding medication safety were described, and factors potentially impacting those aspects were explored.

Research methods

This cross-sectional survey recruited from 18 districts and counties in Harbin, China. The knowledge, cultural beliefs, and behavior for medication safety were obtained from a questionnaire. Both univariate and multivariate analyses were used to explore the factors that impacted medication safety.

Research results

The mean scores for knowledge, cultural beliefs, and behavior were 59.41, 40.66, and 60.97, respectively. The medication knowledge score was affected by age ($P = 0.044$), education ($P < 0.001$), and working status ($P = 0.015$); the cultural beliefs score was significantly affected by education ($P < 0.001$); working status ($P = 0.011$) and education ($P = 0.003$) were significantly associated with behavior score.

Research conclusions

Knowledge, cultural beliefs, and behavior about medication safety in the general population were moderate, and the main impact factors were age, education, and working status.

Research perspectives

The elderly, individuals with a low education level, and the unemployed should receive further health education to ensure the safe use of medications in Harbin, China.

FOOTNOTES

Author contributions: Liu XT conceived and designed the experiments; Liu XT, Wang N, Zhu LQ, and Wu YB performed the experiments; Liu XT and Wang N analyzed the data and wrote the paper; Liu XT contributed reagents/materials/analysis tools; and all author shave read and approved the final version of this manuscript.

Supported by 2021 Science Popularization Research Project of National Medical Information Network, Chinese Pharmaceutical Association, No. CMEI2021KPYJ00101.

Institutional review board statement: This study was approved by the ethics committee of the Fourth Hospital of Harbin Medical University.

Informed consent statement: All patients who met the inclusion criteria were informed of the purpose of the study with the delivery of an information sheet and were invited to participate. All of them expressed their verbal consent and there was no refusal to participate.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Country/Territory of origin: China

ORCID number: Xuan-Tong Liu 0000-0003-1979-8158.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Zhang YL

REFERENCES

1 **Garrouste-Orgeas M**, Philippart F, Bruel C, Max A, Lau N, Misset B. Overview of medical errors and adverse events. *Ann Intensive Care* 2012; **2**: 2 [PMID: 22339769 DOI: 10.1186/2110-5820-2-2]
2 **Ulucanlar S**. Letter in response to: Greenhalgh T, Ozbilgin MF, Prainsack B, Shaw S. Moral entrepreneurship, the power-knowledge nexus, and the Cochrane "crisis". J Eval Clin Pract 2019;1-9. *J Eval Clin Pract* 2019; **25**: 726-727 [PMID: 31087490 DOI: 10.1111/jep.13173]
3 **Zhou M**, Wang H, Zeng X, Yin P, Zhu J, Chen W, Li X, Wang L, Liu Y, Liu J, Zhang M, Qi J, Yu S, Afshin A, Gakidou E, Glenn S, Krish VS, Miller-Petrie MK, Mountjoy-Venning WC, Mullany EC, Redford SB, Liu H, Naghavi M, Hay SI, Murray CJL, Liang X. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2019; **394**: 1145-1158 [PMID: 31248666 DOI: 10.1016/S0140-6736(19)30427-1]
4 **Chinese Medical Association**. [Guideline for primary care of drug-induced liver injury (2019)]. *Chin J Gener Pract* 2020; **19**: 868-875
5 **Liu C**, Yan S, Wang Y, Wang J, Fu X, Song H, Tong R, Dong M, Ge W, Yang H, Wang C, Xia P, Zhao L, Shen S, Xie J, Xu Y, Ma P, Li H, Lu S, Ding Y, Jiang L, Lin Y, Wang M, Qiu F, Feng W, Yang L. Drug-Induced Hospital-Acquired Acute Kidney Injury in China: A Multicenter Cross-Sectional Survey. *Kidney Dis (Basel)* 2021; **7**: 143-155 [PMID: 33824870 DOI: 10.1159/000510455]
6 **Aspden P**, Aspden P. Preventing medication errors: Medication errors. *N Engl J Med* 2007; **357**: 624-625 [DOI: 10.1056/NEJMbkrev58255]
7 **Arena S**. Letter to the editorResponse to: Russo A, Capogrosso P, La Croce G, *et al*. Serenoa repens, selenium and lycopene to manage lower urinary tract symptoms suggestive for benign prostatic hyperplasia. Expert Opin Drug Saf. 2016 Jun;1:1-10. *Expert Opin Drug Saf* 2016; **15**: 1449 [PMID: 27558894 DOI: 10.1080/14740338.2016.1228556]
8 **Formica D**, Sultana J, Cutroneo PM, Lucchesi S, Angelica R, Crisafulli S, Ingrasciotta Y, Salvo F, Spina E, Trifirò G. The economic burden of preventable adverse drug reactions: a systematic review of observational studies. *Expert Opin Drug Saf* 2018; **17**: 681-695 [PMID: 29952667 DOI: 10.1080/14740338.2018.1491547]
9 **Paolone G**, Mazzitelli C, Formiga S, Kaitsas F, Breschi L, Mazzoni A, Tete G, Polizzi E, Gherlone E, Cantatore G. One-year impact of COVID-19 pandemic on Italian dental professionals: a cross-sectional survey. *Minerva Dent Oral Sci* 2022; **71**: 212-222 [PMID: 34851068 DOI: 10.23736/S2724-6329.21.04632-5]
10 **Gherlone E**, Polizzi E, Tetè G, Capparè P. Dentistry and Covid-19 pandemic: operative indications post-lockdown. *New Microbiol* 2021; **44**: 1-11 [PMID: 33135082]
11 **Wu YX**, Wang EH, Zhao XJ, Han FX, Zhang JG, Cui L, Chen J, Wu PP. Knowledge, attitude, and practice of medication among Haikou residents. *Ann Palliat Med* 2021; **10**: 6883-6891 [PMID: 34237986 DOI: 10.21037/apm-21-1295]
12 **World Health Organization**. Guidelines for the Regulatory Assessment of Medicinal Products for Use in Self-Medication. [cited 15 October 2022]. Available from: http://apps.who.int/medicinedocs/en/d/Js2218e/
13 **Amoako EP**, Richardson-Campbell L, Kennedy-Malone L. Self-medication with over-the-counter drugs among elderly adults. *J Gerontol Nurs* 2003; **29**: 10-15 [PMID: 13677155 DOI: 10.3928/0098-9134-20030801-05]
14 **Du P**, Li L. [The development trend of education achievement of the elderly in China]. Population & Development 2022; 28: 59-67
15 **Zaprutko T**, Koligat D, Michalak M, Wieczorek M, Józiak M, Ratajczak M, Szydłowska K, Miazek J, Kus K, Nowakowska E. Misuse of OTC drugs in Poland. *Health Policy* 2016; **120**: 875-881 [PMID: 27344198 DOI: 10.1016/j.healthpol.2016.06.008]
16 **Delavar F**, Pashaeypoor S, Negarandeh R. The effects of self-management education tailored to health literacy on medication adherence and blood pressure control among elderly people with primary hypertension: A randomized controlled trial. *Patient Educ Couns* 2020; **103**: 336-342 [PMID: 31451361 DOI: 10.1016/j.pec.2019.08.028]
17 **Chinese Pharmaceutical Association**. KAP survey on drug use behavior risk among Chinese residents. [cited 15 October 2022]. Available from: https://www.wjx.cn/jq/35349073.aspx
18 **Li Y**, Gai D, Han C, Ma X, Yuan S, Feng X. The influencing of drug use risk among Beijing residents. *Clin Med J* 2019; **17**: 59-63 [DOI: 10.3969/j.issn.1672-3384.2019.03.014]
19 **Alsulami SL**, Sardidi HO, Almuzaini RS, Alsaif MA, Almuzaini HS, Moukaddem AK, Kharal MS. Knowledge, attitude and practice on medication error reporting among health practitioners in a tertiary care setting in Saudi Arabia. *Saudi Med J* 2019; **40**: 246-251 [PMID: 30834419 DOI: 10.15537/smj.2019.3.23960]
20 **Al-Mutairi A**, AlFayyad I, Altannir Y, Al-Tannir M. Medication safety knowledge, attitude, and practice among hospital pharmacists in tertiary care hospitals in Saudi Arabia: a multi-center study. *Arch Public Health* 2021; **79**: 130 [PMID: 34253257 DOI: 10.1186/s13690-021-00616-1]

21 **Lee M**, Kim K, Rhew K, Choi KH. A Knowledge, Attitude, and Practice Survey on Medication Safety in Korean Older Adults: An Analysis of an Ageing Society. *Healthcare (Basel)* 2021; **9** [PMID: 34683048 DOI: 10.3390/healthcare9101365]

22 **Xu X**, Yang Y, Fan Q, Zhu Z. The knowledge, attitude and practice of hospital pharmacists on the safety issues of antitumor agents for the patients discharged in China. *Transl Cancer Res* 2021; **10**: 201-209 [PMID: 35116252 DOI: 10.21037/tcr-20-2418]

23 **Liu ZR**, Deng YH. Status of medication education among residents in Guangdong province. *Chin J Public Health* 2014; **30**: 767-769 [DOI: 10.11847/zgggws2014-30-06-23]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 2966-2980

DOI: 10.12998/wjcc.v11.i13.2966

ISSN 2307-8960 (online)

SYSTEMATIC REVIEWS

Palliative oral care in terminal cancer patients: Integrated review

Ana Rute Preis Silva, Augusto Vanni Bodanezi, Emanuely Silva Chrun, Mariah Luz Lisboa, Alessandra R de Camargo, Etiene Andrade Munhoz

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Dasuqi SA, Saudi Arabia; El-Gendy HA, Egypt

Received: December 21, 2022
Peer-review started: December 21, 2022
First decision: February 8, 2023
Revised: March 7, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 6, 2023

Ana Rute Preis Silva, Augusto Vanni Bodanezi, Alessandra R de Camargo, Department of Dentistry, Federal University of Santa Catarina, Florianopolis 88040-379, Brazil

Emanuely Silva Chrun, Department of Pathology, Federal University of Santa Catarina, Florianopolis 88040900, Brazil

Mariah Luz Lisboa, Professor Polydoro São Thiago Ernani Hospital, Federal University of Santa Catarina, Florianopolis 88040900, Brazil

Etiene Andrade Munhoz, Department of Dentistry, Health Science Centre, Federal University of Santa Catarina, Florianopolis 88040-379, Brazil

Corresponding author: Etiene Andrade Munhoz, DDS, MSc, PhD, Associate Professor, Professor, Department of Dentistry, Health Science Centre, Federal University of Santa Catarina, Delfino Conti St, Florianopolis 88040-379, Brazil. etiamfob@yahoo.com

Abstract

BACKGROUND

Palliative care (PC) aims to improve quality of life in patients and its families against life threatening diseases, through suffering's prevention and relief. It is the duty of the dental surgeon to possess the knowledge needed to treat a patient with little life span, in order to establish an adequate treatment plan for each situation.

AIM

To synthesize the published evidence on oral conditions, impact, management and challenges in managing oral conditions among palliative patients.

METHODS

Articles were selected from PubMed and Scopus electronic platforms, using a research strategy with diverse descriptors related to "palliative care", "cancer" and "oral health". The article's selection was done in two phases. The first one was performed by the main researcher through the reading of the abstracts. In the second phase two researchers selected eligible articles after reading in full those previous selected. Data was tabulated and analyzed, obtaining information about what is found in literature related to this subject and what is necessary to be approached in future researches about PC.

RESULTS

As results, the total of 15 articles were eligible, being one a qualitative analysis, 13

(92.8%) clinical trials and one observational study. Of the 15 articles, 8 (53.4%) involved questionnaires, while the rest involved: one systematic review about oral care in a hospital environment, 2 oral exams and oral sample collection, one investigation of terminal patient's (TP) oral assessment records, 2 collection of oral samples and their respective analysis and one treatment of the observed oral complications.

CONCLUSION

It can be concluded that the oral manifestations in oncologic patients in terminal stage are, oral candidiasis, dry mouth, dysphagia, dysgeusia, oral mucositis and orofacial pain. Determining a protocol for the care of these and other complications of cancer – or cancer therapy – based on scientific evidence with the latest cutting-edge research results is of fundamental importance for the multidisciplinary team that works in the care of patients in PC. To prevent complications and its needed to initial the dentist as early as possible as a multidisciplinary member. It has been suggested palliative care protocol based on the up to date literature available for some frequent oral complications in TP with cancer. Other complications in terminal patients and their treatments still need to have further studying.

Key Words: Palliative care; Oral lesion; Terminal patients, Oral mucositis, Oral candidiasis

Core Tip: Palliative care aims to improve quality of life in patients in terminal diseases, through suffering's prevention and relief. It is the duty of the dental surgeon to possess the knowledge needed to treat them. This integrative review aimed to synthesize the published evidence on oral conditions and their management among palliative patients. The most prevalent oral manifestations in end-stage cancer patients are xerostomia, oral candidiasis, dysphagia, dysgeusia, oral mucositis, and orofacial pain. Information on the behavior of oral manifestations and their treatments is lacking and there is little participation of the dental community. Also, updated protocols should be stablished. Palliative care, oral lesion, terminal patients Palliative care, oral lesion, terminal patients.

Citation: Silva ARP, Bodanezi AV, Chrun ES, Lisboa ML, de Camargo AR, Munhoz EA. Palliative oral care in terminal cancer patients: Integrated review. *World J Clin Cases* 2023; 11(13): 2966-2980
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/2966.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.2966

INTRODUCTION

The World Health Organization (WHO), in its concept updated in 2002, defines palliative care (PC) as "an approach that improves the quality of life of patients and their families, in the face of problems associated with life-threatening diseases, through prevention and relief of suffering, early identification, impeccable assessment and treatment of pain and other physical symptoms, spiritual, psychological and social"[1].

In the final stage of life the human being becomes physically and psychologically vulnerable and for this reason requires constant care. Despite science evolution, most areas of medicine still encounter many difficulties to adequately care terminal patients. As stated in the Venice Declaration adopted by the 35th General Assembly of the World Medical Association in 1983, "the duty of the physician is to heal and when this is not possible, alleviate suffering and act in the protection of the best interests of his patient"[2].

Palliative care guarantees the best possible quality of life for the patient, according to their values, needs and preferences, in order to comfort him and his family. Such care must be interdisciplinary not only to reduce pain and other symptoms from the disease, but also to provide emotional support[3].

The latest WHO data shows that cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, with an incidence of 18094716 new cases of neoplasms that year[4]. According to McDonnell and Lenz, 2006 75%-99% of person who underperforms chemotherapy will present adverse oral effects, such as oral mucositis[5].

The treatments of oral complications are crucial for maintaining comfort, feeding and phonation, since the most prevalent oral manifestations in terminally ill cancer patients are: mucositis, stomatitis, nausea, vomiting, candidiasis, nutritional deficiency, dehydration, taste impairment and xerostomia[6].

To date, there is scarce evidence on the preventive and therapeutic measures to be performed by dentists in terminal patients. Within the studies of the palliative care, the areas of medicine, nursing and physiotherapy are more frequent as can be seen in the manual written by WHO[7].

Nevertheless, dentists should be familiar with dental treatments of terminal patients to define appropriate actions and to cooperate with other health professionals to contribute to patients' well-being.

This integrative review aimed to synthesize the published evidence on oral conditions, impact, management and challenges in managing oral conditions among palliative patients.

MATERIALS AND METHODS

This integrative review was conducted utilizing the five steps outlined by review guidelines Souza *et al* [8], Sladdin *et al*[9]: (1) Problem identification: "What oral manifestations are present and what dental interventions are indicated for patients diagnosed with end-stage cancer?"; (2) Literature search: The search keys and databases were defined. PubMed, Scopus databases and also selected articles found in the reference lists are used. The search strategy applied was: ("palliative care"[All Fields] OR "end of life care"[All Fields] OR "palliative medicine"[All Fields] OR "terminal patients"[All Fields]) AND ("oral health"[All Fields] OR "dental health"[All Fields] OR "dental"[All Fields] OR "oral complications"[All Fields]OR "oral treatments"[All Fields] OR "oral lesions"[All Fields] OR "oral diseases"[All Fields] OR "dentistry"[All Fields] OR "oral management"[All Fields] OR "dental care"[All Fields] OR "oral infections"[All Fields] OR "oral care"[All Fields] OR "special care dentistry"[All Fields] OR "oral interventions"[All Fields] OR "bucal management"[All Fields] OR "dental management"[All Fields] OR "bucal treatments"[All Fields] OR "dental treatments"[All Fields]) AND ("oncology"[All Fields] OR "cancer"[All Fields] OR "neoplasms"[All Fields]). To remove duplicate articles, Endnote web software was used; (3) Data evaluation: Based on the abstracts, a reviewer (ARPS) selected the full- text articles that met the following inclusion criteria: published in English, Portuguese or Spanish, systematic review articles, cross-sectional, longitudinal studies and clinical trials published up to 2022, which brought information about oral care in terminal cancer patients. Exclusion criteria were case reports, literature review articles, theses, dissertations and articles focusing on the quantity or quality of health professionals; (4) Data analysis: Two researchers (ARPS and ESC) read in full the previously selected articles and included those that met the previously established criteria, independently. In case of disagreement, a third researcher was consulted to define or not to include the article. Items included in the table: author(s), year of publication, objectives, study population and sample size (if applicable), methodology, important results and measures used (if applicable), important findings and possible methodological flaws); and (5) Presentation: The articles were divided into studies or reviews. Possible research failures were analyzed and quantified. Aspects that require further investigation, the different types of dental interventions and the number of studies and evidence in the literature were pointed out.

RESULTS

The search in the databases recovered a total of 405 articles (Figure 1). Of these, 49 were duplicated and 293 were excluded because abstracts did not meet the inclusion criteria. Of the 63 articles with potential for inclusion, one was excluded because it was in Japanese and 3 could not be recovered by physical and digital means, leaving 59 articles. There was doubt in 1 abstract, which was excluded after a third expert analysis and discussion with the reviewers.

Of the 58 articles remaining and read in full, 27 were excluded because they were in disagreement with the inclusion criteria, 16 were excluded because they were not related to dentistry and 1 article was excluded because it was repeated (Figure 1).

Of the 15 articles included (summarized in Table 1), Gillam *et al*[10], was based on qualitative analysis and the other 14 articles were based on quantitative analysis being 13 (92.8%) clinical trials[11-23] and one observational study[24].

Also among the included studies, 10 presented data on the site of origin of the tumour, being lung[13,15,18,23,24] and gastrointestinal tract[11,16,19,21] breast[18,22] and prostate[26] the most common. Five articles reported the prevalence of patients with head and neck cancer[15,18,19,20,24].

The prevalence of deleterious habits of patients was investigated in three studies[11,13,20].

Among the 15 studies included, only 3 aimed to analyze therapies for different oral diseases[21,22,23], while 9 analyzed the prevalence of different oral manifestations[11-19]. The objective of the remaining 3 studies was related to the quality of life of terminal patients[20] and the dental management of these patients[10,24].

The results found in the selected articles have a wide variety. A single article compared groups with long and short remaining life time[14].

Table 1 Summary of the articles selected in the integrative review

Ref.	Country	Title	Type	Category	Objective	Method	Sample	Results	Summary
Gillam *et al*[10], 2006, United Kingdom	United Kingdom	The assessment and implementation of mouth care in palliative care: a review	Systematic review	Manegement	Review existing literature published between 95 and 99 to determine whether oral care was effectively implemented in the configuration of palliative care	On a nursing basis (CINHAL), they found 11 articles (does not make clear the descriptors)	11 articles	Studies with different tools used to view oral health and many studies report lack of training of nurses (72% of nursing colleges do not teach written oral evaluation methods)	The need for physicians and nurses to have a basic knowledge about diseases and oral care, but no study speaks as. It is important to have an evaluation tool
Wilberg *et al*[11], 2012, Norway	Norway	Oral health is na important issue in end- of-life cancer care	Croos-sectional	Oral manifestation	Investigate the prevalence of oral and dental problems in cancer patients receiving palliative care. Specifically, it was to examine oral health and prevalencia of oral morbidity through patient reports and oral examination. Also investigating information related to oral problems was received by patients	First the interview was done through a symptom reporting tool, and then a clinical oral examination and oral mucosa swab collection. If candidiasis was confirmed, treatment was given	99 patients	Average age 64, 47% men, cancer GI 21%, lung 19% prostate. 11%. 50.5% caries. Change of palate 68%, while 56% had problem eating, xerostomia 78% and 41% for + 3 months, 70% increase in friction in mirror test, general oral discomfort 67%. No significant difference when commencing the remedies with the patients with the symptoms described. Microbiol evidence. 86%, 34% clinical and biolog. 14% use prosthesis. Average lost teeth 5.7, 22% received information about adverse cancer effects, 38% how to reduce xerostomia	Microbiological evidence of candida in 86%, 34% clinical and biological. The 9 under treatment still had (uncertain effect). 22% received information on adverse effects of cancer, 38% of how to reduce xerostomia and 31% of the importance of oral hygiene (little, but satisfied). Alt. taste and xerostomia significantly related to oral morbidity (general discomfort). Caries largest number
Davies *et al*[12], 2008, United Kingdom	United Kingdom	Oral candidosis in community-based patients with advanced cancer	Croos-sectional	Oral manifestation	Determine the epidemiology, etiology, clinical and microbio-logical characteristics of oral candidiasis among community patients	Questionnaire, clinical examination, measurement of saliva production and swab collection of those who demonstrated clinical dinal of candidiasis. They isolated the collected species, if necessary, DNA sequencing	390 patients	Mean age 73, 65% women, breast cancer 23%, bronchio and colon and prostata 11%. 70% had candida on microbionogic examination and 13% in microb. And in the clinician. 63% a species, 31% 2 species. C. albicans 75%. C.gabrata 2nd most frequent. Presence of candidiasis has not been associated with age, gender, or use of systemic antibiotic. 67% xerostomia. Presence of candidiasis associated with severity of xerostomia, use of corticosteroids, ECOG and dentures	In agreement with other studies: Candidiasis becomes more common in patients near death (ECOG), increases with the high severity of xerostomia, but not with the use of antibiotics. No agreement: association between candidiasis and the use of systemic corticosteroids
Oneschuk *et al*[13], 2000, Canada	Canada	A survey of mouth pain and dryness in patients with advanced cancer	Croos-sectional	Oral manifestation	Determine the prevalence of dry mouth and/or oral pain in patients with advanced cancer, and whether they were present, quantify the intensity of these symptoms, whether treatment was offered by the health team and which when symptoms were expressed, the author's main opinion on the cause of these symptoms and the relative importance to the patient compared to other symptoms or	11-item questionnaire on oral pain and dry mouth and its intensity and importance of symptoms. Found from the oral examination were documented verbally and/or visually and the possible cause is documented	99 patients	Average age 70, 58% women, lung cancer 28%, GI 27%. 16 of the 99 had oral pain, 10 of them in the gums, and the mean intensity was 5 on a scale from 0 to 10. 88% had dry mouth, with an average intensity of 6.3. 24% had dry mouth before cancer diagnosis and 31% pain. 28.2% saw the dentist after diagnosis. 56% mentioned pain for the caregiver and 44% for dry mouth. After reviewing the patients' medical documentation, only one of them had documented the pain complaint and 5 dry mouth	88% dry mouth and 16% pain. Moderate importance in relation to other symptoms - more or less half of patients report their problems, and there are few documentations of these. The recommendations for dry mouth: drinking liquids, mouthwash with bicarbonate and use of oral antifungic. Only 1 of the 2 who had candida and pain were advised to use topical antifungic

					problems they experienced			complaints. Of the 44%, 69% received advice on treatment. Found most common were candidiasis and presence of denture	
Matsuo *et al*[14], 2016, Japan	Japan	Associations between oral complications and days to death in palliative care patients	Clinical trial	Oral manifestation	Investigate the association between the incidence of oral complications and DTD in patients in palliative care	They reviewed the reports and evaluations of oral conditions of terminal patients between April 2013 and March 2014. In the evaluation, clinical examination was taken and food intake was evaluated. Data from blood tests (leukocytes) for inflammation and DTD were evaluated. Divided into long and short DTD	105 patients	Cancer pancreas/bile 18%, gastrointestinal tract (16%). Carie 16.3% in long, 10.7% short 13.3%T. Xerostomia 54% long and 78% short (significantly higher). Candida 10.7 and 10.2%, 10.4%T. Inflammation of the tongue, bleeding spots and dysphagia also (43% and 20%). Long group 50% requires oral care support and 76% in short (different). The more attention needed and more xerostomia, the shorter the DTD	Major problems when arriving near the day of death and the problems began to progress with the time of hospitalization. Xerostomia, inflammation of the tongue, bleeding spots and dysphagia
Bagg *et al* [15], 2003, Glasgow	Glasgow	High prevalence of non-albicans yeasts and detection of anti- fungal resistance in the oral flora of patients with advanced cancer	Croos-sectional	Oral manifestation	Examine in detail the oral mycological flora in a wide range of patients with advanced cancer, receiving care in three different centers	Collected demographic details and therapy information, examination of the oral cavity by a qualified dentist and collection of a tongue swab, subsequently inoculated and incubated	207 patients	Average age 67.9, 45% men, lung cancer 18%, breast 16%, oral 5%. 81% denture, 50% edentulum. 48% with clinical evidence of xerostomia, 26% candida. No difference between denture use and fungic infection. 22% had antifungic treatment. 65% of the isolates had 1 species, 30% 2, 5%. 3. 47% with heavy density. 79%. C. albicans. 71% fluconazole, 55% for itraconazole. resistance-related xerostomia	Most of the isolates were of C. albicans in cancer patients (previous exposure to fluconazole?). By the use of immunosuppressants and antifungics, C. glabrata is now a pathological and more resistant species
Burge *et al* [16], 1993, Canada	Canada	Dehydration symptoms of palliative care cancer patients	Croos-sectional	Oral manifestation	Determine the severity and distribution of symptoms associated with dehydration in hospitalized palliative care patients and determine the association between the severity of these symptoms and commonly used dehydration measures.	Patients completed two questionnaires, 24 h apart. The nurses took the questionnaire as well. A blood sample was collected in the 24-h interval (sodium, urea and osmolarity). They measured how much liquid they ingested	52 patients	Average age 64.4, 50% women, gastrointestinal cancer 27%, lung 27%. Oral diseases and survival were not related. No association was found in the multivariate analysis. You can't list the meds.Fatigue was the most reported symptom. Patients who reported head and other symptoms also reported dry mouth and bad taste in the mouth (most). It's not a blind study, so it has this bias. Longer survival time is associated with less thirst	Most patients had symptoms of thirst. It's not a blind study, so it has this bias. Fatigue was the most reported symptom. No association between thirst and variables. Clinics argue that the thirst and intake of liquids decrease near death. However, longer survival time is associated with less thirst
Fischer *et al*[17], 2014, United States	United States	Oral health conditions affect functional and social activities of terminally ill cancer patients	Croos-sectional	Oral manifestation	To characterize oral diseases in patients with end-stage cancer in palliative care to determine the presence, severity, and social/functional impact of oral diseases, which affect quality of life	Questionnaire on xerostomia, taste change, orofacial pain and impact of diseases. "Self-report" and oral clinical examination	104 patients	29% between 50-64 yr, 59% women. 98% had salivary dysfunction and 60% had moderate to severe dysfunction. Erythema 50%, ulceration 20%, fungic infection 36%. Xerostomia was a frequent and moderate complaint. Ulcers associated with the presence of orofacial pain and social impact. Xerostomia, change in taste and orofacial pain associated with social impact. Hyposal-ivation associated with social and	Hyposalivation has a social and functional impact and is a frequent complaint with moderate severity. Orofacial pain and change in taste has social impact. Presence of fungic infection similar to other studies

								functional impact	
Sweeney *et al*[18], 1998, United Kingdom	United Kingdom	Oral disease in terminally ill cancer patients with xerostomia	Croos-sectional	Oral manifestation	Descreve sinais e sintomas orais de um grupo de pacientes com cancer terminal, todos com xerostomia, os quais foram subsequentemente tratados com um substituto salivar em spray	Pacientes que relataram consecutivamente boca seca para o staff. Questionario, sintomas registrados por escala analogica visual 0-6, exame bucal visual e coleta de cultura da língua e assoalho e quantidade de saliva	70 patients	Mean age 66, 64% men, lung and breast cancer, 2.8% oral. 10% caries. 90% evidence xerostomia clinic, 9% C. pseudom sign.97% reported by day and 84% at night, 66% speech difficulty, 57% taste change, 51% difficulty eating, 31% pain. 40% of the prosthesis users had a problem with it. 65% had mucosal abnormalities, of these 20% erythema and 20% lingual saburra. C. albicans more common and C. glabrata 2nd most common	66% speech difficulty, 57% change in taste, 51% difficulty eating, 31% pain. 67% of the patients had fungic disease in the isolates. Good hygiene. S. aureus 26% suggested cause of mucositis, as well as coliforms (19%). Herpes was relatively low
Xu *et al* [19], 2013, China	China	Investigation of the oral infections and manifestations seen in patients with advanced cancer	Croos-sectional	Oral manifestation	To investigate the focus of oral infections between cancer groups and treatment methods, in addition to describing and comparing epidemiology, independent risk factors	Data collection, oral examination and oral cavity swab collection for microbio-logical isolation	850 patients	Average age 48, 57% men, cancer GI 17%, hematological 15%, 13% head and neck. Oral infections 46%, of these 52% with candidiasis (72% had fungal colony), 20.5% mucositis, 15.4% herpes. A logistic regression analysis showed that malnutrition and prosthesis use are independent risk factors for oral infection.Head and neck cancer had more infections and hematologic the second. Chemo and radiotherapy had higher infection	Candidiasis more prevalent, followed by mucositis. Disparity in oral infection data in these patients (various possible reasons). Head and neck cancer and hematologic. Prosthesis and nutrition are risk factors
Thanvi *et al*[20], 2014, India	India	Impact of dental considerations on the quality of live of oral cancer patients	Croos-sectional	Quality of live	Understand the role of the dentist and the impact on quality of life in a patient with oral cancer in a palliative care unit	History of oral cancer treatment, clinical examination and quality of life questionnaire	50 patients	64% women. Age measured 57. All oral cancer. 98% of the patients had some deleterious habit, 58% smokers. 12% had information before therapy. 74% had sensitivity and 50% limitation in mouth opening (evaluated root carie, atrition and sharp cuspides). 78% worsened The QOL, of these only 2% had dental considerations	Dental treatment was not done in 76% of patients who had already undergone treatment, 2% received consideration. Mouth opening sensitivity and limitation (did not evaluate xerostomia, mucositis, but evaluated "sharp cusps", atrition and root caries). 78% worsened QOL
Bagg *et al* [21], 2005, United Kingdom	United Kingdom	Voriconazole susceptibility of yeasts isolated from the mouths of patients with advanced cancer	Croos-sectional	Treatment	Determine the susceptibility of voriconazole to a large collection of well-characterized fungal isolates from the oral cavity of patients with advanced cancer	199 oral samples isolated from swab and oral rinse. Suscept-ibility test for fluconazole, itraconazole and voriconazole	199 patients	Breast cancer, bronchio, prostata and large intestine. 270 yeast species, C. albicans 59%, C. glabrata 19%, C. dubliniensis 7%. 76% flucona, and 14% fluconazole resistant. Of the fluconazole resistant, 7 sensitive to itraconazole and 41 resistant. Of the 49 resistant to itraconazole, 41 was also fluconazole and 8 senseless. 15% resistant to fluconazole and itraconazole, mostly C. glabrata and C. albicans. C. glabrata was 54% of fluconazole resistant	Voriconazol é mais potente que fluconazol ou itraconazol contra leveduras isoladas de boca de pacientes com cancer avançado, e é mais potente com aqueles resistentes a fluconazol e itraconazol
Bagg *et al* [22], 2006, United	United Kingdom	Susceptibility to Melaleuca altern-ifolia (tea tree) oil	Croos-sectional	Treatment	Examine in vitro susceptibility to TTO from a collection of well-characterized yeasts, including	301 Yeasts isolated and MIC measurement for TTO	199 patients	Breast cancer, bronchio, prostata and large intestine. MIC 50 was 0.5% for C. albicans and C. dubliniensis and 0.25%	Treatment should be considered a potent preventive or therapeutic agent of oral candidiasis in these

Kingdom		of yeasts isolated from the mouths od patients with advanced cancer			azol-resistant strains isolated from the mouth of patients with advanced cancer			for C. glabrata, C. tropicalis and S. cerevisiae. MIC 90 for C. albicans, glabrata and dubliniensis was 1%. All itraconazole and fluconazole resistant were susceptible to TTO at commercially available concentrations	patients. As a water-based filler or adjuvant the regular washing
Nakajima *et al*[23], 2017, Japan	Japan	Characteristics of oral problems and effects od oral care in terminally ill catient with cancer	Clinical trial	Treatment	Investigate oral problems in the terminal stage of cancer and improves through oral care focusing on dry mouth	Divided into good oral and bad intake (115A and 158B) to 30% for good. Incidence of dry mouth and its severity (0-3), stomatitis, candidiasis.Standard oral care for dry mouth by nurses (hydration, brushing and cleaning or massage), and therapy for dry mouth and stomatitis. Special care if it did not improve	273 patients	Average age 62.4A and 66.2B, 144 men and 129 women. Lung cancer 38A 48B, Liver/bile/pancreas 18A 30B, Head and neck 5A 8B. Dry mouth 38.3%A 81%B 63%T. Stomatitis 10.4%A 16.5%B 13.9%T. Candidiasis 6.1%A 22.8%B 15.8%T. All with stomatitis and candidiasis had dry mouth. Severe dry mouth 20%A 64%B. Dry mouth treatment: grade 2 B needed specialist (85%A 83%B), grade 3 also (80%A 81%B) Overall improved 80% or more	B significantly higher than A: Dry mouth and candidiasis. Interventions improved 80% or more dry mouth. Importance of oral care before the problem worsens. Oral care is better than artificial hydration for dry mouth. The registration of oral conditions by staff is not 100% (limitations, improve)
Ezenwa *et al*[24], 2016, United States	United States	Caregiver's perspectives on oral health problems of end-of-life cancer patients	Cross-sectional study	Management	Describe caregivers' awareness of oral health problems, compare caregivers' problems with patients' problems and explore the influence of caregivers' socio-demographic characteristics on their awareness of oral problems	Caregivers and patients answered questionnaires separately. Caregivers and patients completed the scale of oral problems	104 patients104 caregivers	Patients: 29-112, 29% between 50-64 yr, 59% women, Lung cancer 26%, colorectal 14%, head and neck 3%. 48% of caregivers(C) were not trained, 30% of c evaluated the problems only when necessary and 13% never evaluated. C underestimated xerostomia and overes-timated the social impact. C with 65+ had lower accuracy in reporting the problems. C with health problem were less aware	48% C without training. C underestimate xerostomia, but is aware of orofacial pain. No difference in race, gender, C's education

DNA: Deoxyribonucleic acid; DTD: Days to death; GI: Gastrointestinal; ECOG: Electrocorticography; MIC: Minimal important change; QOL: Quality of life; TTO: Tea Tree Oi.

Four studies reported the prevalence of caries disease in terminal patients[11,14,18,20] and only one investigated the prevalence of dental plaque in these patients[11]. Regarding the presence of teeth, only the articles by Bagg *et al*[15], and Davies *et al*[12], calculated the prevalence of edentulous patients. Wilberg *et al*[11], found that 69% of patients aged ≥ 60 years had a ≥ than 20 teeth. The presence of prosthesis was evaluated by Bagg *et al*[15], Davies *et al*[12], Sweeney *et al*[18] and Wilberg *et al*[11] (26.7% of the articles), with a prevalence of 81%, 57%, 80% and 14%, respectively.

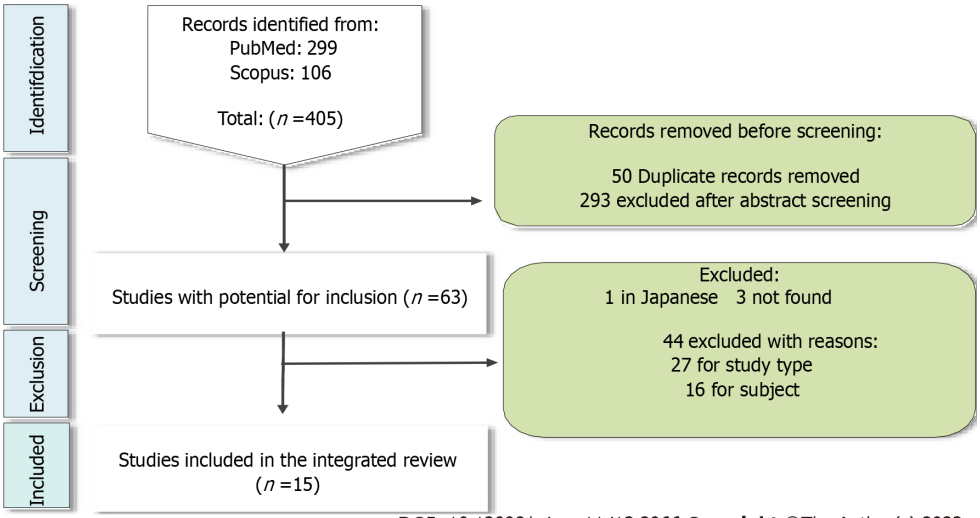
A total of nine articles brought data on the prevalence of oral *Candida* species in patients with advanced stage cancer[11-19,23], seven of them approached microbiological analyses of the fungus[11,12,15,18,19,21,22] and three investigations evaluated susceptibility to different antifungals drugs[15,21,22].

Of the selected studies, seven involved analyses of microbiological isolates of the oral mucosa[11,12,15,18,19,21,22].

The percentage of patients with xerostomia was evaluated in 8 articles (Table 2)[11,12,13,14,15,17,18,23]. The only article that brought data on the type of treatment used for this condition was that of Oneschuk *et al*[13].

Table 2 Prevalence of oral complications in examined patients (%)

Ref.	Xerostomia	Eat/Swallowing problems	Mucositis	Dysgeusia	Oral pain
Fischer *et al*[17], 2014	91	61	-	71	23
Sweeney *et al*[18], 1998	90	-	-	-	31
Oneschuk *et al*[13], 2000	88	-	-	-	16.1
Wilberg *et al*[11], 2012	78	56	-	68	-
Davies *et al*[12], 2008	67	-	-	-	-
Matsuo *et al*[14], 2016	64.7	29.5	-	-	-
Nakajima[23], 2017	63	-	13.9	-	-
Bagg *et al*[15], 2003	48	-	-	-	-
Xu *et al*[19], 2013	-	-	20.5	-	-
Mean	73.7	48.8	17.2	70	23.3



DOI: 10.12998/wjcc.v11.i13.2966

Figure 1 Fluxogram.

Table 2 presents ther variables also addressed in articles. Two studies reported, the prevalence of changes in taste or dysgeusia[11,17] and three evaluated problems when eating[11,14,17].

Facial pain and intraoral pain were addressed in three articles[13,17,18] whereas oral mucositis or stomatitis was reported in two studies[19,23]. Only Thanvi *et al*[20], investigated mouth opening limitation and only Xu *et al*[19], researched herpes simplex prevalence in terminal patients.

Fischer *et al*[17], also brings the prevalence of dysphagia (61%), dysgeusia (71%), facial pain (23%) and intraoral pain (52%)[17]. Oneschuk *et al*[13], and Sweeney *et al*[18], also studied oral pain, with a prevalence of 16.1% and 31%, respectively. In addition to these variables, Thanvi *et al*[20], obtained a 50% prevalence of patients with limited mouth opening, Xu *et al*[19], found 15.4% of patients with herpes simplex and 20.5% with oral mucositis, while Nakajima[23], 2017, obtained 13.9% of patients with stomatitis.

The only study based on qualitative analysis was a systematized review, published by Gillam *et al*[10], where 11 articles found in a nursing database were analyzed, published in 1995 and 1999. No demographic data was specified from the studies reviewed by Gillam *et al*[10].

DISCUSSION

From the results obtained, it was observed that the single study based on qualitative analysis had nurses providing oral care to palliative patients[10]. It should also be emphasized that four of the published articles were written by professionals from other health areas[10,13,16,23]. The scarcity of investigations involving dentists demonstrates that this professional is not currently part of most teams that care for

terminally ill patients. There seems to be a vast field of action for which dentists should be qualified. From the moment a dentist becomes part of the healthcare hospital team there happens an improvement of 37.25% in the accuracy of diagnosis of oral lesions[25].

Given that most studies analyzed were cross-sectional and not longitudinal, it makes impossible to gather information on the evolution of oral manifestations and therapeutic responses over time[11-22, 24].

Demographically, the majority of the patients studied were women with a mean age of 63.8 years and diagnosed with lung and gastrointestinal tract cancer and for this reason special attention is needed for the diagnosis of oral lesions in this specific audience[11-13,15-20,23,24].

As most studies were published between 2006 and 2016, it can be inferred that dental treatment and management in PC among PT is a subject considered recent and constantly growing, which justifies the scarcity of qualified data found on the topic in the literature[10,12,14,17,24].

Most studies used the questionnaire tool[11,12,13,16,17,18,20,24], either to obtain demographic information[20] or to record symptoms of patients[11,13,16-18] and caregivers' opinions[24]. Such a tool can be useful even to record the symptoms of PT by caregivers, besides being a complement to oral examinations performed, either by caregivers or researchers.

Oral complications

Oral candidiasis: The prevalence of candidiasis in the oral mucosa of patients under palliative care [11] was investigated in nine of the selected articles[12-15,17-19,23]. The mean prevalence of oral candidiasis presented in those was high when compared to the mean detected for the healthy population (2% to 14%)[26]. Oral candidiasis is a frequent disease in systematically compromised patients, such as patients with end-stage cancer. Which reflects that more knowledge is still needed about the diagnosis and treatment of this disease in PT.

Mothibe *et al*[27] suggested that patients using prosthesis with cancer have a higher capacity for growth of oral candida. However, Bagg *et al*[15], found no associations between the use of prosthesis and the presence of oral candida in terminal patients. Another interesting finding was that the presence of oral candida seems to be related to the low food intake by patients[23].

On the microbiology of the oral cavity of palliative patients with cancer, the presence of C. albicans was identified in 58.2% of the patients included in the seven studies analyzed whereas C. glabrata was present in 24.5%[11,12,15,18,19,21,22]. Although the second most prevalent species in oral fungal infections, *C. glabrata* is not susceptible to certain antifungals[21,22].

The most prevalent oral candidiasis were erythemenous candidiasis and acute pseudomembranous candidiasis[12,15]. Erythemate candidiasis was prevalent in patients who used removable prostheses. Since a high percentage of palliative patients uses removable oral prostheses[11], it is important that patients and/or caregivers make the correct and regular hygiene of both the oral cavity and prostheses to prevent prosthetic stomatitis[15,18].

Pseudomembranous candidiasis of multifocal type was reported in 48% of patients investigated being the oral/jugal mucosa (48%) and the tongue (44%) the most affected sites[12,15].

A positive association was found between hyposalivation and oral candidiasis [12]. The hypofunction of the salivary glands can decrease the function of superficial cleansing of saliva, decrease its antifungal activity (because it decreases the amount of enzymes such as histatins and lysozymes) and reduce the pH of saliva which favors the proliferation of candida in the mouth.

About 75% of fungi were susceptible to fluconazole[21] and for this reason it will likely continue as the first treatment option. 53% of the isolated C. glabrata was resistant to fluconazole and also presented a low rate of therapeutic response to voriconazole[15,21] usually effective on more resistant candida species[21]. These results are in agreement with those of Wilberg *et al*[11], where 27% of patients undergoing antifungal treatment still had clinical signs of the disease.

Regarding the form of prescription of fluconazole, the latest cutting-edge research results state that the administration of daily doses of 100 to 200 mg can be recommended[28,29], and dose adjustment is needed for a renal patient[30] (Table 3). The susceptibility of fungi to melaleuca oil with positive results was also studied, concluding that this agent should be considered as a potential preventive agent and can be used as an adjuvant to oral hygiene[22].

Xerostomia and hyposalivation: Dry mouth sensation in patients with end-stage cancer was the second most frequent complication reported in studies[11-15,17,18,23]. The prevalence of xerostomia in palliative patients ranged from 91% to 48% (Table 2)[15,17], indices relatively high when compared to those of normal population (0%-30%)[31,32]. Matsuo *et al*[14], observed that palliative patients with a short life expectancy had a significantly higher prevalence of xerostomia than those with longer life estimative. Adverse effects of drugs used to reduce pain such as opioids could justify those high indices [17]. Interestingly, only 22% of patients received information about xerostomia as an adverse effect of the drugs used in antineoplastic therapies [17]. In severe cases, the dentist should discuss with the doctor the possibility of replacing the medications that cause this symptom[23].

Hyposalivation has also a significant association with the functional and social impact of patients as well as low food intake[17]. Improving dry mouth sensation can thus help with other oral problems[23]. The adequacy of oral hygiene improves dry mouth symptom regardless of the degree of food intake[23]

Table 3 Suggested palliative care protocol based on the literature available for some frequent oral complications in terminal patient's with cancer

Oral complications	Therapeutical measures
Oral candidiasis	Fluconazole: 100 to 200 mg/d
	In case of resistance: Itraconazole or variconazole and mouth rinsing with melaleuca oil after oral hygiene
Xerostomia	Daily and frequent water sip intake
	Artificial saliva use
	In severe cases: Discuss the possibility of replacing causative drugs
Dysgeusia	Discontinues 10 mo after antineoplastic therapy, on average
	In severe cases: Discuss the possibility of replacing causative drugs
Mucositis	Cryotherapy: Ice stones and ice cream kept in mouth decrease risk of mucositis and relieve pain (prescription according to chemotherapy)
	Low-level laser therapy
	Cold chamomile-based tea solutions

but only 31% of patients were informed about the importance of oral hygiene[23].

Despite being a frequent complication, patients classified xerostomia as of moderate importance when compared to other symptoms experienced at that palliative moment[13]. In the study of Oneschuk *et al*[13], about half of the patients (56%) who reported xerostomia also reported the symptom to the doctor and of these only 69% were advised to seek one or more treatments for symptom relief. Patients may believe that this information is of no clinical importance, that there is no need to treat it or that treatment options are limited.

The recommended treatments for xerostomia are to drink frequently sips of water and to use artificial saliva in spray[13] (Table 3).

Caries and plaque: In the only study on the topic included in this review, 24% of patients presented with moderate or severe amount of visible plaque[11]. Consumption of easy-to-chew carbohydrates (dietary supplement) and cognitive restrictions to perform adequate oral hygiene contribute to plaque accumulation. Besides, hyposalivation increases the tooth's susceptibility to demineralization.

Patients closer to death need greater help with oral care and that the inability of self-care is an indicator for the caregiver to perform oral hygiene properly. Matsuo *et al*[14], found a positive correlation between caries incidence and the number of days of life remaining. Poor oral hygiene is associated with oral diseases including caries and periodontitis. Teeth with active caries may cause pain and discomfort in the terminal phase of life, hindering feeding and compromising well-being.

This demonstrates the necessity to improve the quality and frequency of oral hygiene, within the limits of the patient's hematological parameters, as well as therapeutic measures to stop cavities progression and to preserve teeth function[33].

The prevalence of caries and plaque in the mouth of the patients studied was addressed in a few articles and it was not determined what posture should be taken in front of these cases, requiring to determine to what extent the dentist should intervene and perform the treatment of these cases[11,14,18,20].

Dysphagia: Difficulty in swallowing seems to be a comorbidity less prevalent than poor oral health among patients with terminal-stage cancer[34]. Wilberg *et al*[11], however, described a significant relationship between the patient's feeding difficulties and their perception of oral morbidity.

The cause of dysphagia in patients with advanced cancer is different from that found in neurological diseases or strokes, as there is a decrease in muscle volume due to malnutrition or cachexia[14].

Dysphagia was significantly more prevalent in patients with a short life time[14], and may be considered a strong criterion of palliactive care necessity[14,17]. Fischer *et al*[17], observed a prevalence of "swallowing problems" almost three times higher than that of Matsuo *et al*[14]. In contrast, Furuya *et al*[35], described that the swallowing function was relatively well-conserved and 46.3% of the participants were capable of nutrition intake solely by mouth[35].

In the study of Furuya *et al*[35], more than half of the participants did not wear their removable dentures despite needing them. Wearing removable dentures improves the ability to masticate and facilitates the swallowing of food. Dentists have a key role in palliative care in terms of supporting nutritional intake *via* dentures[35].

In addition to the absence of teeth and incompatibilities of removable prostheses, reduction of saliva and diseases such as candidiasis and mucositis could also be related to dysphagia[23,36].

The treatment of dysphagia is still a challenge. More recent studies show that exercises can improve dysphagia symtoms[37] and that electrical stimulation has not brought benefits[38].

Hypogeusia and dysgeusia: Changes in taste are extremely common in cancer palliative patients due to the adverse effects of drugs such as keratolytic agents, chemotherapeutic and cancer medication, antihistamine, antibiotics and angiotensin-converting enzyme inhibitors, analgesics, bisphosphonates and antidepressants[11,39]. The study by Wilberg *et al*[11], stated that the change in taste is related to higher oral morbidity.

In the two articles included, taste changes were reported by 62%[11] and 78% of individuals[17]. This complication can have a great influence on oral function and, consequently, on the nutritional status and quality of patients' life.

Dentists can help alleviate this symptom through identification, discussion with the multidisciplinary team, oral hygiene improvement and prescription of potential therapies such as anti-xerostomia agents and photo biomodulation[40].

Orofacial pain: Orofacial pain is a concern that affects social interaction of palliative patients and interferes with their quality-of-life[17]. The mean number of patients that reported orofacial pain in the studies included was 23.3% to orofacial and 52% to intraoral pain[17].

Ten of the 16 terminal patients included in the study by Oneschuk *et al*[13], complained of localized pain in the gums. Although the gum may be a painful oral site, oral cavities and prostheses incompatibilities were not examined by a dentist to rule out potential sources of referred pain.

No studies were found on the treatment of orafacial pain in terminal patients, however the subject is widely studied in patients in general. Up to date studies shows several therapies reported, among them counseling therapy; occlusal appliances; manual therapy; laser therapy; dry needling; intramuscular injection of local anesthesia (LA) or botulinum toxin-A (BTX-A); muscle relaxants; hypnosis/relaxation therapy; oxidative ozone therapy; and placebo[41].

Oral mucositis: Oral mucositis is an acute and painful side effect of antineoplastic therapies (chemotherapy and head and neck radiotherapy). It affects non-ceratinized surfaces such as the entire gastrointestinal tract and is characterized by pain, ulceration and difficulties in feeding and phonation [42].

In the two studies included on the subject, 17.2% of the patients investigated had mucositis[19,23]. This incidence is lower than that found for mucositis during chemotherapy and radiotherapy treatment probably because these therapies are often interrupted when the patient are in palliative care. These authors, also, did not relate the type of antineoplastic therapy (radiotherapy or chemotherapy) to the prevalence of mucositis and, for this reason, the toxicity of these therapies in the oral mucosa could not be analyzed. In the study by Xu *et al*[19], chemotherapy in conjunction with radiotherapy were associated with a higher prevalence of oral infections in general (68.4%) compared to chemoterapic (52%) or radiotherapy (53.9%) treatments in an isolated way[19].

Pain caused by mucositis is poorly tolerated by patients and is accentuated especially during the act of food intake[42]. The lack of information on this complication in the selected articles is worrisome because in addition to its prevalence being relatively high, the pain caused is poorly tolerated by patients and the reduction of this symptomatology should be studied more deeply.

In the literature there are many studies on mucositis during cancer treatment or during hematopoietic stem cell transplantation[43,44], however, there is a gap in the literature when it comes to respective therapeutic oncological PT.

With regard to oral mucositis in particular, we found that cryotherapy, where the patient makes the use of ice stones, ice cream or ice cream in the oral cavity 5 min before and 30 min after chemotherapy or longer periods, can contribute to the reduction of the degree of oral mucositis and the time of pain caused by the lesions[45,46]. In addition to cryotherapy, on recent studies, researchers recommend the use of low-power laser therapy, photodynamic therapy, honey, the use of chamomile tea as a mouthwash with good results[47-53].

Management of terminal cancer patients

Professionals involved in the treatment of terminally ill cancer patients are the key to establishing adequate oral health care[24]. In a hospital setting will be cared for by nurses and other health professionals, ideally including a dentist on the team. However, if you live with family members in a permanent care home, the nearest caregiver may be a family member or person hired by the family[10,24]. In the study by Ezenwa *et al*[24], 79% of the caregivers were family members, most of them women (77%) aged between 50 and 64 years (46%)[24] and only 48% became caregivers from formal training. Furthermore, more than half of the caregivers interviewed in the study reported that the patient's oral hygiene is one of the functions under their responsibility and of these, 81% mentioned the importance of this task in detecting potential oral problems developed by the patient. However, 30% of the caregivers examined the oral cavity only when necessary and 13% had never questioned the patient about possible oral problems. Furthermore, through the responses obtained from caregivers and patients, xerostomia was evaluated less frequently, suggesting that this symptom is underestimated by caregivers[24].

Gillam *et al*[10], reviewed 11 articles and 7 of them highlighted the lack of training and education of nurses[18,54-59].

Most nursing courses do not adequately teach oral health care, which reflects the lack of training of nurses working in CP centers. The training of oral hygiene techniques performed by dentists for caregivers can improve the quality of care offered, the speed in the diagnosis of oral alterations and the response to patient complaints

Determining a protocol for the care of these and other complications of cancer – or cancer therapy – based on scientific evidence with the latest cutting-edge research results is of fundamental importance for the multidisciplinary team that works in the care of patients in PC. The protocols used in the articles included in this review were not standardized, a fact that hindered the analysis, interpretation of discussion of the data analyzed by this study. The authors summarized on Table 3 the Suggested palliative care protocol based on the up to date literature available for some frequent oral complications in TP with cancer.

The care of patients under PC should not be neglected by professionals in this area, it should be treated seriously for us dentists, to be more effective in care.

Based on the information obtained and all aspects discussed, it is noted that the literature is still scarce when it comes to oral manifestations in terminal cancer patients under CP. Data such as the prevalence of mucositis, orofacial pain, dysgeusia and dysphagia were addressed in a few articles of the review, and a better evaluation is needed to determine the real prevalence of these diseases.

As a consequence, the treatment of mucositis, dysgeusia, dysphagia and oral pain should be studied in depth in PT.

CONCLUSION

Finally, it can be obtained through this integrative review that the most prevalent oral manifestations in end-stage cancer patients are xerostomia, oral candidiasis, dysphagia, dysgeusia, oral mucositis, and orofacial pain.

The information on the behavior of oral manifestations and their treatments in patients under palliative care, especially in the long term, is lacking and there is little participation of the dental community in research on the subject and training of caregivers of terminal lye patients under palliative care. Dentists can be helpful on alleviate the symptom of these oral manifestations in TP, improving the quality of live in these final days.

ARTICLE HIGHLIGHTS

Research background

Resume the scientific evidence on oral conditions among palliative patients and its management.

Research motivation

Update the dentist for diagnosis and treatment of oral complication in a multidisciplinary palliative care team.

Research objectives

Synthesize the published evidence on oral conditions, impact, management and challenges in its managing among palliative patients.

Research methods

Integrative review.

Research results

The total of 15 articles were eligible, analyzed and a protocol established.

Research conclusions

Oral manifestations are, oral candidiasis, dry mouth, dysphagia, dysgeusia, oral mucositis and orofacial pain. Determining a protocol for the care, based on scientific evidence, is fundamental for the multidisciplinary team that works in the care of terminal patients.

Research perspectives

Other complications in terminal patients and their treatments still need to have further studying.

FOOTNOTES

Author contributions: Silva ARP, Chrun ES and Lisboa ML contributed selecting eligible articles, reading in full those previous selected articles, collecting, tabulating and analyzing data; Munhoz EA, de Camargo AR and Bodanezi AV contributed on conception and design of the work; or the acquisition, analysis, or interpretation of data for the work; Munhoz EA also contributed on drafting the work and revising it critically for important intellectual content; All authors had revised and approved the final version of the manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Brazil

ORCID number: Augusto Vanni Bodanezi 0000-0003-4822-1868; Emanuely Silva Chrun 0000-0001-5569-9371; Alessandra R de Camargo 0000-0002-3988-7249; Etiene Andrade Munhoz 0000-0003-2652-4630.

S-Editor: Liu JH
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **WHO**. WHO Definition of Palliative Care. WHO. Available from: http://www.who.int/cancer/palliative/definition/en/
2 **WMA**. The World Medical Association-WMA Declaration of Venice on Terminal Illness. 2017. Available from: https://www.wma.net/policies- post/wma-declaration-of-venice-on-terminal-illness/
3 **American Academy of Hospice and Palliative Medicine**; Center to Advance Palliative Care; Hospice and Palliative Nurses Association; Last Acts Partnership; National Hospice and Palliative Care Organization. National Consensus Project for Quality Palliative Care: Clinical Practice Guidelines for quality palliative care, executive summary. *J Palliat Med* 2004; **7**: 611-627 [PMID: 15588352 DOI: 10.1089/jpm.2004.7.611]
4 **WHO**. International Agency for Research on Cancer: Estimated number of new cases in 2020, World, both sexes, all ages (excl. NMSC). Available from: https://gco.iarc.fr/today/online-analysis-table?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=1&include_nmsc=0&include_nmsc_other=1
5 **McDonnell AM**, Lenz KL. Palifermin: role in the prevention of chemotherapy- and radiation-induced mucositis. *Ann Pharmacother* 2007; **41**: 86-94 [PMID: 17190850 DOI: 10.1345/aph.1G473]
6 **Wiseman M**. The treatment of oral problems in the palliative patient. *J Can Dent Assoc* 2006; **72**: 453-458 [PMID: 16772071]
7 **WHO**. Palliative care: Symtom mamagement and end of life care. Gnova: World Helh Organization 2004. Available from: http://www.who.int/hiv/pub/imai/primary_palliative/en/
8 **Souza MT**, Silva MD, Carvalho Rd. Integrative review: what is it? *Einstein (Sao Paulo)* 2010; **8**: 102-106 [PMID: 26761761 DOI: 10.1590/S1679-45082010RW1134]
9 **Sladdin I**, Ball L, Bull C, Chaboyer W. Patient-centred care to improve dietetic practice: an integrative review. *J Hum Nutr Diet* 2017; **30**: 453-470 [PMID: 28124489 DOI: 10.1111/jhn.12444]
10 **Gillam JL**, Gillam DG. The assessment and implementation of mouth care in palliative care: a review. *J R Soc Promot Health* 2006; **126**: 33-37 [PMID: 16478014 DOI: 10.1177/1466424006061174]
11 **Wilberg P**, Hjermstad MJ, Ottesen S, Herlofson BB. Oral health is an important issue in end-of-life cancer care. *Support Care Cancer* 2012; **20**: 3115-3122 [PMID: 22434497 DOI: 10.1007/s00520-012-1441-8]
12 **Davies AN**, Brailsford SR, Beighton D, Shorthose K, Stevens VC. Oral candidosis in community-based patients with advanced cancer. *J Pain Symptom Manage* 2008; **35**: 508-514 [PMID: 18242047 DOI: 10.1016/j.jpainsymman.2007.07.005]
13 **Oneschuk D**, Hanson J, Bruera E. A survey of mouth pain and dryness in patients with advanced cancer. *Support Care Cancer* 2000; **8**: 372-376 [PMID: 10975686 DOI: 10.1007/s005200050005]
14 **Matsuo K**, Watanabe R, Kanamori D, Nakagawa K, Fujii W, Urasaki Y, Murai M, Mori N, Higashiguchi T. Associations between oral complications and days to death in palliative care patients. *Support Care Cancer* 2016; **24**: 157-161 [PMID: 25962615 DOI: 10.1007/s00520-015-2759-9]
15 **Bagg J**, Sweeney MP, Lewis MA, Jackson MS, Coleman D, Al MA, Baxter W, McEndrick S, McHugh S. High prevalence of non-albicans yeasts and detection of anti-fungal resistance in the oral flora of patients with advanced cancer.

Palliat Med 2003; **17**: 477-481 [PMID: 14526879 DOI: 10.1191/0269216303pm793oa]

16 **Burge FI**. Dehydration symptoms of palliative care cancer patients. *J Pain Symptom Manage* 1993; **8**: 454-464 [PMID: 7525778 DOI: 10.1016/0885-3924(93)90188-2]

17 **Fischer DJ**, Epstein JB, Yao Y, Wilkie DJ. Oral health conditions affect functional and social activities of terminally ill cancer patients. *Support Care Cancer* 2014; **22**: 803-810 [PMID: 24232310 DOI: 10.1007/s00520-013-2037-7]

18 **Sweeney MP**, Bagg J, Baxter WP, Aitchison TC. Oral disease in terminally ill cancer patients with xerostomia. *Oral Oncol* 1998; **34**: 123-126 [PMID: 9682775 DOI: 10.1016/S1368-8375(97)00076-6]

19 **Xu L**, Zhang H, Liu J, Chen X. Investigation of the oral infections and manifestations seen in patients with advanced cancer. *Pak J Med Sci* 2013; **29**: 1112-1115 [PMID: 24353702 DOI: 10.12669/pjms.295.3493]

20 **Thanvi J**, Bumb D. Impact of dental considerations on the quality of life of oral cancer patients. *Indian J Med Paediatr Oncol* 2014; **35**: 66-70 [PMID: 25006287 DOI: 10.4103/0971-5851.133724]

21 **Bagg J**, Sweeney MP, Davies AN, Jackson MS, Brailsford S. Voriconazole susceptibility of yeasts isolated from the mouths of patients with advanced cancer. *J Med Microbiol* 2005; **54**: 959-964 [PMID: 16157550 DOI: 10.1099/jmm.0.45720-0]

22 **Bagg J**, Jackson MS, Petrina Sweeney M, Ramage G, Davies AN. Susceptibility to Melaleuca alternifolia (tea tree) oil of yeasts isolated from the mouths of patients with advanced cancer. *Oral Oncol* 2006; **42**: 487-492 [PMID: 16488180 DOI: 10.1016/j.oraloncology.2005.10.002]

23 **Nakajima N**. Characteristics of Oral Problems and Effects of Oral Care in Terminally Ill Patients With Cancer. *Am J Hosp Palliat Care* 2017; **34**: 430-434 [PMID: 26903536 DOI: 10.1177/1049909116633063]

24 **Ezenwa MO**, Fischer DJ, Epstein J, Johnson J, Yao Y, Wilkie DJ. Caregivers' perspectives on oral health problems of end-of-life cancer patients. *Support Care Cancer* 2016; **24**: 4769-4777 [PMID: 27358170 DOI: 10.1007/s00520-016-3328-6]

25 **Saleh HA**, Lisboa ML, Flausino CS, Pilat SFM, Moral JAGD, de Andrade Munhoz E, de Camargo AR. The Practice of Hospital Dentistry in a Reference Hospital in Brazil. *Int J Dent Oral Health* 2019; **5**: 1-4 [DOI: 10.16966/2378-7090.304]

26 **Martorano-Fernandes L**, Dornelas-Figueira LM, Marcello-Machado RM, Silva RB, Magno MB, Maia LC, Del Bel Cury AA. Oral candidiasis and denture stomatitis in diabetic patients: Systematic review and meta-analysis. *Braz Oral Res* 2020; **34**: e113 [PMID: 32965459 DOI: 10.1590/1807-3107bor-2020.vol34.0113]

27 **Mothibe JV**, Patel M. Pathogenic characteristics of Candida albicans isolated from oral cavities of denture wearers and cancer patients wearing oral prostheses. *Microb Pathog* 2017; **110**: 128-134 [PMID: 28655563 DOI: 10.1016/j.micpath.2017.06.036]

28 **Patil S**, Rao RS, Majumdar B, Anil S. Clinical Appearance of Oral Candida Infection and Therapeutic Strategies. *Front Microbiol* 2015; **6**: 1391 [PMID: 26733948 DOI: 10.3389/fmicb.2015.01391]

29 **Williams DW**, Kuriyama T, Silva S, Malic S, Lewis MA. Candida biofilms and oral candidosis: treatment and prevention. *Periodontol 2000* 2011; **55**: 250-265 [PMID: 21134239 DOI: 10.1111/j.1600-0757.2009.00338.x]

30 **Yagasaki K**, Gando S, Matsuda N, Kameue T, Ishitani T, Hirano T, Iseki K. Pharmacokinetics and the most suitable dosing regimen of fluconazole in critically ill patients receiving continuous hemodiafiltration. *Intensive Care Med* 2003; **29**: 1844-1848 [PMID: 13680113 DOI: 10.1007/s00134-003-1980-z]

31 **López-Pintor RM**, Casañas E, González-Serrano J, Serrano J, Ramírez L, de Arriba L, Hernández G. Xerostomia, Hyposalivation, and Salivary Flow in Diabetes Patients. *J Diabetes Res* 2016; **2016**: 4372852 [PMID: 27478847 DOI: 10.1155/2016/4372852]

32 **Pina GMS**, Mota Carvalho R, Silva BSF, Almeida FT. Prevalence of hyposalivation in older people: A systematic review and meta-analysis. *Gerodontology* 2020; **37**: 317-331 [PMID: 32965067 DOI: 10.1111/ger.12497]

33 **Paris S**, Banerjee A, Bottenberg P, Breschi L, Campus G, Doméjean S, Ekstrand K, Giacaman RA, Haak R, Hannig M, Hickel R, Juric H, Lussi A, Machiulskiene V, Manton D, Jablonski-Momeni A, Santamaria R, Schwendicke F, Splieth CH, Tassery H, Zandona A, Zero D, Zimmer S, Opdam N. How to Intervene in the Caries Process in Older Adults: A Joint ORCA and EFCD Expert Delphi Consensus Statement. *Caries Res* 2020; **54**: 1-7 [PMID: 33291110 DOI: 10.1159/000510843]

34 **Furuya J**, Suzuki H, Hidaka R, Matsubara C, Motomatsu Y, Kabasawa Y, Tohara H, Sato Y, Miyake S, Minakuchi S. Association between oral health and advisability of oral feeding in advanced cancer patients receiving palliative care: a cross-sectional study. *Support Care Cancer* 2022; **30**: 5779-5788 [PMID: 35344101 DOI: 10.1007/s00520-022-06984-w]

35 **Furuya J**, Suzuki H, Hidaka R, Koshitani N, Motomatsu Y, Kabasawa Y, Tohara H, Sato Y, Minakuchi S, Miyake S. Factors affecting the oral health of inpatients with advanced cancer in palliative care. *Support Care Cancer* 2022; **30**: 1463-1471 [PMID: 34529140 DOI: 10.1007/s00520-021-06547-5]

36 **Raza A**, Karimyan N, Watters A, Emperumal CP, Al-Eryani K, Enciso R. Efficacy of oral and topical antioxidants in the prevention and management of oral mucositis in head and neck cancer patients: a systematic review and meta-analyses. *Support Care Cancer* 2022; **30**: 8689-8703 [PMID: 35680672 DOI: 10.1007/s00520-022-07190-4]

37 **Greco E**, Simic T, Ringash J, Tomlinson G, Inamoto Y, Martino R. Dysphagia Treatment for Patients With Head and Neck Cancer Undergoing Radiation Therapy: A Meta-analysis Review. *Int J Radiat Oncol Biol Phys* 2018; **101**: 421-444 [PMID: 29726363 DOI: 10.1016/j.ijrobp.2018.01.097]

38 **Langmore SE**, McCulloch TM, Krisciunas GP, Lazarus CL, Van Daele DJ, Pauloski BR, Rybin D, Doros G. Efficacy of electrical stimulation and exercise for dysphagia in patients with head and neck cancer: A randomized clinical trial. *Head Neck* 2016; **38** Suppl 1: E1221-E1231 [PMID: 26469360 DOI: 10.1002/hed.24197]

39 **Mortazavi H**, Shafiei S, Sadr S, Safiaghdam H. Drug-related Dysgeusia: A Systematic Review. *Oral Health Prev Dent* 2018; **16**: 499-507 [PMID: 30574604 DOI: 10.3290/j.ohpd.a41655]

40 **Sevryugin O**, Kasvis P, Vigano M, Vigano A. Taste and smell disturbances in cancer patients: a scoping review of available treatments. *Support Care Cancer* 2021; **29**: 49-66 [PMID: 32734392 DOI: 10.1007/s00520-020-05609-4]

41 **Al-Moraissi EA**, Conti PCR, Alyahya A, Alkebsi K, Elsharkawy A, Christidis N. The hierarchy of different treatments for myogenous temporomandibular disorders: a systematic review and network meta-analysis of randomized clinical trials. *Oral Maxillofac Surg* 2022; **26**: 519-533 [PMID: 34674093 DOI: 10.1007/s10006-021-01009-y]

42 **Volpato LE**, Silva TC, Oliveira TM, Sakai VT, Machado MA. Radiation therapy and chemotherapy-induced oral mucositis. *Braz J Otorhinolaryngol* 2007; **73**: 562-568 [PMID: 17923929 DOI: 10.1016/S1808-8694(15)30110-5]

43 **Lalla RV**, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, McGuire DB, Migliorati C, Nicolatou-Galitis O, Peterson DE, Raber-Durlacher JE, Sonis ST, Elad S; Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer* 2014; **120**: 1453-1461 [PMID: 24615748 DOI: 10.1002/cncr.28592]

44 **Herbers AH**, de Haan AF, van der Velden WJ, Donnelly JP, Blijlevens NM. Mucositis not neutropenia determines bacteremia among hematopoietic stem cell transplant recipients. *Transpl Infect Dis* 2014; **16**: 279-285 [PMID: 24621081 DOI: 10.1111/tid.12195]

45 **Sharifi H**, Heydari A, Salek R, Emami Zeydi A. Oral cryotherapy for preventing chemotherapy-induced oral mucositis: An effective but yet neglected strategy. *J Cancer Res Ther* 2017; **13**: 386-387 [PMID: 28643769 DOI: 10.4103/0973-1482.188301]

46 **Riley P**, Glenny AM, Worthington HV, Littlewood A, Clarkson JE, McCabe MG. Interventions for preventing oral mucositis in patients with cancer receiving treatment: oral cryotherapy. *Cochrane Database Syst Rev* 2015; **2015**: CD011552 [PMID: 26695736 DOI: 10.1002/14651858.CD011552.pub2]

47 **Legouté F**, Bensadoun RJ, Seegers V, Pointreau Y, Caron D, Lang P, Prévost A, Martin L, Schick U, Morvant B, Capitain O, Calais G, Jadaud E. Low-level laser therapy in treatment of chemoradiotherapy-induced mucositis in head and neck cancer: results of a randomised, triple blind, multicentre phase III trial. *Radiat Oncol* 2019; **14**: 83 [PMID: 31118057 DOI: 10.1186/s13014-019-1292-2]

48 **Lai CC**, Chen SY, Tu YK, Ding YW, Lin JJ. Effectiveness of low level laser therapy versus cryotherapy in cancer patients with oral mucositis: Systematic review and network meta-analysis. *Crit Rev Oncol Hematol* 2021; **160**: 103276 [PMID: 33716203 DOI: 10.1016/j.critrevonc.2021.103276]

49 **Mazokopakis EE**, Vrentzos GE, Papadakis JA, Babalis DE, Ganotakis ES. Wild chamomile (Matricaria recutita L.) mouthwashes in methotrexate-induced oral mucositis. *Phytomedicine* 2005; **12**: 25-27 [PMID: 15693704 DOI: 10.1016/j.phymed.2003.11.003]

50 **Tavakoli Ardakani M**, Ghassemi S, Mehdizadeh M, Mojab F, Salamzadeh J, Hajifathali A. Evaluating the effect of Matricaria recutita and Mentha piperita herbal mouthwash on management of oral mucositis in patients undergoing hematopoietic stem cell transplantation: A randomized, double blind, placebo controlled clinical trial. *Complement Ther Med* 2016; **29**: 29-34 [PMID: 27912953 DOI: 10.1016/j.ctim.2016.08.001]

51 **Pavesi VC**, Lopez TC, Martins MA, Sant'Ana Filho M, Bussadori SK, Fernandes KP, Mesquita-Ferrari RA, Martins MD. Healing action of topical chamomile on 5-fluoracil induced oral mucositis in hamster. *Support Care Cancer* 2011; **19**: 639-646 [PMID: 20424869 DOI: 10.1007/s00520-010-0875-0]

52 **de Oliveira AB**, Ferrisse TM, Basso FG, Fontana CR, Giro EMA, Brighenti FL. A systematic review and meta-analysis of the effect of photodynamic therapy for the treatment of oral mucositis. *Photodiagnosis Photodyn Ther* 2021; **34**: 102316 [PMID: 33940208 DOI: 10.1016/j.pdpdt.2021.102316]

53 **Khanjani Pour-Fard-Pachekenari A**, Rahmani A, Ghahramanian A, Asghari Jafarabadi M, Onyeka TC, Davoodi A. The effect of an oral care protocol and honey mouthwash on mucositis in acute myeloid leukemia patients undergoing chemotherapy: a single-blind clinical trial. *Clin Oral Investig* 2019; **23**: 1811-1821 [PMID: 30206708 DOI: 10.1007/s00784-018-2621-9]

54 **Adams R**. Qualified nurses lack adequate knowledge related to oral health, resulting in inadequate oral care of patients on medical wards. *J Adv Nurs* 1996; **24**: 552-560 [PMID: 8876416 DOI: 10.1046/j.1365-2648.1996.22416.x]

55 **Andersson P**, Persson L, Hallberg IR, Renvert S. Testing an oral assessment guide during chemotherapy treatment in a Swedish care setting: a pilot study. *J Clin Nurs* 1999; **8**: 150-158 [PMID: 10401348 DOI: 10.1046/j.1365-2702.1999.00237.x]

56 **Dodd MJ**, Larson PJ, Dibble SL, Miaskowski C, Greenspan D, MacPhail L, Hauck WW, Paul SM, Ignoffo R, Shiba G. Randomized clinical trial of chlorhexidine versus placebo for prevention of oral mucositis in patients receiving chemotherapy. *Oncol Nurs Forum* 1996; **23**: 921-927 [PMID: 8829162]

57 **Ganley B**. Mouth care for the patient undergoing head and neck radiotherapy: a survey of radiation oncology nurses. *Oncol Nurs Forum* 1996; **23**: 1619-23

58 **Longhurst RH**. An evaluation of the oral care given to patients when staying in hospital. *Prim Dent Care* 1999; **6**: 112-115 [PMID: 11819874]

59 **Ransier A**, Epstein JB, Lunn R, Spinelli J. A combined analysis of a toothbrush, foam brush, and a chlorhexidine-soaked foam brush in maintaining oral hygiene. *Cancer Nurs* 1995; **18**: 393-396 [PMID: 7585494 DOI: 10.1097/00002820-199510000-00009]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 2981-2991

DOI: 10.12998/wjcc.v11.i13.2981

ISSN 2307-8960 (online)

META-ANALYSIS

Effect of preoperative inspiratory muscle training on postoperative outcomes in patients undergoing cardiac surgery: A systematic review and meta-analysis

Jing Wang, Yu-Qiang Wang, Jun Shi, Peng-Ming Yu, Ying-Qiang Guo

Specialty type: Rehabilitation

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Awad AK, Egypt; Grigoriev E; Ong H, Malaysia

Received: November 12, 2022
Peer-review started: November 12, 2022
First decision: January 30, 2023
Revised: February 10, 2023
Accepted: March 31, 2023
Article in press: March 31, 2023
Published online: May 6, 2023

Jing Wang, Yu-Qiang Wang, Jun Shi, Ying-Qiang Guo, Department of Cardiovascular Surgery, Sichuan University West China Hospital, Chengdu 610041, Sichuan Province, China

Peng-Ming Yu, Rehabilitation Medicine Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Corresponding author: Ying-Qiang Guo, MD, PhD, Chief Doctor, Doctor, Surgeon, Department of Cardiovascular Surgery, Sichuan University West China Hospital, No. 37 Guoxue Lane, Wuhou District, Chengdu 610041, Sichuan Province, China. drguoyq@wchscu.cn

Abstract

BACKGROUND

Cardiovascular disease is the most prevalent disease worldwide and places a great burden on the health and economic welfare of patients. Cardiac surgery is an important way to treat cardiovascular disease, but it can prolong mechanical ventilation time, intensive care unit (ICU) stay, and postoperative hospitalization for patients. Previous studies have demonstrated that preoperative inspiratory muscle training could decrease the incidence of postoperative pulmonary complications.

AIM

To explore the effect of preoperative inspiratory muscle training on mechanical ventilation time, length of ICU stay, and duration of postoperative hospitalization after cardiac surgery.

METHODS

A literature search of PubMed, Web of Science, Cochrane Library, EMBASE, China National Knowledge Infrastructure, WanFang, and the China Science and Technology journal VIP database was performed on April 13, 2022. The data was independently extracted by two authors. The inclusion criteria were: (1) Randomized controlled trial; (2) Accessible as a full paper; (3) Patients who received cardiac surgery; (4) Preoperative inspiratory muscle training was implemented in these patients; (5) The study reported at least one of the following: Mechanical ventilation time, length of ICU stay, and/or duration of postoperative hospitalization; and (6) In English language.

RESULTS

We analyzed six randomized controlled trials with a total of 925 participants. The pooled mean difference of mechanical ventilation time was -0.45 h [95% confidence interval (CI): -1.59-0.69], which was not statistically significant between the intervention group and the control group. The pooled mean difference of length of ICU stay was 0.44 h (95%CI: -0.58-1.45). The pooled mean difference of postoperative hospitalization was -1.77 d in the intervention group *vs* the control group [95%CI: -2.41-(-1.12)].

CONCLUSION

Preoperative inspiratory muscle training may decrease the duration of postoperative hospitalization for patients undergoing cardiac surgery. More high-quality studies are needed to confirm our conclusion.

Key Words: Preoperative inspiratory muscle training; Cardiac surgery; Heart surgery; Mechanical ventilation; Intensive care unit; Duration of postoperative hospitalization

Core Tip: For cardiac surgery patients, the use of inspiratory muscle training could reduce the incidence of postoperative pulmonary complications according to previous research. Our study demonstrated that it could shorten the duration of postoperative hospitalization and thus may decrease overall costs. More research is needed to explore the effect of inspiratory muscle training on mechanical ventilation time and length of intensive care unit stay.

Citation: Wang J, Wang YQ, Shi J, Yu PM, Guo YQ. Effect of preoperative inspiratory muscle training on postoperative outcomes in patients undergoing cardiac surgery: A systematic review and meta-analysis. *World J Clin Cases* 2023; 11(13): 2981-2991

URL: https://www.wjgnet.com/2307-8960/full/v11/i13/2981.htm

DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.2981

INTRODUCTION

Cardiovascular disease (CVD) has a high incidence rate and high mortality worldwide. CVD has been one of the most prevalent causes of death in the United States since 1975, accounting for 25% of all deaths[1]. The World Health Organization reported that in 2015 CVD caused an estimated 17.7 million deaths globally, making CVD the most prevalent cause of death worldwide. The economic burden of CVD is greater than that of Alzheimer's disease and diabetes, with calculated indirect costs of $237 billion per year and a projected increase to $368 billion by 2035[2]. A study reported a national economic loss of $8.8 trillion from 2012 to 2030 due to CVD in China[3]. Cardiac surgery is an important treatment for coronary heart disease and other structural heart diseases. Due to the complex surgical procedures, surgical trauma, and long surgery time, patients often need postoperative mechanical ventilation and intensive care unit (ICU) admission for observation and further treatment. Meanwhile, postoperative pulmonary complications (PPCs) are one of the major causes of prolonged hospitalization and death[4,5]. Indeed, pulmonary complications following coronary artery bypass graft (CABG) operation were reported to be associated with significantly longer hospital stays (8.2 d *vs* 10.0 d, 95% confidence interval [CI]: 0.3-3.3)[6]. The incidence of PPCs prolongs the hospitalization length and thus increases the hospitalization expenses. Vonlanthen *et al*[7] performed a cost analysis of 1200 patients undergoing major surgery and revealed that costs increased with the severity of postoperative complications. This increase in costs is up to 5 times that of a similar surgery without complications. Thompson *et al*[8] included 618495 patients who underwent an intra-abdominal surgery. They found that postoperative hospital-acquired pneumonia increased the mean hospitalization length by 11 d, which translated to a mean increase in total hospital charges of $31000 (study performed in the year 2000). Other studies have also demonstrated that postoperative complications can increase the expense of surgery[9-11].

Preoperative inspiratory muscle training (IMT) has attracted increasing attention from doctors. Previous studies demonstrated that preoperative IMT can reduce the incidence of PPCs. Hulzebos *et al*[12] reported that preoperative IMT reduced the incidence of PPCs and the postoperative stay in hospital in patients at high risk of developing pulmonary complications after CABG surgery. Katsura *et al*[13] found evidence that preoperative IMT was associated with a reduction in postoperative atelectasis, pneumonia, and duration of hospital stay in adults after cardiac and major abdominal surgery. Fagevik Olsén *et al*[14] reported that preoperative physiotherapy education and training sessions can reduce PPC incidence in patients receiving open major abdominal surgery. Boden *et al*[15]

confirmed the findings in their trial in 2017. However, there are few studies reporting the effects of preoperative IMT on length of mechanical ventilation, length of ICU stay, and duration of postoperative hospitalization. Our study aimed to answer the following questions: (1) Does preoperative IMT shorten the time of mechanical ventilation and ICU stay; and (2) Does preoperative IMT reduce the duration of postoperative hospitalization and thus save money for patients?

MATERIALS AND METHODS

Literature search

We searched the English literature databases, which included PubMed, Web of Science, Cochrane Library, and EMBASE, and Chinese literature databases, which included China National Knowledge Infrastructure, WanFang, and China Science and Technology journal VIP. Our search strategies were composed of: (1) Patients (experimental: Cardiac surgery/heart surgery); (2) Intervention (preoperative IMT/preoperative respiratory muscle training); (3) Control (-); and (4) Outcome (mechanical ventilation/MV/intensive care unit/ICU/postoperative stay in hospital/duration of postoperative hospitalization). We searched the databases through April 13, 2022. Two researchers independently assessed the eligibility of papers by title and abstract. When there was insufficient information to judge the qualification of the study in the title and abstract, the whole paper was assessed. When the two researchers disagreed, a third researcher was consulted to reach consensus.

Study selection

The inclusion criteria were: (1) Randomized controlled trial; (2) Accessible as full paper; (3) Cardiac surgery patient(s); (4) Preoperative IMT; (5) Data on at least one of the following: Mechanical ventilation time, length of ICU stay, and/or duration of postoperative hospitalization; and (6) In English language.

Quality of study characteristics

We used the Cochrane bias risk assessment tool in Review Manager (RevMan) computer program version 5.4, which is a reliable tool for the assessment of the risk of bias in randomized controlled trials in systematic reviews, to assess the bias risk of the included studies[16].

Data extraction

Data on author, year, journal, and country of the studies were obtained. Data on patient age, patient sex, type of surgery, intervention (including strength, frequency, time), and outcomes (mechanical ventilation time, length of ICU stay, and duration of postoperative hospitalization) were collected. The data were collected from tables or from the main text. For example, we collected the duration of postoperative hospitalization from the study by Hulzebos *et al*[12] and from the main text in the study by Valkenet *et al*[6]. However, some data were reported in ranges or interquartile ranges, such as those in the study of Hulzebos *et al*[12]. For these studies, we used the tool on the website (http://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html) to estimate the sample mean and standard deviation from the sample size, median, range, and/or interquartile range. The data were independently extracted by two authors (Wang J and Wang YQ).

Statistical analysis

This meta-analysis aimed to evaluate the effect of IMT on mechanical ventilation time, length of ICU stay, and postoperative hospitalization in cardiac surgery patients. RevMan5.4 and Stata statistical software (Release 14; StataCorp LP, College Station, TX, United States) were used to perform the statistical analyses; of note, the results obtained from each program were the same. We chose the randomized effects model to analyze the data. The principal summary measurement used was the pooled mean difference (95%CI). We provided forest plots for every outcome.

RESULTS

The flowchart of selected studies is presented in Figure 1. After the initial search, 311 citations were selected. After a review of abstracts and full-text articles, six trials[6,12,17-20] met the inclusion criteria. The risk of bias assessment of the included studies is presented in Figure 2.

Characteristics of included studies

The characteristics of the included trials are presented in Table 1. A total of 925 participants were involved in the six included studies. The sample sizes of the included trials ranged from 43 to 276, consisting primarily of male participants. The integrated age was 66.97 years, and the sex ratio in every study showed no significant effect. The intervention strategies and control methods were similar in each

Table 1 Characteristics of the six included studies

No.	Ref.	Country	Intervention	Control	Intervention group			Control group		
					Patients (male: female)	Mean age	Surgery type	Patients (male: female)	Mean age	Surgery type
1	Hulzebos *et al*[12], 2006	Netherlands	Threshold IMT + incentive spirometry + education in an active cycle of breathing techniques + forced expiration techniques	Usual care (*i.e.* instruction on deep breathing maneuvers, coughing, and early mobilization) + postoperative incentive spirometry, chest physical therapy, and mobilization scheme	139 (108:31)	66.5 (9.0)	CABG: 139	137 (107:30)	67.3 (9.2)	CABG: 137
2	Savci *et al* [17], 2011	Turkey	Threshold IMT + mobilization + active exercises of upper and lower limbs + breathing exercises + coughing techniques	Usual care (mobilization, active exercises of upper and lower limbs, breathing exercises, and coughing techniques)	22 (19:3)	62.82 (8.69)	CABG: 22	21 (19:2)	57.48 (11.48)	CABG: 21
3	Moises *et al*[18], 2014	Brazil	Threshold IMT + breathing exercises + postoperative physical therapy	Guidelines ward routine + postoperative physical therapy	35 (23:12)	58.90 ± 9.53	CABG: 35	35 (29:6)	61.40 ± 8.43	CABG: 35
4	Valken *et al*[6], 2016	Netherlands	Threshold IMT + incentive spirometry + education (deep breathing maneuvers, coughing, and early mobilization)	Postoperative deep breathing maneuvers, coughing, and early mobilization incentive spirometry and chest physical therapy	119 (93:26)	66 (9.2)	CABG: 99; CABG + valve:20	116 (93:23)	67.5 (9.7)	CABG: 87; CABG + valve: 29
5	Chen *et al* [19], 2019	China	Threshold IMT + usual care (education coughing, and early mobilization) and abdominal breathing training + postoperative chest physical therapy and mobilization scheme	Threshold IMT [the intensity was fixed at the minimum load of the device (9 cmH2O)] + usual care (education coughing and early mobilization) and abdominal breathing training + postoperative chest physical therapy and mobilization scheme	98 (73:25)	61.68 ± 8.12	CABG: 69; valve: 18; CABG + valve: 11	99 (68:31)	61.68 ± 7.73	CABG: 70; valve: 21; CABG + valve: 8
6	Weber *et al*[20], 2021	Germany	Threshold IMT + walking below the threshold of subjective exhaustion + mobilization protocol and individual physio-therapy	Postoperative physio-therapy	58 (27:31)	82.2 ± 5.8	TAVR: 58	50 (26:24)	81.7 ± 5.0	TAVR: 50

For threshold inspiratory muscle training, patients must generate a preset pressure to allow airflow for each breath. Once that threshold is achieved, inspiratory flow is not dependent on patient effort. This means that threshold loading is the easiest of these inspiratory muscle training methods to standardize and prescribe for patients. CABG: Coronary artery bypass grafting; IMT: Inspiratory muscle training; TAVR: Transcatheter aortic valve replacement.

trial (Table 2). There was no significant difference in the type of operation. Most patients received CABG, and some of them received valve surgery [including transcatheter aortic valve replacement (TAVR)].

Outcome

Mechanical ventilation time: Three studies[17-19] reported on the duration of mechanical ventilation. The pooled mean difference of -0.45 h (95%CI: -1.59-0.69) and low heterogeneity (I^2 =0) showed no statistically significant effect on mechanical ventilation time (Figure 3).

Length of ICU stay: Data from four studies[17-20] indicated a nonsignificant effect on the length of ICU stay with a pooled mean difference of 0.44 h (95%CI: -0.58-1.45) and low heterogeneity (I^2 = 0) (Figure 4). Excluding patients who received TAVR did not affect the results (Figure 5).

Duration of postoperative hospitalization: A meta-analysis of six trials[6,12,17-20] reporting the length of postoperative hospitalization yielded a pooled mean difference of -1.77 d [95%CI: -2.41-(-1.12)] for the intervention group *vs* the control group. This difference was statistically significant (Figure 6).

Table 2 Inspiratory muscle training used in each study

No.	Ref.	Length	Frequency	Duration	Supervision	Intensity
1	Hulzebos *et al*[12], 2006	≥ 2 wk preoperatively	Once a day	20 mins	6 times a week without supervision and once a week with supervision	30% of MIP. Resistance increases incrementally, based on the RPE scored on the Borg scale
2	Savci *et al*[17], 2011	5 d preoperatively + 5 d postoperatively	Twice a day	30 mins	Each session was under the supervision of a physical therapist	15% of MIP. The resistance was increased incrementally between 15% and 45% based on patient's tolerance in the following days
3	Moises *et al*[18], 2014	Preoperative (length not mentioned)	Once a day	20 mins	Each session was under supervision	40% of MIP. Intensity increase not mentioned
4	Valkenet *et al*[6], 2016	Not mentioned	Once a day	20 min	6 times a week without supervision and once a week with supervision	30% of MIP. Increased incrementally based on the RPE as scored on the Borg scale. If patients recorded an RPE score < 5 after a training session, they were instructed to increase the inspiratory load of the threshold device by 5% before the next training session. The threshold load was unchanged for RPE scores ≥ 5
5	Chen *et al*[19], 2019	5 d preoperatively	Twice a day	20 min	Each session was under the supervision of a physical therapist	30% of MIP. Increased incrementally, based on the RPE scored on the Borg18 scale. If the RPE was less than 5, the resistance of the inspiratory threshold trainer was then increased incrementally by 5%. Training loads were adjusted to maintain 30% of the maximal inspiratory pressure every day
6	Weber *et al*[20], 2021	≥ 2 wk preoperatively	Once a day	20 min	Not mentioned	Not mentioned

MIP: Maximum inspiratory pressure; RPE: Rate of perceived exertion.

Excluding patients who received TAVR did not affect the results (Figure 7).

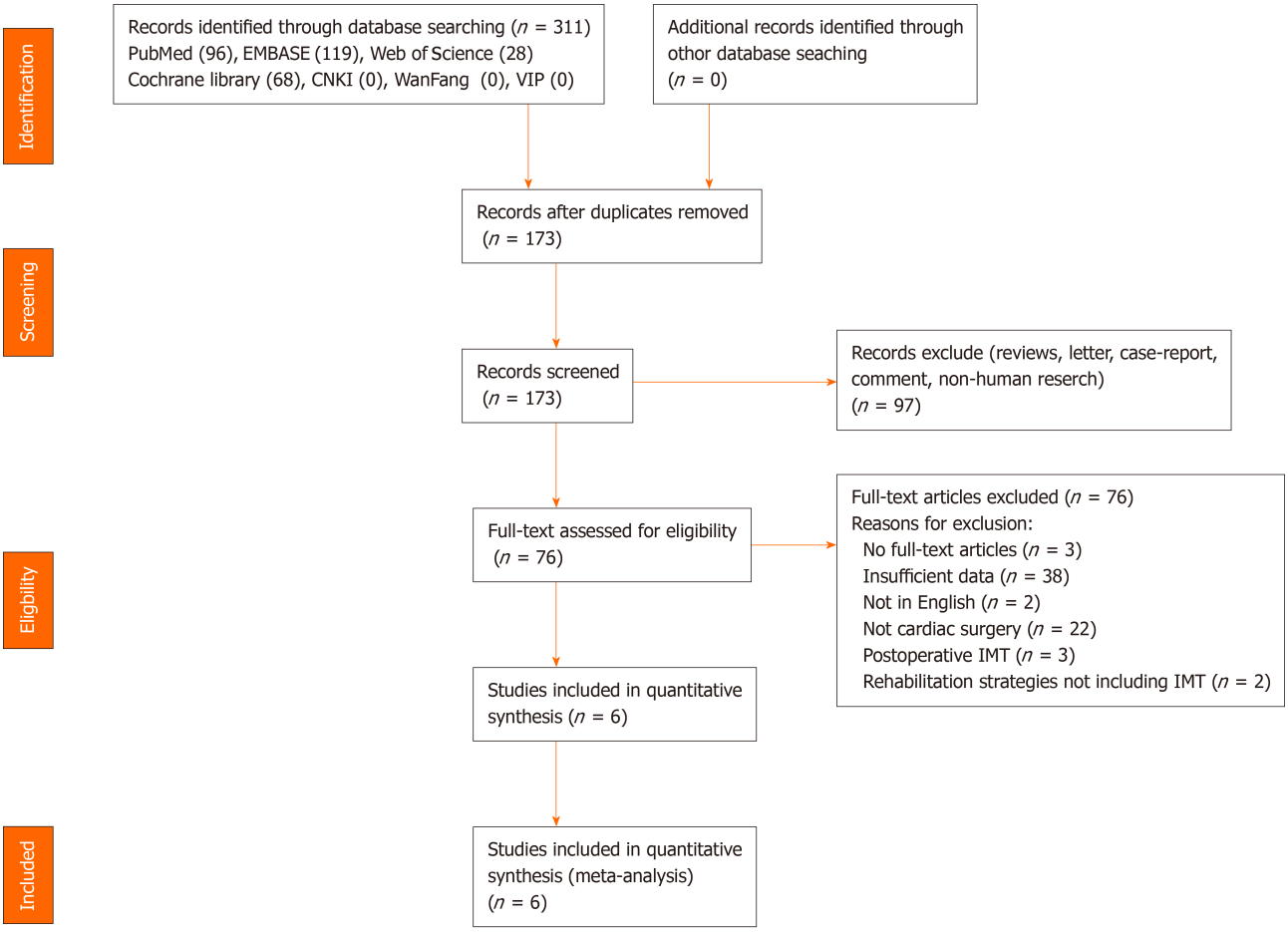
DISCUSSION

This is the first systematic review and meta-analysis to explore the effect of preoperative IMT on mechanical ventilation time, length of ICU stay, and duration of postoperative hospitalization after cardiac surgery.

Preoperative IMT

A summary of IMT in each study is presented in Table 2. All studies used threshold IMT. Patients received training greater than or equal to 2 wk, once a day, and lasting 20 min in the study of Hulzebos *et al*[12] and that of Weber *et al*[20]. Meanwhile, 5 d of preoperative training, twice a day, and lasting 30 min or 20 min was used in the study of Savci *et al*[17] and that of Chen *et al*[19], respectively. All patients were under supervision of a physical therapist in the studies. Studies by Hulzebos *et al*[12], Valkenet *et al*[6], and Chen *et al*[19] started the training with 30% of the maximum inspiratory pressure. Savci *et al*[17] started training with 15% of maximum inspiratory pressure, and Moises *et al*[18] with 40% of maximum inspiratory pressure. Weber *et al*[20] did not mention the starting intensity. We found no effect of preoperative IMT on mechanical ventilation time or length of ICU stay in cardiac surgery patients. Snowdon *et al*[21] concluded in their systematic review that preoperative intervention shortened the time to extubate from mechanical ventilation by a pooled mean difference of 0.14 d (95%CI: 0.01-0.26), which was different from our result. Interventions in their included studies were diversified and included anesthesia clinics or preadmission clinics, IMT, education booklets, *etc*. This likely explains the differences between our study and theirs. Because of the few studies reporting on these two outcomes, any conclusions should be made with caution.

Our study found that preoperative IMT did have a statistically significant effect on the duration of postoperative hospitalization. Katsura *et al*[13] reported that preoperative IMT could reduce the duration of hospitalization in patients receiving cardiac and major abdominal surgery. However, they included mostly abdominal surgery, which was different from our study. Snowdon *et al*[21] reported that preoperative intervention reduced hospitalization for elderly patients (> 63 years), with a pooled mean difference of -1.32 d [95%CI: -2.36-(-0.28)], similar to our study. Cook *et al*[22] reported that preoperative threshold IMT had the potential to reduce postoperative hospitalization and pulmonary complications after cardiac surgery, which was the same as our study. However, their study did not include the studies of Valkenet *et al*[6] and Weber *et al*[20]. Reducing the duration of hospitalization may



DOI: 10.12998/wjcc.v11.i13.2981

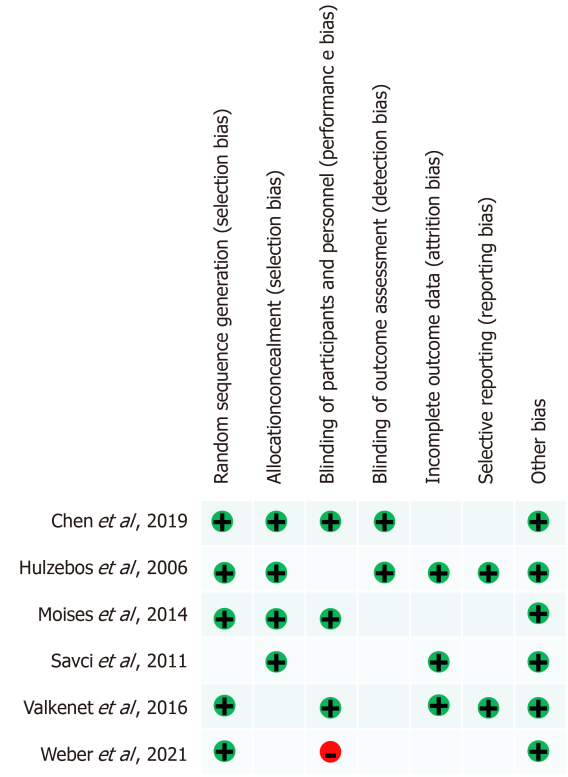
Figure 1 Flowchart of literature search. After the initial search, 311 articles were selected. After a review of abstracts and full-text articles, only six trials met the inclusion criteria. CNKI: Chinese National Knowledge Infrastructure; IMT: Inspiratory muscle training.

reduce hospitalization expenses for patients. It has been hypothesized that preoperative IMT would increase the muscle strength of the patients and lead to less PPCs. Several studies (summarized in the Introduction section) have confirmed this hypothesis. We hypothesized that less postoperative complications and decreased hospitalization would in turn decrease hospitalization expenses. With the shorter postoperative stay in the hospital, patients may pay less for medicines, nursing, room and board, *etc*. Further cost analysis studies should be conducted to confirm our hypothesis.

With the popularity of the use of diagnosis-related groups, medical costs have caught the increasing attention of doctors and patients. In a health economic analysis of a randomized trial implemented by Boden *et al*[23] in Australia, participants were randomly divided into two groups (intervention group and control group). The intervention involved respiratory education and breathing exercise training with a physiotherapist. The control group received the information booklet only. They found that the mean estimate of net savings provided a return on investment of approximately 800% ($8 saved by the hospital for every $1 spent on physiotherapy to provide education and breathing exercise training to patients before surgery). This means that from the hospital's perspective, preoperative physiotherapy was cost-effective. A meta-analysis by Takura *et al*[24] found that cardiac rehabilitation (CR) significantly improved cost/quality-adjusted life-years in the CR arm compared with the usual care arm [standardized mean difference: -0.31, 95%CI: -0.53-(-0.09)], which means that CR is cheaper and more effective than usual care. Preoperative IMT is one method of CR, and we can speculate that it could also decrease hospital expenses.

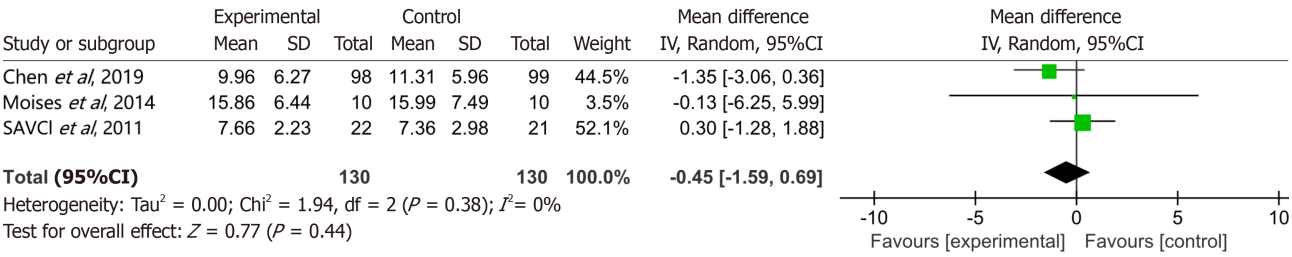
Limitations

The most important limitation of our study was that few studies met our inclusion criteria. This led to a small sample size, which may influence the precision and accuracy of our study. At the same time, we did not obtain the patient level data from the studies. The second limitation was the heterogeneity. There were some differences among the interventions in these included studies. The length, frequency, duration, intensity, and supervision of IMT were different in each study. The details of each intervention are shown in Table 2. These differences could lead to heterogeneity of our results, and we



DOI: 10.12998/wjcc.v11.i13.2981 **Copyright** ©The Author(s) 2023.

Figure 2 Risk of bias summary for each included study.

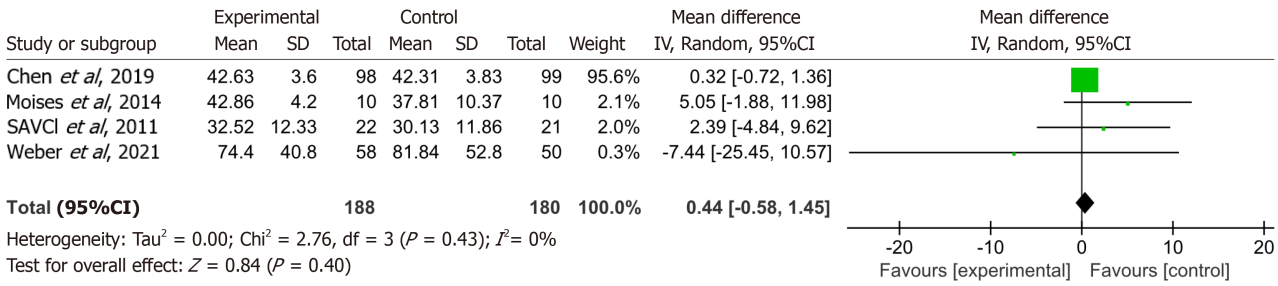


DOI: 10.12998/wjcc.v11.i13.2981 **Copyright** ©The Author(s) 2023.

Figure 3 Effect of preoperative inspiratory muscle training on mechanical ventilation time. The pooled mean difference of -0.45 h (95%CI: -1.59 to 0.69) and low heterogeneity (I^2 = 0) showed no statistically significant effect on mechanical ventilation time in patients with preoperative inspiratory muscle training after cardiac surgery. SD: Standard deviation.

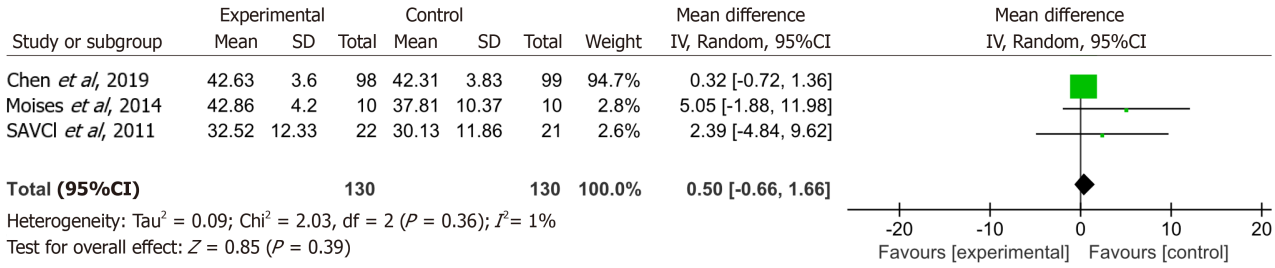
cannot determine which training method is the best. In addition, the standards for extubating and hospital discharge are different in each country, hospital, and even doctor. These factors would lead to heterogeneity. The third limitation was that the type of operation in the included studies was mostly CABG, which did not include other cardiac surgeries *(e.g.*, valve replacement and aortic dissection). Thus, we cannot claim the positive effect of preoperative IMT on the above outcomes in patients with all types of cardiac surgery.

The fourth limitation is the data obtained. Data about mechanical ventilation time were expressed as ranges or interquartile ranges in the studies by Hulzebos *et al*[12], Sobrinho *et al*[18], and Chen *et al*[19]. Data on the length of ICU stay were expressed as ranges or interquartile ranges in the studies of Sobrinho *et al*[18] and Chen *et al*[19]. Data on the duration of hospitalization were also expressed as ranges or interquartile ranges in the studies by Hulzebos *et al*[12] and Sobrinho *et al*[18]. We used the tool on the website (http://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html) to estimate the sample mean and standard deviation from the sample size, median, range, and/or interquartile range for the above studies. This conversion decreases the precision and accuracy of data and can lead to statistical error. More high-quality studies are needed to explore the effect of preoperative IMT on mechanical ventilation time, length of ICU stay, and duration of postoperative hospitalization after cardiac surgery.



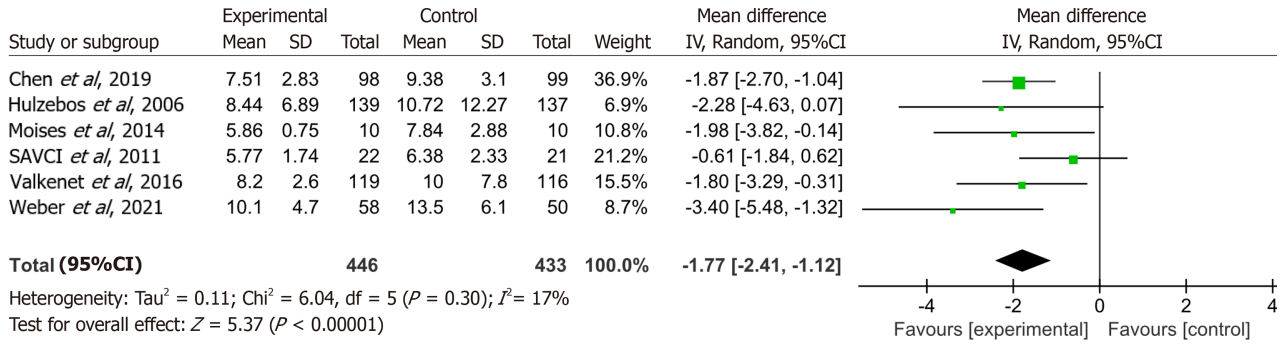
DOI: 10.12998/wjcc.v11.i13.2981 **Copyright** ©The Author(s) 2023.

Figure 4 Effect of preoperative inspiratory muscle training on length of intensive care unit stay. The result indicated a nonsignificant effect on the length of intensive care unit stay with a pooled mean difference of 0.44 h (95%CI: -0.58 to 1.45) and low heterogeneity (I^2 = 0) in cardiac surgery patients (including transcatheter aortic valve replacement) receiving preoperative inspiratory muscle training. Weight refers to the contribution of each study to the meta-analytic estimate of effect. SD: Standard deviation.



DOI: 10.12998/wjcc.v11.i13.2981 **Copyright** ©The Author(s) 2023.

Figure 5 Effect of preoperative inspiratory muscle training on length of intensive care unit stay. The result indicated a nonsignificant effect on the length of intensive care unit stay with a pooled mean difference of 0.50 h (95%CI: -0.66 to 1.66) and low heterogeneity (I^2 = 1) in cardiac surgery patients (excluding transcatheter aortic valve replacement) receiving preoperative inspiratory muscle training. SD: Standard deviation.

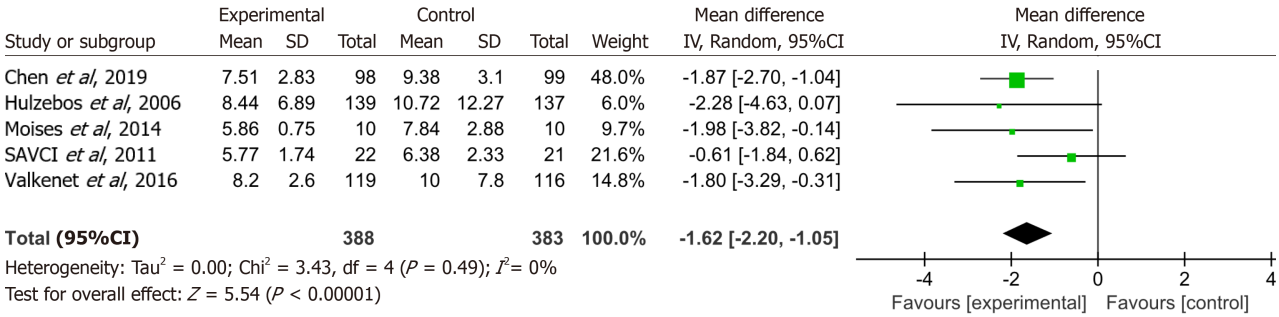


DOI: 10.12998/wjcc.v11.i13.2981 **Copyright** ©The Author(s) 2023.

Figure 6 Impact of preoperative inspiratory muscle training on the duration of postoperative hospitalization. The result indicated a significant positive effect on the duration of postoperative hospitalization with a pooled mean difference of -1.77 d [95%CI: -2.41-(-1.12)] in cardiac surgery patients (including transcatheter aortic valve replacement) receiving preoperative inspiratory muscle training. SD: Standard deviation.

Clinical application

As we have found, preoperative IMT may decrease the length of postoperative hospitalization and potentially lessen expenses in the hospital to save money for patients. Thus, we recommend that preoperative IMT be implemented in hospitals or at home for patients who are waiting for cardiac surgery. However, we cannot determine the best length, frequency, duration, intensity, and supervision of IMT for patients. More studies are needed to find the best way to carry out IMT in hospitals or at home.



DOI: 10.12998/wjcc.v11.i13.2981

Figure 7 Impact of preoperative inspiratory muscle training on the duration of postoperative hospitalization excluding patients who received transcatheter aortic valve replacement. The result indicated a significant positive effect on the duration of postoperative hospitalization with a pooled mean difference of -1.62 d [95%CI: -2.20-(-1.05)] in cardiac surgery patients (excluding transcatheter aortic valve replacement) receiving preoperative inspiratory muscle training. SD: Standard deviation.

CONCLUSION

Preoperative IMT, as an important part of physical therapy, may decrease the duration of postoperative hospitalization and may decrease hospital costs for patients undergoing cardiac surgery. Meanwhile, IMT does not appear to lessen the time to extubate from mechanical ventilation or the duration of ICU stay.

ARTICLE HIGHLIGHTS

Research background

The effect of preoperative inspiratory muscle training (IMT) on mechanical ventilation time, length of intensive care unit stay, and duration of postoperative hospitalization after cardiac surgery are unknown.

Research motivation

Decreasing pulmonary complications can lead to shorter hospital stays. This in turn could decrease costs for the patient and the hospital.

Research objectives

To evaluate whether preoperative IMT is effective in improving postoperative outcomes such as the mechanical ventilation time, length of intensive care unit stay, and duration of postoperative hospitalization in patients receiving cardiac surgery.

Research methods

Several databases were searched to obtain eligible randomized controlled trials. Outcomes were mechanical ventilation time, length of intensive care unit stay, and duration of postoperative hospitalization**.**

Research results

The pooled mean difference of -0.45 h [(95%CI): -1.59-0.69] showed no statistically significant effect on mechanical ventilation time. The pooled mean difference 0.44 h (95%CI: -0.58-1.45) showed no statistically significant effect on length of intensive care unit stay. The pooled mean difference showed -1.77 d [95%CI: -2.41-(-1.12)] for postoperative hospitalization.

Research conclusions

Preoperative IMT may decrease the duration of postoperative hospitalization for patients undergoing cardiac surgery.

Research perspectives

More high-quality studies are needed to confirm our conclusion.

FOOTNOTES

Author contributions: Wang J and Yu PM designed the study; Wang J and Wang YQ searched the literature and extracted the data; Shi J contributed to data verification; Wang J, Yu PM, and Wang YQ analyzed the data; Wang J, Wang YQ, Shi J, Yu PM, and Guo YQ interpreted the data; Wang J drafted the manuscript; Wang YQ, Shi J, Yu PM, and Guo YQ critically reviewed the manuscript; Guo YQ had full access to all the data and carries responsibility for the decision to submit it for publication; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest to report.

PRISMA 2009 Checklist statement: We performed this systematic review and meta-analysis according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. Meanwhile, it has been registered with PROSPERO (ID: CRD42022333441).

Country/Territory of origin: China

ORCID number: Peng-Ming Yu 0000-0001-9908-2349; Ying-Qiang Guo 0000-0003-4894-2614.

S-Editor: Xing YX
L-Editor: Wang TQ
P-Editor: Xing YX

REFERENCES

1 **Benjamin EJ**, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation* 2018; **137**: e67-e492 [PMID: 29386200 DOI: 10.1161/CIR.0000000000000558]

2 **Dunbar SB**, Khavjou OA, Bakas T, Hunt G, Kirch RA, Leib AR, Morrison RS, Poehler DC, Roger VL, Whitsel LP; American Heart Association. Projected Costs of Informal Caregiving for Cardiovascular Disease: 2015 to 2035: A Policy Statement From the American Heart Association. *Circulation* 2018; **137**: e558-e577 [PMID: 29632217 DOI: 10.1161/CIR.0000000000000570]

3 **Bloom DE**, Cafiero ET, Mcgovern ME. The Economic Impact of Non-communicable Disease in China and India: Estimates, Projections, and Comparisons. *IZA Discussion Papers* 2013 [DOI: 10.3386/w19335]

4 **Apostolakis E**, Filos KS, Koletsis E, Dougenis D. Lung dysfunction following cardiopulmonary bypass. *J Card Surg* 2010; **25**: 47-55 [PMID: 19549041 DOI: 10.1111/j.1540-8191.2009.00823.x]

5 **Jensen L**, Yang L. Risk factors for postoperative pulmonary complications in coronary artery bypass graft surgery patients. *Eur J Cardiovasc Nurs* 2007; **6**: 241-246 [PMID: 17347049 DOI: 10.1016/J.EJCNURSE.2006.11.001]

6 **Valkenet K**, Trappenburg JCA, Hulzebos EH, van Meeteren NLU, Backx FJG. Effects of a pre-operative home-based inspiratory muscle training programme on perceived health-related quality of life in patients undergoing coronary artery bypass graft surgery. *Physiotherapy* 2017; **103**: 276-282 [PMID: 27569662 DOI: 10.1016/j.physio.2016.02.007]

7 **Vonlanthen R**, Slankamenac K, Breitenstein S, Puhan MA, Muller MK, Hahnloser D, Hauri D, Graf R, Clavien PA. The impact of complications on costs of major surgical procedures: a cost analysis of 1200 patients. *Ann Surg* 2011; **254**: 907-913 [PMID: 21562405 DOI: 10.1097/SLA.0b013e31821d4a43]

8 **Thompson DA**, Makary MA, Dorman T, Pronovost PJ. Clinical and economic outcomes of hospital acquired pneumonia in intra-abdominal surgery patients. *Ann Surg* 2006; **243**: 547-552 [PMID: 16552208 DOI: 10.1097/01.sla.0000207097.38963.3b]

9 **Hemmila MR**, Jakubus JL, Maggio PM, Wahl WL, Dimick JB, Campbell DA Jr, Taheri PA. Real money: complications and hospital costs in trauma patients. *Surgery* 2008; **144**: 307-316 [PMID: 18656640 DOI: 10.1016/j.surg.2008.05.003]

10 **Dimick JB**, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell DA Jr. Hospital costs associated with surgical complications: a report from the private-sector National Surgical Quality Improvement Program. *J Am Coll Surg* 2004; **199**: 531-537 [PMID: 15454134 DOI: 10.1016/j.jamcollsurg.2004.05.276]

11 **Khan NA**, Quan H, Bugar JM, Lemaire JB, Brant R, Ghali WA. Association of postoperative complications with hospital costs and length of stay in a tertiary care center. *J Gen Intern Med* 2006; **21**: 177-180 [PMID: 16606377 DOI: 10.1111/j.1525-1497.2006.00319.x]

12 **Hulzebos EH**, Helders PJ, Favié NJ, De Bie RA, Brutel de la Riviere A, Van Meeteren NL. Preoperative intensive

inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. *JAMA* 2006; **296**: 1851-1857 [PMID: 17047215 DOI: 10.1001/jama.296.15.1851]

13 **Katsura M**, Kuriyama A, Takeshima T, Fukuhara S, Furukawa TA. Preoperative inspiratory muscle training for postoperative pulmonary complications in adults undergoing cardiac and major abdominal surgery. *Cochrane Database Syst Rev* 2015; **2015**: CD010356 [PMID: 26436600 DOI: 10.1002/14651858.CD010356.pub2]

14 **Fagevik Olsén M**, Hahn I, Nordgren S, Lönroth H, Lundholm K. Randomized controlled trial of prophylactic chest physiotherapy in major abdominal surgery. *Br J Surg* 1997; **84**: 1535-1538 [PMID: 9393272 DOI: 10.1111/j.1365-2168.1997.02828.x]

15 **Boden I**, Skinner EH, Browning L, Reeve J, Anderson L, Hill C, Robertson IK, Story D, Denehy L. Preoperative physiotherapy for the prevention of respiratory complications after upper abdominal surgery: pragmatic, double blinded, multicentre randomised controlled trial. *BMJ* 2018; **360**: j5916 [PMID: 29367198 DOI: 10.1136/bmj.j5916]

16 **Higgins JPT TJ**, Chandler J, Cumpston M. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022) [DOI: 10.1002/14651858.ed000142]

17 **Savci S**, Degirmenci B, Saglam M, Arikan H, Inal-Ince D, Turan HN, Demircin M. Short-term effects of inspiratory muscle training in coronary artery bypass graft surgery: a randomized controlled trial. *Scand Cardiovasc J* 2011; **45**: 286-293 [PMID: 21793631 DOI: 10.3109/14017431.2011.595820]

18 **Sobrinho MT**, Guirado GN, Silva MA. Preoperative therapy restores ventilatory parameters and reduces length of stay in patients undergoing myocardial revascularization. *Rev Bras Cir Cardiovasc* 2014; **29**: 221-228 [PMID: 25140472 DOI: 10.5935/1678-9741.20140021]

19 **Chen X**, Hou L, Zhang Y, Liu X, Shao B, Yuan B, Li J, Li M, Cheng H, Teng L, Guo M, Wang Z, Chen T, Liu J, Liu Y, Liu Z, Guo Q. The effects of five days of intensive preoperative inspiratory muscle training on postoperative complications and outcome in patients having cardiac surgery: a randomized controlled trial. *Clin Rehabil* 2019; **33**: 913-922 [PMID: 30722696 DOI: 10.1177/0269215519828212]

20 **Weber M**, Klein U, Weigert A, Schiller W, Bayley-Ezziddin V, Wirtz DC, Welz A, Werner N, Grube E, Nickenig G, Sinning JM, Ghanem A. Use of Pre- and Intensified Postprocedural Physiotherapy in Patients with Symptomatic Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement Study (the 4P-TAVR Study). *J Interv Cardiol* 2021; **2021**: 8894223 [PMID: 33531881 DOI: 10.1155/2021/8894223]

21 **Snowdon D**, Haines TP, Skinner EH. Preoperative intervention reduces postoperative pulmonary complications but not length of stay in cardiac surgical patients: a systematic review. *J Physiother* 2014; **60**: 66-77 [PMID: 24952833 DOI: 10.1016/j.jphys.2014.04.002]

22 **Cook A**, Smith L, Anderson C, Ewing N, Gammack A, Pecover M, Sime N, Galley HF. The effect of Preoperative threshold inspiratory muscle training in adults undergoing cardiac surgery on postoperative hospital stay: a systematic review. *Physiother Theory Pract* 2022; 1-14 [PMID: 35196184 DOI: 10.1080/09593985.2022.2025548]

23 **Boden I**, Robertson IK, Neil A, Reeve J, Palmer AJ, Skinner EH, Browning L, Anderson L, Hill C, Story D, Denehy L. Preoperative physiotherapy is cost-effective for preventing pulmonary complications after major abdominal surgery: a health economic analysis of a multicentre randomised trial. *J Physiother* 2020; **66**: 180-187 [PMID: 32680742 DOI: 10.1016/j.jphys.2020.06.005]

24 **Takura T**, Ebata-Kogure N, Goto Y, Kohzuki M, Nagayama M, Oikawa K, Koyama T, Itoh H. Cost-Effectiveness of Cardiac Rehabilitation in Patients with Coronary Artery Disease: A Meta-Analysis. *Cardiol Res Pract* 2019; **2019**: 1840894 [PMID: 31275640 DOI: 10.1155/2019/1840894]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 2992-3001

DOI: 10.12998/wjcc.v11.i13.2992

ISSN 2307-8960 (online)

META-ANALYSIS

Efficacy and safety of intravenous tranexamic acid in total shoulder arthroplasty: A meta-analysis

Hua-Mei Deng

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Arslan M, Turkey; Mahmoud MZ, Saudi Arabia

Received: January 9, 2023
Peer-review started: January 9, 2023
First decision: February 20, 2023
Revised: March 8, 2023
Accepted: March 27, 2023
Article in press: March 27, 2023
Published online: May 6, 2023

Hua-Mei Deng, The Second Affiliated Hospital, Guangzhou University of Chinese Medicine, Guangzhou 510120, Guangdong Province, China

Corresponding author: Hua-Mei Deng, MM, Professor, The Second Affiliated Hospital, Guangzhou University of Chinese Medicine, No. 111 Dade Road, Yuexiu District, Guangzhou 510120, Guangdong Province, China. szydenghm@126.com

Abstract

BACKGROUND

Total shoulder arthroplasty (TSA) results in a large amount of perioperative blood loss due to severe trauma.

AIM

To investigate the safety and efficacy of intravenous tranexamic acid (TXA) in TSA.

METHODS

We searched the PubMed, Cochrane Library, Embase and Web of Science databases for randomized controlled trials (RCTs) on the use of TXA in TSA. And all the results were checked and assessed by Reference Citation Analysis (https://www.referencecitationanalysis.com/). A meta-analysis was performed with Review Manager 5.3 to calculate the odds ratio (OR) or weighted mean difference (WMD) of related outcome indicators.

RESULTS

A total of 5 RCTs with level 1 evidence were included. There were 369 cases, with 186 in the TXA group and 183 in the placebo group. The meta-analysis showed that TXA can significantly reduce total blood loss during the perioperative period [WMD = -249.56, 95% confidence interval (CI): -347.6 to -151.52, $P < 0.0001$], and the incidence of adverse reactions was low (OR = 0.36, 95%CI: 0.16-0.83, $P = 0.02$). Compared with the placebo group, the TXA group had significantly less total haemoglobin loss (WMD = -34.39, 95%CI: -50.56 to -18.22), less haemoglobin fluctuation before and after the operation (WMD = -0.6, 95%CI: -0.93 to -0.27) and less 24-h drain output (WMD = -136.87, 95%CI: -165.87 to -106.49). There were no significant differences in the operation time ($P = 0.11$) or hospital length of stay ($P = 0.30$) between the two groups.

CONCLUSION

The application of intravenous TXA in the perioperative period of TSA can

significantly reduce the total volume of perioperative blood loss and reduce the incidence of adverse reactions, so TXA is worthy of widespread clinical use.

Key Words: Intravenous; Tranexamic acid; Total shoulder arthroplasty; Placebo; Meta-analysis

Core Tip: The development and application of total shoulder arthroplasty (TSA) have been slower than those of total knee and total hip arthroplasty, and there is still a lack of advanced evidence-based evidence about the application of tranexamic acid (TXA) in the perioperative period of TSA. Therefore, a meta-analysis was conducted to determine the efficacy and safety of intravenous TXA in the perioperative period of TSA.

Citation: Deng HM. Efficacy and safety of intravenous tranexamic acid in total shoulder arthroplasty: A meta-analysis. *World J Clin Cases* 2023; 11(13): 2992-3001
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/2992.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.2992

INTRODUCTION

Total shoulder arthroplasty (TSA) is commonly used in the treatment of end-stage rotator cuff arthropathy, irreparable rotator cuff tears, primary glenohumeral arthritis and traumatic shoulder arthritis[1-4]. When conservative treatment methods, such as analgesic drugs, local hormone injections, and physical therapy, cannot relieve pain or improve shoulder joint range of motion, TSA often significantly relieves pain, improves the range of motion and improves the quality of life of patients[5-7]. Due to developments and improvements in shoulder replacement medical technology and replacement materials, the number of total shoulder replacements is increasing[8]. Studies have shown that the volume of intraoperative blood loss during total shoulder replacement can reach between 354 mL and 361 mL[9,10]. For patients undergoing primary TSA, the probability of blood transfusion is between 2.4% and 9.5%[11,12]. The presence of anaemia and the need for blood transfusion after surgery may increase the incidence of complications. Common complications include angina pectoris, myocardial infarction, thrombosis, and even death[13,14].

Tranexamic acid (TXA) is a fibrinolytic inhibitor that can reversibly block the binding site of lysine, which is compatible with fibrinogen; inhibit fibrinolytic reactions; prevent blood clots from being dissolved by fibrinolytic enzymes; and reduce the extent of perioperative bleeding[15,16]. TXA has been shown to significantly reduce the amount of blood loss in total knee and total hip arthroplasty[17-19]. Therefore, TXA has been widely used in total joint replacement for perioperative blood management. However, because the development and application of TSA have been slower than those of total knee and total hip arthroplasty, there is still a lack of advanced evidence-based evidence about the application of TXA in the perioperative period of TSA. Therefore, through the inclusion of high-quality randomized controlled trials (RCTs), a meta-analysis was conducted to determine the efficacy and safety of intravenous TXA in the perioperative period of TSA, thereby providing a high-quality evidence-based basis for clinical application.

MATERIALS AND METHODS

This meta-analysis was conducted in strict accordance with the preferred reporting items for systematic reviews and meta-analyses statement[20]. All the data used in this study are provided in the text and Supplementary materials.

Data sources and search strategy

PubMed, Embase, Cochrane Library and Web of Science were searched. The retrieval time was from the establishment of each database to November 15, 2022. The combination of MeSH terms and entry words to search the above four databases was used. The key words included "tranexamic acid", "tranexamic acid", "antimicrobial agents", "cyklokapron", "transamin", "total shoulder arthroplasty", "total shoulder replacement" and "shoulder replacement arthroplasty". Additionally, Reference Citation Analysis (https://www.referencecitationanalysis.com/) was used to check and supplement the search results. Supplementary material includes the search strategy used for each database.

Study selection

The inclusion criteria were as follows: (1) All patients were treated with TSA or reverse TSA; (2) the experimental group was treated with intravenous TXA, and the control group was treated with a placebo; (3) the type of study was an RCT; and (4) one of the following outcome measures were reported: Total blood loss, adverse events, operative time, total haemoglobin loss, hospital length of stay, change in haemoglobin level and 24-h drain output. There were no language restrictions.

The exclusion criteria were as follows: (1) Studies with incomplete original data; and (2) duplicate studies including the same population.

Data extraction and quality assessment

The extracted data included basic information (first author, year of publication, country, research type, sample size, age, *etc.*), the primary outcome indicators, the secondary outcome indicators, and information related to the quality of the study.

The primary outcomes were as follows: Total blood loss and adverse events. The secondary outcomes were as follows: Operative time, total haemoglobin loss, hospital length of stay, change in haemoglobin level, and 24-h drain output.

Version 2.0 (Rob 2.0) of the risk of bias assessment tool recommended by Cochrane was used to evaluate the quality of the studies[21]. The evaluation tool evaluates the risk of bias in five areas. If the evaluation results of all five areas are low risk, then the overall risk of bias is low. If the assessment result of any one of the areas is high risk or the assessment results of multiple areas are possible risk, then the overall risk level is high.

Statistical analysis

Review Manager 5.3 software (Cochrane Collaboration, United Kingdom) was used for data analysis. The continuous variables are represented by weighted mean differences (WMDs) and 95% confidence intervals (CIs), while the categorical variables are represented by odds ratios (ORs) and 95%CIs. $P < 0.05$ was considered statistically significant. I^2 was used to evaluate the heterogeneity of the consolidated data. $I^2 < 50\%$ indicated low heterogeneity, and a fixed-effects model was used for these data; $I^2 > 50\%$ indicated high heterogeneity, and a random-effects model was used for these data. The latter group of results should be interpreted carefully. Stata 14.0 software was used to perform Egger's and Begg's tests to quantitatively evaluate publication bias for the outcome indicators with data retrieved from 3 or more articles.

RESULTS

Search results and study characteristics

A total of 158 articles were retrieved, including 41 from PubMed, 26 from Cochrane Library, 40 from Embase and 51 from Web of Science. After duplicate studies were excluded and the full texts were read, five articles were included. The process of literature retrieval and the reasons for exclusion are shown in Figure 1. This meta-analysis included five RCTs[22-26] from four countries, two[23,26] of which were from the United States. The clinical evidence level of 5 studies[22-26] was 1. A total of 369 cases were included, including 186 cases in the experimental group and 183 cases in the placebo group. Among the five RCTs, only two studies reported that in the trial group and the placebo group, blood transfusion was needed due to excessive blood loss[25,26]. The basic characteristics of the studies included in this study are shown in Table 1.

Study quality assessment

In this study, the Cochrane randomized controlled trial risk of bias assessment tool 2.0 was used to evaluate the quality of the 5 included articles. All five articles[22-26] were considered to have a low risk of bias. The above results of the literature quality evaluation showed that the methodological quality of the five studies[22-26] included in this study was very high. All the included studies used the double-blinding method for clinical research. The risk of bias results for each study are shown in Figure 2.

Primary outcomes

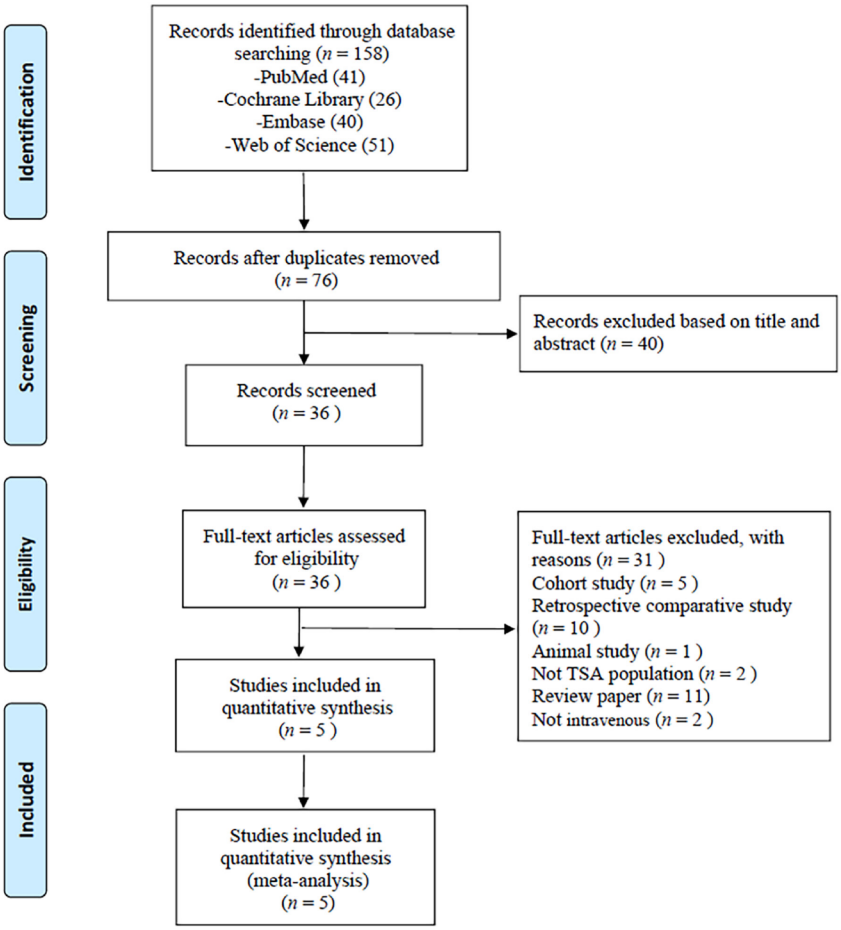
Total blood loss (mL): Four RCTs[22-24,26] reported total blood loss in TSA. There were 163 cases in the experimental group and 161 cases in the placebo group. The heterogeneity among the studies was large ($P = 0.31$, $I^2 = 16\%$), and a fixed-effects model was used for meta-analysis. The results showed that there was a significant difference in the total amount of bleeding between the two groups [weighted mean difference (WMD) = -249.56, 95%CI: -347.6 to -151.52, $P < 0.0001$], which indicated that TXA can significantly reduce bleeding in TSA (Figure 3A).

Adverse events: All the included studies[22-26] reported the occurrence of adverse reactions. There was no heterogeneity among the studies ($P = 0.57$, $I^2 = 0\%$), so a fixed-effects model was used. The meta-

Table 1 Basic information of the studies included in the meta-analysis

Ref.	Country	Study design (LOE)	Sample		Average age, yr		Intervention		Surgery	Transfusion	
			TXA	Placebo	TXA	Placebo	TXA	Placebo		TXA	Placeo
Cunningham *et al* [22], 2021	Switzerland	RCT (Level I)	31	29	72 ± 8	73 ± 9	TXA, 2 g, IV	An equivalent volume of NS, IV	TSA or RTSA	0	0
Cvetanovich *et al* [23], 2018	United States	RCT (Level I)	52	56	67.7 ± 10.9	65.2 ± 9.2	TXA, 1 g, IV	An equivalent volume of NS, IV	TSA	0	0
Pauzenberger *et al* [24], 2017	Austria	RCT (Level I)	27	27	70.3 ± 9.3	71.3 ± 7.9	100 mL NS infused with 1 g of TXA, IV	100 ml NS, IV	TSA or RTSA	0	0
Garcia *et al*[25], 2022	Portugal	RCT (Level I)	23	22	76.7 ± 7.1	75.7 ± 5.7	TXA, 1 g, IV	Without the TXA infusion	TSA or RTSA	3	2
Vara *et al*[26], 2017	United States	RCT (Level I)	53	49	67 ± 9	66 ± 9	TXA, 10 mg/kg, IV	An equivalent volume of NS, IV	RTSA	3	7

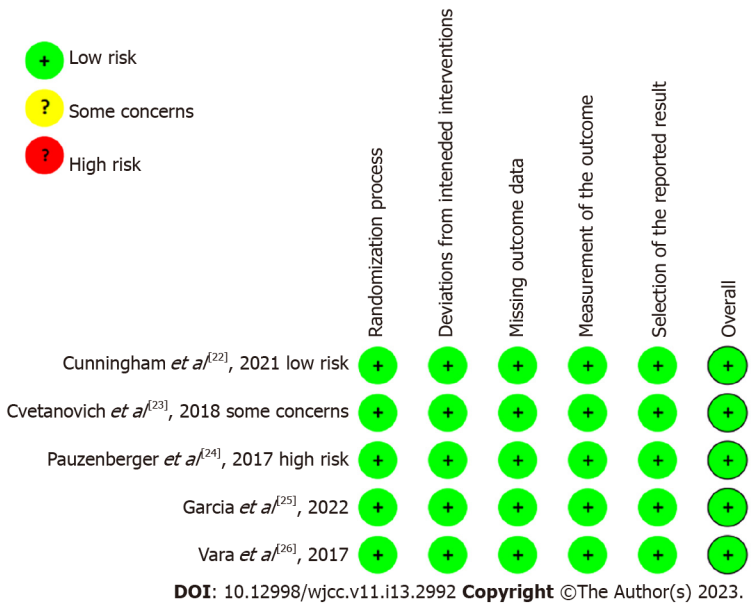
TXA: Tranexamic acid; NS: Normal saline; IV: Intravenous; LOE: Level of evidence; RCT: Randomized controlled trial; TSA: Total shoulder arthroplasty; RTSA: Reverse total shoulder arthroplasty.



DOI: 10.12998/wjcc.v11.i13.2992

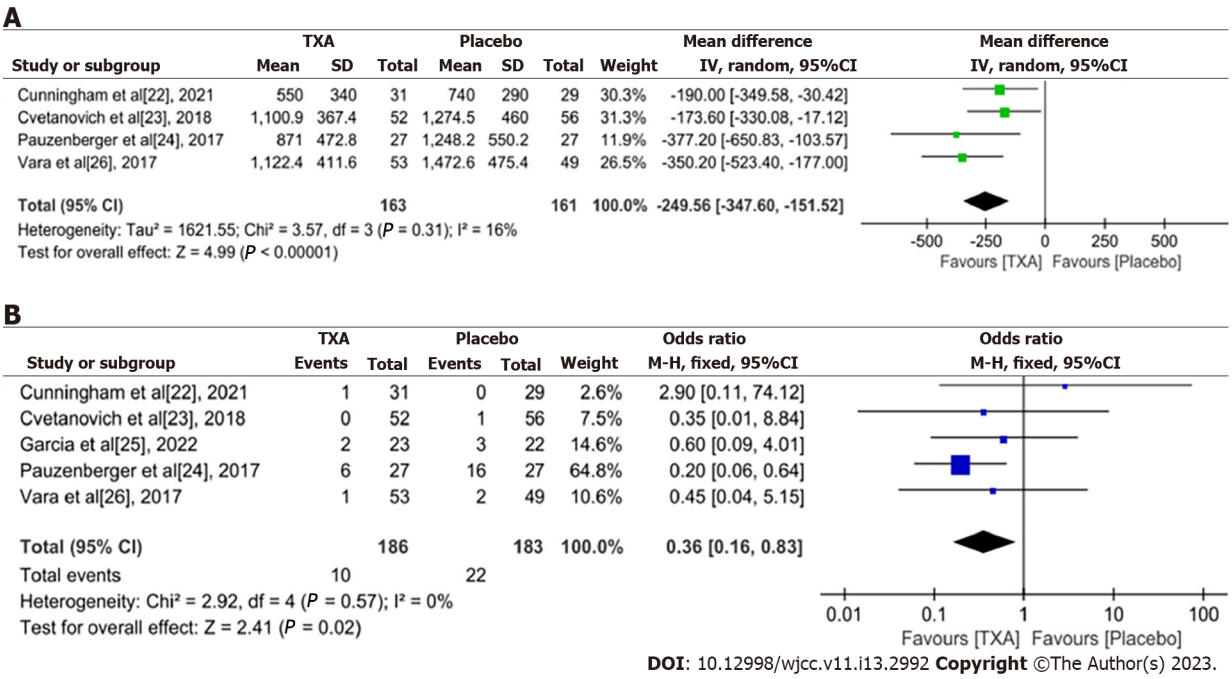
Figure 1 Preferred reporting items for systematic reviews and meta-analyses statement flow diagram. TSA: Total shoulder arthroplasty; PRISMA: Preferred reporting items for systematic reviews and meta-analyses.

analysis showed that compared with the placebo group, the TXA group had significantly fewer adverse events and higher safety (OR = 0.36, 95%CI: 0.16-0.83, P = 0.02) (Figure 3B).



DOI: 10.12998/wjcc.v11.i13.2992 **Copyright** ©The Author(s) 2023.

Figure 2 Results of the risk-of-bias assessments for the included studies.



DOI: 10.12998/wjcc.v11.i13.2992 **Copyright** ©The Author(s) 2023.

Figure 3 Forest plot. A: Total blood loss; B: Adverse events. TXA: tranexamic acid; IV: Intravenous.

Secondary outcomes

Operative time (minutes): Three studies[22,23,26] compared operation time. There was no heterogeneity among the studies (P = 0.64, I^2 = 0%), so a fixed-effects model was used for statistical analysis. The results showed that there was no significant difference in operation time between the experimental group and the placebo group (WMD = -4.01, 95%CI: -8.88 to 0.86, P = 0.11) (Figure 4A).

Total haemoglobin loss (g): Two studies[23,26] compared total haemoglobin loss between the experimental and placebo groups. The heterogeneity between the two studies was small (P = 0.24, I^2 = 29%), so a fixed-effects model was used for analysis. The meta-analysis showed that the experimental group had less haemoglobin loss than did the placebo group (WMD = -34.39, 95%CI: -50.56 to -18.22, P < 0.0001) (Figure 4B).

Change in haemoglobin level (g/dL): Two studies[23,26] compared haemoglobin levels before and after TSA. There was no heterogeneity among the three studies (P = 1.00, I^2 = 0%), so a fixed-effects model

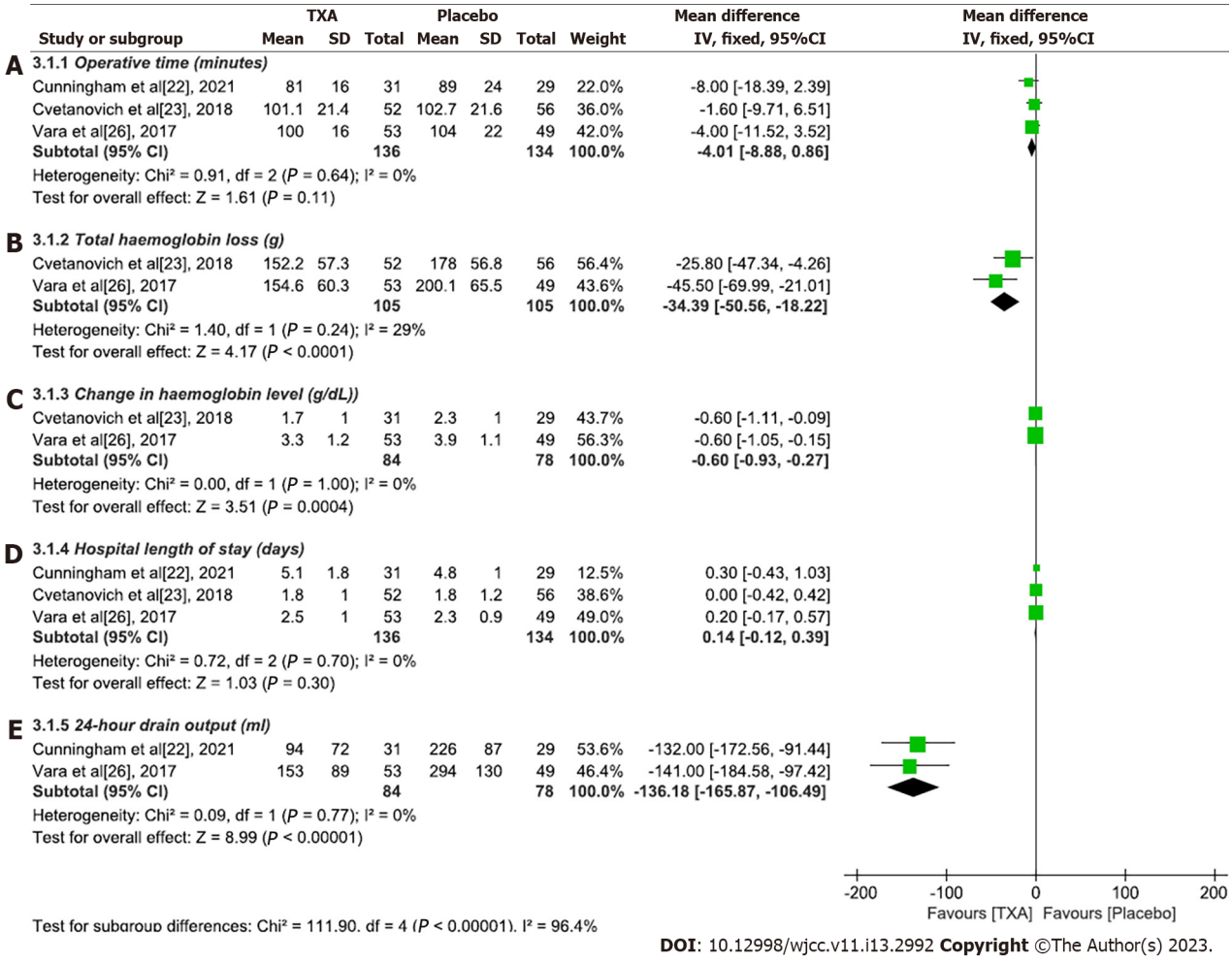


Figure 4 Forest plot. A: Operative time; B: Total haemoglobin loss; C: Change in haemoglobin Level; D: Hospital length of stay; E: 24-h drain output. TXA: Tranexamic acid; IV: Intravenous.

was used for analysis. The results of the meta-analysis showed that the haemoglobin level of the experimental group fluctuated less before and after the operation (WMD = -0.6, 95%CI: -0.93 to -0.27, P < 0.0001), which indicated that TXA could significantly reduce bleeding in shoulder replacement patients (Figure 4C).

Hospital length of stay (days): A fixed-effects model was used to analyse the length of stay data of three studies[22,23,26] (P = 0.70, I^2 = 0%). The results showed that there was no statistically significant difference in the length of hospital stay between the experimental group and the placebo group (WMD = 0.14, 95%CI: -0.12 to 0.39, P = 0.30) (Figure 4D).

Twenty-four-hour drain output (mL): A total of two studies[22,26] compared the 24-h postoperative drainage volume between the experimental group and the placebo group. The homogeneity of the two studies was good (P = 0.77, I^2 = 0%), so a fixed-effects model was used for analysis. The results showed that the 24-h drainage volume of the experimental group was significantly less than that of the placebo group, indicating that TXA can reduce the drainage volume after TSA (WMD = -136.87, 95%CI: -165.87 to -106.49, P < 0.0001) (Figure 4E).

Publication bias

Begg's and Egger's tests were performed to assess the publication bias of the studies. No evidence of publication bias was found for the WMD of total blood loss (Begg's test, P = 0.734, Egger's test, P = 0.634) or the OR of adverse events (Begg's test, P = 0.734, Egger's test, P = 0.379). There was no publication bias in the WMD of the hospital length of stay or operational time. The statistical results of publication bias of each index are shown in Supplementary Table 1.

DISCUSSION

Whether TXA, an antifibrinolytic agent, can effectively reduce perioperative blood loss without increasing the risk of adverse reactions in TSA still lacks high-level evidence-based support. The efficacy of TXA in various surgical procedures has been confirmed, and it has higher efficacy and leads to fewer drug-related complications than other antifibrinolytic drugs[27,28]. The purpose of this study was to investigate the efficacy of intravenous TXA in reducing bleeding and its safety in the perioperative period of TSA through a meta-analysis of high-quality RCTs with level 1 evidence. The results of this meta-analysis showed that the application of intravenous TXA in TSA can not only significantly reduce the total volume of perioperative blood loss but is also safe. The secondary outcome measures also showed that TXA can significantly reduce total haemoglobin loss, reduce fluctuations in haemoglobin levels before and after the operation, and reduce postoperative drainage. In addition, this study showed that compared with a placebo, intravenous TXA did not significantly differ in terms of operation time or length of hospital stay. This study showed that TXA can significantly reduce the total volume of perioperative blood loss in TSA. Studies[29,30] have shown that TXA is a lysine derivative that cannot convert fibrinolysin into activated fibrinolysin by occupying the action site of fibrinolysin and cannot dissolve blood clots to promote haemostasis. With the widespread application of TXA in joint surgery[31,32], especially in total knee and total hip arthroplasty, the good haemostatic effect and safety of TXA have been recognized by the majority of scholars. Abildgaard *et al*[33] reviewed 168 cases and found that TXA can significantly reduce perioperative blood loss, haemoglobin fluctuations and postoperative drainage volume. Clay *et al*[34] analysed the blood loss and haematocrit of 435 patients who underwent shoulder replacement, and the results confirmed the above conclusion.

In addition, based on the secondary outcome indicators that were compared between the intravenous TXA and placebo groups, the perioperative application of TXA can significantly reduce the total haemoglobin loss, reduce the absolute value of haemoglobin fluctuations before and after surgery, and reduce the amount of postoperative drainage. These findings also confirm that intravenous TXA can reduce perioperative bleeding in TSA, which is very important. Operation time and blood loss are two factors that affect each other. An increase in the operation time increases the wound exposure time and blood loss. An increase in blood loss increases the operation time. The meta-analysis showed that there was no significant difference in the operation time between the intravenous TXA group and the placebo group. When the influence of operation time is excluded, the haemostatic effect of TXA can be more accurately assessed. The results of this meta-analysis also suggest that intravenous TXA is not an influencing factor of the length of hospital stay.

In terms of safety, TXA led to fewer adverse reactions than placebo (OR = 0.36, 95%CI: 0.16-0.83). By reviewing the 5 included studies[22-26], this study found that the main adverse reaction of TXA was haematoma, and no severe adverse reactions were reported. In contrast, adverse reactions such as skin allergies, haematoma and deep vein thrombosis occurred in the placebo group. Carbon *et al*[35] retrospectively analysed the data of 71174 patients retrieved from a national claims database and found that the use of TXA was not associated with an increased incidence of complications in patients who underwent TSA. Our results are consistent with those of Carbon *et al*[35], which supports the widespread use of TXA in the perioperative period of TSA.

Strengths and limitations

The conclusions of this systematic review and meta-analysis come from only RCTs with level 1 evidence, and the heterogeneity was very low, which indicates that the above conclusions are supported by a very high level of evidence. This meta-analysis showed that TXA is efficacious and safe in TSA to a certain extent, but there are some limitations of the study: (1) Although the quality of the RCTs included in this meta-analysis was high, the total number of included studies and total sample size were relatively small; and (2) data on the total haemoglobin loss and 24-h drainage volume were retrieved from only two studies, which may have affected the reliability of the results. There is no doubt that multicentre, large-sample prospective RCTs are needed in the future to further verify the findings of this study. In TSA, the impact of intravenous TXA on medical costs and patient satisfaction in the postoperative period should also be evaluated, which will be conducive to comprehensive evaluation of the clinical value of intravenous TXA.

CONCLUSION

Our meta-analysis revealed that the application of intravenous TXA can significantly reduce total blood loss and is safe for application in TSA, so TXA is worthy of widespread clinical application. In addition, we also found that the application of TXA did not influence the operation time or length of hospital stay.

ARTICLE HIGHLIGHTS

Research background

Total shoulder arthroplasty (TSA) results in a large amount of perioperative blood loss due to severe trauma.

Research motivation

Therefore, through the inclusion of high-quality randomized controlled trials (RCTs), a meta-analysis was conducted to determine the efficacy and safety of intravenous tranexamic acid (TXA) in the perioperative period of TSA, thereby providing a high-quality evidence-based basis for clinical application.

Research objectives

The purpose of this meta-analysis was to investigate the safety and efficacy of intravenous TXA in TSA.

Research methods

Meta-analysis.

Research results

A total of 5 RCTs with level 1 evidence were included. There were 369 cases, with 186 in the TXA group and 183 in the placebo group. The meta-analysis showed that TXA can significantly reduce total blood loss during the perioperative period [WMD = -249.56, 95% confidence interval (CI): -347.6 to -151.52, $P < 0.0001$], and the incidence of adverse reactions was low (OR = 0.36, 95%CI: 0.16-0.83, $P = 0.02$). Compared with the placebo group, the TXA group had significantly less total haemoglobin loss (WMD = -34.39, 95%CI: -50.56 to -18.22), less haemoglobin fluctuation before and after the operation (WMD = -0.6, 95%CI: -0.93 to -0.27) and less 24-h drain output (WMD = -136.87, 95%CI: -165.87 to -106.49). There were no significant differences in the operation time ($P = 0.11$) or hospital length of stay ($P = 0.30$) between the two groups.

Research conclusions

The application of intravenous TXA in the perioperative period of TSA can significantly reduce the total volume of perioperative blood loss and reduce the incidence of adverse reactions, so TXA is worthy of widespread clinical use.

Research perspectives

Multicentre, large-sample prospective RCTs are needed in the future to further verify the findings of this study. In TSA, the impact of intravenous TXA on medical costs and patient satisfaction in the postoperative period should also be evaluated, which will be conducive to comprehensive evaluation of the clinical value of intravenous TXA.

FOOTNOTES

Author contributions: Deng HM designed and conducted the study; Deng HM read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: China

ORCID number: Hua-Mei Deng 0000-0001-6856-138X.

S-Editor: Li L
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Kazley JM**, Cole KP, Desai KJ, Zonshayn S, Morse AS, Banerjee S. Prostheses for reverse total shoulder arthroplasty. *Expert Rev Med Devices* 2019; **16**: 107-118 [PMID: 30669890 DOI: 10.1080/17434440.2019.1568237]

2 **Kim DM**, Alabdullatif F, Aldeghaither M, Shin MJ, Kim H, Park D, Kholinne E, Jeon IH, Koh KH. Do Modern Designs of Metal-Backed Glenoid Components Show Improved Clinical Results in Total Shoulder Arthroplasty? *Orthop J Sports Med* 2020; **8**: 2325967120950307 [PMID: 33062762 DOI: 10.1177/2325967120950307]

3 **An KY**, Park JY, Yoon TR. Subscapularis-sparing deltopectoral approach in reverse total shoulder arthroplasty. *Int Orthop* 2022; **46**: 2845-2851 [PMID: 36190532 DOI: 10.1007/s00264-022-05591-y]

4 **Hagen MS**, Allahabadi S, Zhang AL, Feeley BT, Grace T, Ma CB. A randomized single-blinded trial of early rehabilitation *vs* immobilization after reverse total shoulder arthroplasty. *J Shoulder Elbow Surg* 2020; **29**: 442-450 [PMID: 31924519 DOI: 10.1016/j.jse.2019.10.005]

5 **Baumgarten KM**. Is stemless total shoulder arthroplasty indicated in elderly patients? *J Shoulder Elbow Surg* 2023; **32**: 260-268 [PMID: 36162630 DOI: 10.1016/j.jse.2022.08.003]

6 **O'Keefe DS**, Hao KA, Teurlings TL, Wright TW, Wright JO, Schoch BS, Farmer KW, Struk AM, King JJ. Survivorship analysis of revision reverse total shoulder arthroplasty. *J Shoulder Elbow Surg* 2022 [PMID: 36584868 DOI: 10.1016/j.jse.2022.11.024]

7 **Schiffman CJ**, Prabhakar P, Hsu JE, Shaffer ML, Miljacic L, Matsen FA 3rd. Assessing the Value to the Patient of New Technologies in Anatomic Total Shoulder Arthroplasty. *J Bone Joint Surg Am* 2021; **103**: 761-770 [PMID: 33587515 DOI: 10.2106/JBJS.20.01853]

8 **Best MJ**, Aziz KT, Wilckens JH, McFarland EG, Srikumaran U. Increasing incidence of primary reverse and anatomic total shoulder arthroplasty in the United States. *J Shoulder Elbow Surg* 2021; **30**: 1159-1166 [PMID: 32858194 DOI: 10.1016/j.jse.2020.08.010]

9 **Saltzman BM**, Chalmers PN, Gupta AK, Romeo AA, Nicholson GP. Complication rates comparing primary with revision reverse total shoulder arthroplasty. *J Shoulder Elbow Surg* 2014; **23**: 1647-1654 [PMID: 24986694 DOI: 10.1016/j.jse.2014.04.015]

10 **Chalmers PN**, Gupta AK, Rahman Z, Bruce B, Romeo AA, Nicholson GP. Predictors of early complications of total shoulder arthroplasty. *J Arthroplasty* 2014; **29**: 856-860 [PMID: 23927910 DOI: 10.1016/j.arth.2013.07.002]

11 **Seok HG**, Park JJ, Park SG. Risk Factors for Periprosthetic Joint Infection after Shoulder Arthroplasty: Systematic Review and Meta-Analysis. *J Clin Med* 2022; **11** [PMID: 35888008 DOI: 10.3390/jcm11144245]

12 **Gupta AK**, Chalmers PN, Rahman Z, Bruce B, Harris JD, McCormick F, Abrams GD, Nicholson GP. Reverse total shoulder arthroplasty in patients of varying body mass index. *J Shoulder Elbow Surg* 2014; **23**: 35-42 [PMID: 24090984 DOI: 10.1016/j.jse.2013.07.043]

13 **Mollon B**, Mahure SA, Ding DY, Zuckerman JD, Kwon YW. The influence of a history of clinical depression on peri-operative outcomes in elective total shoulder arthroplasty: a ten-year national analysis. *Bone Joint J* 2016; **98-B**: 818-824 [PMID: 27235526 DOI: 10.1302/0301-620X.98B6.37208]

14 **Kirksey M**, Chiu YL, Ma Y, Della Valle AG, Poultsides L, Gerner P, Memtsoudis SG. Trends in in-hospital major morbidity and mortality after total joint arthroplasty: United States 1998-2008. *Anesth Analg* 2012; **115**: 321-327 [PMID: 22652311 DOI: 10.1213/ANE.0b013e31825b6824]

15 **Huang GP**, Jia XF, Xiang Z, Ji Y, Wu GY, Tang Y, Li J, Zhang J. Tranexamic Acid Reduces Hidden Blood Loss in Patients Undergoing Total Knee Arthroplasty: A Comparative Study and Meta-Analysis. *Med Sci Monit* 2016; **22**: 797-802 [PMID: 26961597 DOI: 10.12659/MSM.895571]

16 **Kim SH**, Jung WI, Kim YJ, Hwang DH, Choi YE. Effect of Tranexamic Acid on Hematologic Values and Blood Loss in Reverse Total Shoulder Arthroplasty. *Biomed Res Int* 2017; **2017**: 9590803 [PMID: 28819631 DOI: 10.1155/2017/9590803]

17 **Yen SH**, Lin PC, Wu CT, Wang JW. Comparison of Effects of a Thrombin-Based Hemostatic Agent and Topical Tranexamic Acid on Blood Loss in Patients with Preexisting Thromboembolic Risk Undergoing a Minimally Invasive Total Knee Arthroplasty. A Prospective Randomized Controlled Trial. *Biomed Res Int* 2021; **2021**: 2549521 [PMID: 33511201 DOI: 10.1155/2021/2549521]

18 **Sershon RA**, Fillingham YA, Abdel MP, Malkani AL, Schwarzkopf R, Padgett DE, Vail TP, Nam D, Nahhas C, Culvern C, Della Valle CJ; Hip Society Research Group. The Optimal Dosing Regimen for Tranexamic Acid in Revision Total Hip Arthroplasty: A Multicenter Randomized Clinical Trial. *J Bone Joint Surg Am* 2020; **102**: 1883-1890 [PMID: 33148955 DOI: 10.2106/JBJS.20.00010]

19 **Shichman I**, Shaked O, Ashkenazi I, Schwarzkopf R, Warschawski Y, Snir N. Tranexamic acid in non-elective primary total hip arthroplasty. *Injury* 2021; **52**: 1544-1548 [PMID: 33092856 DOI: 10.1016/j.injury.2020.10.056]

20 **Rethlefsen ML**, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB; PRISMA-S Group. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. *Syst Rev* 2021; **10**: 39 [PMID: 33499930 DOI: 10.1186/s13643-020-01542-z]

21 **Sterne JAC**, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898 [PMID: 31462531 DOI: 10.1136/bmj.l4898]

22 **Cunningham G**, Hughes J, Borner B, Mattern O, Taha ME, Smith MM, Young AA, Cass B. A single dose of tranexamic acid reduces blood loss after reverse and anatomic shoulder arthroplasty: a randomized controlled trial. *J Shoulder Elbow Surg* 2021; **30**: 1553-1560 [PMID: 33421559 DOI: 10.1016/j.jse.2020.11.022]

23 **Cvetanovich GL**, Fillingham YA, O'Brien M, Forsythe B, Cole BJ, Verma NN, Romeo AA, Nicholson GP. Tranexamic acid reduces blood loss after primary shoulder arthroplasty: a double-blind, placebo-controlled, prospective, randomized controlled trial. *JSES Open Access* 2018; **2**: 23-27 [PMID: 30675563 DOI: 10.1016/j.jses.2018.01.002]

24 **Pauzenberger L**, Domej MA, Heuberer PR, Hexel M, Grieb A, Laky B, Blasl J, Anderl W. The effect of intravenous tranexamic acid on blood loss and early post-operative pain in total shoulder arthroplasty. *Bone Joint J* 2017; **99-B**: 1073-1079 [PMID: 28768785 DOI: 10.1302/0301-620X.99B8.BJJ-2016-1205.R1]

25 **Garcia T**, Fragão-Marques M, Pimentão P, Pinto M, Pedro I, Martins C. Tranexamic acid in total shoulder arthroplasty under regional anesthesia: a randomized, single blinded, controlled trial. *Braz J Anesthesiol* 2022; **72**: 220-227 [PMID: 35144837 DOI: 10.1016/j.bjane.2021.02.011]

26 **Vara AD**, Koueiter DM, Pinkas DE, Gowda A, Wiater BP, Wiater JM. Intravenous tranexamic acid reduces total blood loss in reverse total shoulder arthroplasty: a prospective, double-blinded, randomized, controlled trial. *J Shoulder Elbow Surg* 2017; **26**: 1383-1389 [PMID: 28162887 DOI: 10.1016/j.jse.2017.01.005]

27 **Sun L**, Guo R, Feng Y. Efficacy and Safety of Tranexamic Acid in Bimaxillary Orthognathic Surgery. *Plast Surg (Oakv)* 2020; **28**: 94-104 [PMID: 32596184 DOI: 10.1177/2292550320925897]

28 **Wright GP**, Wolf AM, Waldherr TL, Ritz-Holland D, Laney ED, Chapman HA, Lane BR, Assifi MM, Chung MH. Preoperative tranexamic acid does not reduce transfusion rates in major oncologic surgery: Results of a randomized, double-blind, and placebo-controlled trial. *J Surg Oncol* 2020; **122**: 1037-1042 [PMID: 32737893 DOI: 10.1002/jso.26142]

29 **Colomina MJ**, Koo M, Basora M, Pizones J, Mora L, Bagó J. Intraoperative tranexamic acid use in major spine surgery in adults: a multicentre, randomized, placebo-controlled trial†. *Br J Anaesth* 2017; **118**: 380-390 [PMID: 28203735 DOI: 10.1093/bja/aew434]

30 **Winter SF**, Santaguida C, Wong J, Fehlings MG. Systemic and Topical Use of Tranexamic Acid in Spinal Surgery: A Systematic Review. *Global Spine J* 2016; **6**: 284-295 [PMID: 27099820 DOI: 10.1055/s-0035-1563609]

31 **Xie J**, Hu Q, Huang Q, Ma J, Lei Y, Pei F. Comparison of intravenous *vs* topical tranexamic acid in primary total hip and knee arthroplasty: An updated meta-analysis. *Thromb Res* 2017; **153**: 28-36 [PMID: 28319822 DOI: 10.1016/j.thromres.2017.03.009]

32 **Wei W**, Dang S, Duan D, Wei L. Comparison of intravenous and topical tranexamic acid in total knee arthroplasty. *BMC Musculoskelet Disord* 2018; **19**: 191 [PMID: 29898707 DOI: 10.1186/s12891-018-2122-7]

33 **Abildgaard JT**, McLemore R, Hattrup SJ. Tranexamic acid decreases blood loss in total shoulder arthroplasty and reverse total shoulder arthroplasty. *J Shoulder Elbow Surg* 2016; **25**: 1643-1648 [PMID: 27106116 DOI: 10.1016/j.jse.2016.02.002]

34 **Clay TB**, Lawal AS, Wright TW, Patrick M, Struk AM, Farmer KW, King JJ. Tranexamic acid use is associated with lower transfusion rates in shoulder arthroplasty patients with preoperative anaemia. *Shoulder Elbow* 2020; **12**: 61-69 [PMID: 33343717 DOI: 10.1177/1758573219841058]

35 **Carbone A**, Poeran J, Zubizarreta N, Chan J, Mazumdar M, Parsons BO, Galatz LM, Cagle PJ. Administration of tranexamic acid during total shoulder arthroplasty is not associated with increased risk of complications in patients with a history of thrombotic events. *J Shoulder Elbow Surg* 2021; **30**: 104-112 [PMID: 32807373 DOI: 10.1016/j.jse.2020.04.050]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3002-3009

DOI: 10.12998/wjcc.v11.i13.3002

ISSN 2307-8960 (online)

CASE REPORT

Awake laparoscopic cholecystectomy: A case report and review of literature

Chiara Mazzone, Maria Sofia, Iacopo Sarvà, Giorgia Litrico, Andrea Maria Luca Di Stefano, Gaetano La Greca, Saverio Latteri

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gálvez Salazar P, Ecuador; Hori T, Japan

Received: September 14, 2022
Peer-review started: September 14, 2022
First decision: October 12, 2022
Revised: October 21, 2022
Accepted: November 10, 2022
Article in press: November 10, 2022
Published online: May 6, 2023

Chiara Mazzone, Maria Sofia, Iacopo Sarvà, Giorgia Litrico, Andrea Maria Luca Di Stefano, Gaetano La Greca, Saverio Latteri, Dipartimento di Scienze Mediche, Chirurgiche e Tecnologie Avanzate "G.F. Ingrassia", Università degli Studi di Catania, Catania 95123, Italy

Corresponding author: Chiara Mazzone, MD, Dipartimento di Scienze Mediche, Chirurgiche e Tecnologie Avanzate "G.F. Ingrassia", Università degli Studi di Catania, Via Santa Sofia 87, Catania 95123, Italy. chiaramazzone1995@gmail.com

Abstract

BACKGROUND

Laparoscopic cholecystectomy (LC) is one of the most widely practiced surgical procedures in abdominal surgery. Patients undergo LC during general anaesthesia; however, in recent years, several studies have suggested the ability to perform LC in patients who are awake. We report a case of awake LC and a literature review.

CASE SUMMARY

A 69-year-old patient with severe pulmonary disease affected by cholelithiasis was scheduled for LC under regional anaesthesia. We first performed peridural anaesthesia at the T8-T9 level and then spinal anaesthesia at the T12-L1 level. The procedure was managed in total comfort for both the patient and the surgeon. The intra-abdominal pressure was 8 mmHg. The patient remained stable throughout the procedure, and the postoperative course was uneventful.

CONCLUSION

Evidence has warranted the safe use of spinal and epidural anaesthesia, with minimal side effects easily managed with medications. Regional anaesthesia in selected patients may provide some advantages over general anaesthesia, such as no airway manipulation, maintenance of spontaneous breathing, effective postoperative analgesia, less nausea and vomiting, and early recovery. However, this technique for LC is not widely used in Europe; this is the first case reported in Italy in the literature. Regional anaesthesia is feasible and safe in performing some types of laparoscopic procedures. Further studies should be carried out to introduce this type of anaesthesia in routine clinical practice.

Key Words: Laparoscopic cholecystectomy; Awake surgery; Awake laparoscopy; Gallstone disease; Regional anaesthesia; Spinal anesthesia; Case report

Core Tip: We present the first Italian case of awake laparoscopic cholecystectomy (LC) in a patient with severe pulmonary disease. The use of regional anesthesia during LC is safe, with minimal side effects, and may provide advantages over general anesthesia.

Citation: Mazzone C, Sofia M, Sarvà I, Litrico G, Di Stefano AML, La Greca G, Latteri S. Awake laparoscopic cholecystectomy: A case report and review of literature. *World J Clin Cases* 2023; 11(13): 3002-3009
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3002.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3002

INTRODUCTION

The first laparoscopic cholecystectomy (LC) was performed in 1996 by Mouret[1]; since then, this procedure has been the gold standard for all benign gallbladder diseases[2-4]. Among these diseases, cholelithiasis is the most common pathology worldwide, with approximately 20 million people affected in the United States, reaching 1.8 million outpatient surgical visits *per* year and 750000 surgical operations, mainly performed laparoscopically[5,6]. Data from European studies, which are few in number compared to United States studies, have reported an incidence of gallstones in < 1/100 people *per* year; they also show that cholelithiasis increases with age and is more common in women than men. The rate of cholecystectomy is highly variable among different European countries, ranging from 62 to 213 *per* 100000 people[5,7,8]. The surgical technique of LC is standardized, and when intraperitoneal conditions allow, it can be performed in approximately 50 min[4]. Enhanced recovery after surgery protocols suggest that laparoscopy ensures greater comfort for the patient and both a better and faster recovery[9]. However, during laparoscopy, the induction of pneumoperitoneum, mechanical ventilation and reverse Trendelenburg position could cause haemodynamic and respiratory mechanism alterations [10,11]. Some patients with cardiovascular or respiratory disease tolerate these physiopathological changes less. These cases are a challenge to both the anaesthesiologist and to the surgeon because they are associated with ventilatory impairments, cardiac problems and other difficulties during the surgical procedure, awakening, and postoperative period. New frontiers in surgery and anaesthesia open up the possibility of subjecting this kind of patient to the same surgical procedures under regional anaesthesia [12].

Herein, we report a case of cholelithiasis in a patient affected by severe respiratory impairment who underwent awake LC, which is the first case in Italy reported in the literature.

CASE PRESENTATION

Chief complaints

A 69-year-old man came to our observation with complaints of invalidating abdominal pain.

History of present illness

Abdominal ultrasound showed a 5-mm infundibular stone, and the patient was scheduled for elective LC.

History of past illness

Past medical history revealed poliomyelitis at a young age with subsequent motor impairment in the left leg and arthrosis in the right knee that made him unable to walk and obliged to use a wheelchair. He had undergone a medium pulmonary lobectomy for lung adenocarcinoma seven years prior.

Personal and family history

He also suffered from idiopathic pulmonary fibrosis, causing chronic respiratory failure and a severe restrictive deficit.

Physical examination

The spirometry has shown: Forced vital capacity (FVC) 55%; forced expiratory volume in 1 second (FEV1) 56%; FEV1/FVC ratio 78% with a reduction in diffusing capacity for carbon monoxide (DLCO) (34%). For these reasons, oxygen therapy 24 h a day at a flow of 2 L/min was prescribed.

Laboratory examinations

Laboratory examinations have no shown an increasing of cholestasis markers.

Imaging examinations

Also imaging examinations have not evidence signs of biliary ducts dilatation. Therefore, the possibility of concurrent choledocholithiasis was excluded.

FINAL DIAGNOSIS

The final diagnosis was gallbladder lithiasis in patient with severe respiratory failure.

TREATMENT

Considering the patient's comorbidity, we decided to perform LC under regional anaesthesia. Clear informed consent was obtained. Pre- and intraoperative monitoring included electrocardiogram, peripheral oxygen levels, and invasive arterial blood pressure (BP). Antibiotic prophylaxis with penicillin was administered.

Using a 19-G × 90 cm an epidural catheter was inserted at the T8-T9 level. Spinal-anaesthesia was performed with a 25-G atraumatic sprotte needle at the T12-L1 level, injecting Ropivacaine (14 mg) and Fentanyl (25 mcg) diluted with saline solution for a total volume of 4 mL.

Five minutes later, the patient received dexmedetomidine 0.2-0.3 mcg/kg/h. Two boluses of 10 mL of 0.8% mepivacaine were peridurally administered.

The achieved level of anaesthesia, as tested by the pin-prick test, was T1.

Pneumoperitoneum was performed by insufflating CO_2 until an intra-abdominal pressure of 8 mmHg was achieved.

At the onset of pneumoperitoneum, the patient complained of shoulder pain. Fentanyl (100 mcg) and two boluses of ketamine (5 mg) with propofol (10 mg) were administered intravenously. The shoulder discomfort regressed enough to be well tolerated during the surgical procedure.

OUTCOME AND FOLLOW-UP

Cholecystectomy was performed by a standard technique, and the operating time was 60 min.

During the procedure, the patient breathed spontaneously and without difficulty.

At the end of the cholecystectomy, the patient had no pain, and the motor skills of the lower limbs started to recover. Vital signs were recorded: Respiratory rate was 15 breaths/min, SaO_2 98%, heart rate (HR) 70 beats/min, and BP 130/70 mmHg.

The patient completely recovered the motility and sensitivity of the legs 2.5 h postoperatively.

The antithrombotic prophylaxis included low molecular weight heparin once a day and early mobilization. Postoperative pain was treated with paracetamol (1 g) three times a day.

The postoperative course was uneventful, with feeding resumed on postoperative day 1. The patient was discharged on postoperative day 2.

DISCUSSION

Laparoscopic procedures have conventionally been performed under general anaesthesia. Nevertheless, the use of regional anaesthesia has been recently introduced in laparoscopic surgery[13]. Evidence has demonstrated the safe use of spinal and epidural anaesthesia, with minimal side effects that can be easily managed with available medications, even if the patient is awake[14]. Indeed, regional anaesthesia may provide some advantages over general anaesthesia, such as a lack of airway manipulation, maintenance of spontaneous breathing, effective postoperative analgesia, minimal nausea and vomiting, and early recovery[10].

Several cases of awake LC have been reported in the scientific literature, as shown in Table 1; however, in Italy, this procedure has not yet been successful.

In 1998, in England, a series of 6 cases was published showing that LC can be performed safely under regional anaesthesia[15].

A large study with 3492 enrolled patients was conducted in India in 2009[16], and many Indian authors have enrolled a large population in the following years[13,17-20].

Table 1 Patients submitted to awake laparoscopic cholecystectomy reported in the literature

Country	Ref.	Year of publication	Number of patients	Main indications
Pennsylvania (United States)	Costantino *et al*[30]	1994	1	Pregnancy
Florida (United States)	Edelman[31]	1994	1	Pregnancy
England	Pursnani *et al*[15]	1998	6	ASA grade III/IV, FEV1/FVC 0.52 due to asthma and COPD
Argentina	Gramatica *et al*[21]	2002	29	Pulmonary disease
Egypt	Hamad and El-Khattary [28]	2003	9	Non-selectively
Netherlands	van Zundert *et al*[32]	2007	20	ASA grade I/II
Turkey	Yuksek *et al*[23]	2008	26	ASA grade I/II
Greece	Tzovaras *et al*[33]	2006	50	ASA grade I/II
India	Sinha *et al*[16]	2009	3492	SA as first choice
Pakistan	Turkstani *et al*[26]	2009	25	ASA grade I/II
Korea	Lee *et al*[27]	2010	11	ASA grade I/II
India	Mehta *et al*[17]	2010	30	Randomly, healthy, ASA grade I/II
India	Kar *et al*[18]	2011	291	Non-selectively
Egypt	Bessa *et al*[29]	2012	86	Randomily
India	Tiwari *et al*[19]	2013	110	Randomily, ASA grade I/II/III
India	Kalaivani *et al*[20]	2014	23	Randomily, ASA grade I/II
India	Hajong *et al*[13]	2014	18	ASA grade I/II
Brasil	Imbelloni[22]	2014	369	SA as first option
Turkey	Bilgi *et al*[24]	2015	96	Non-selectively
Turkey	Donmez *et al*[25]	2017	24	Randomily
Total			4717	

ASA: American Society of Anaesthesiologists physical status classification; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; COPD: Chronic obstructive pulmonary disease.

A total of 398 awake LCs have been performed in South America[21,22], 146 in Turkey[23-25], 25 in Pakistan[26], 11 in Korea[27], 95 in Egypt[28,29], and 2 in the United States[30,31].

The scientific literature has shown only 76 cases in the last 20 years in Europe[15,32,33], but none of these were performed in Italy.

There have been two case reports of successful LC under epidural anaesthesia in pregnant patients during the third trimester[30,31]; in these cases, regional anesthesia (RA) could be very useful because it does not cause significant changes in foetal HR, variability in HR or uterine tone[34].

Kim *et al*[35] presented a case report in which a patient requiring cholecystectomy due to bronchiectasis and consequent poor functional capacity underwent epidural anaesthesia and did not report any complications or difficulties in the execution of the intervention or in the postoperative period. In this case, as in our case, the use of regional anaesthesia was a choice due to the patient's severe respiratory disease[35].

Hausman *et al*[36], in a retrospective cohort study, examined patients with severe chronic obstructive pulmonary disease; approximately 2644 patients were subjected to regional anaesthesia and 2644 to general anaesthesia during different surgical procedures. The study found that patients who received general anaesthesia had a higher incidence of postoperative pneumonia (3.3% *vs* 2.3%), prolonged ventilator dependence (2.1% *vs* 0.9%), and unplanned postoperative intubation (2.6% *vs* 1.8%). Composite morbidity was higher in the group undergoing general anaesthesia (15.4% *vs* 12.6%). Postoperative morbidity and complications in patients who were already respiratory defecated were lower in the group undergoing regional anaesthesia[36].

During awake LC, one of the key points is where to perform anaesthesia at the spinal cord level and whether it is better to perform epidural or subarachnoid (spinal) anaesthesia.

A high block, namely, T2-T4 levels, is required to abolish the discomfort of surgical stimulation of upper gastrointestinal structures[22,37].

In a study conducted in 2014, 369 patients were enrolled for LC under spinal anaesthesia, comparing lumbar versus thoracic puncture and evaluating the best anaesthetic dose. Thoracic puncture and low doses of hyperbaric bupivacaine (7.5 mg) resulted in better haemodynamic stability, less hypotension, and a shorter duration of both sensory and motor block than lumbar spinal anaesthesia using the conventional dose (15 mg)[22].

In our case, we achieved a sensory block at the T1 level, performing epidural anaesthesia at the T8-T9 level and spinal anaesthesia at the T12-L1 level; furthermore, the patient did not show any discomfort.

The first to use combined anaesthesia was van Zundert *et al*[38] in 2006 when he published a case report of an awake LC showing that the combined spinal/epidural anaesthesia technique, applied in the lower thoracic region (T10 level), can be used to provide a segmental subarachnoid block[38].

Donmez *et al*[25], in a prospective randomized study, submitted 28 patients to combined spinal/epidural anaesthesia at the L2-L3 levels and then inserted an epidural catheter cephalically[25].

We preferred to perform a spinal puncture at the T12-L1 level to avoid puncturing the dura mater in the thoracic region and then insert an epidural catheter at the T8-T9 level.

During laparoscopy, CO_2 insufflation could cause severe irritation to the parietal peritoneum, producing severe abdominal pain and discomfort[39]; for this reason, some authors have preferred to perform awake LC insufflating nitrous oxide[28], but it is not currently used. We created the pneumoperitoneum by insufflating CO_2 for its high water solubility and its high capacity of exchange in the lungs. Our patient complained of shoulder pain during pneumoperitoneum insufflation, which was easily treated without any consequence.

One of the most important problems of LC under spinal anaesthesia is the inadequate relaxation of abdominal muscles, resulting in difficulties in performing the procedure[8,40].

Tzovaras *et al*[33] demonstrated that surgery can be performed safely without exceeding 8 mmHg of pneumoperitoneum[33].

During cholecystectomy, the pneumoperitoneum pressure is approximately 12-15 mmHg[41]. In our case, spinal anaesthesia did not modify the surgical technique except for the reduction of intraperitoneal pressure to 8 mmHg to avoid vagal reflex and bradycardia. In fact, despite the low pressure and the consequent reduced camera, the cholecystectomy surgical technique used was the French position, which is usual in our clinical practice, and did not require any change in technique. For this reason, according to the surgeon's expertise, there are no local contraindications for cholecystectomy under RA, as shown in Table 2.

The main indication for cholecystectomy under RA is symptomatic gallbladder lithiasis. Even patients affected by acute or chronic cholecystitis can be approached with this technique; however, in these cases, advanced laparoscopic skills are required to guarantee a safe procedure.

In the case of suspected calculus of the main biliary tract or in the case of previous biliary pancreatitis occurrences, magnetic resonance cholangiopancreatography is mandatory; if choledocholithiasis is confirmed, the patient will be submitted to preoperative endoscopic retrograde cholangiopancreatography.

Of course, even patients with benign gallbladder wall disease can be treated by cholecystectomy under RA; however, if malignancy is suspected, laparoscopy is not the standard of care[42].

The only contraindications, for which general anesthesia (GA) rather than RA is necessary, are the anaesthetic ones: Coagulopathic states[43], infection of the injection site and sepsis, patient rejection and hypovolemia uncorrected[44].

In the reported case, no intraoperative complications occurred.

No cases of anaesthetic technique conversion due to surgical problems have been reported in the literature. However, the conversion from RA to GA was reported in 33 of 4717 (0.7%) cases of anaesthesiologic complications. In 17 cases (0.36%) conversion was due to intolerable shoulder pain[13,18-20,23,27,28]; in 15 cases (0.31%) conversion was due to patient anxiety[16,19]; and in 1 case (0.02%) conversion was due to nausea and vomiting[19].

In our opinion, the main indication for conversion from RA to GA, according to Tiwari *et al*'s study, is surgical bleeding not easily controlled[19].

Other complications, such as biliary leakage or poor bleeding that is normally resolvable laparoscopically, can be managed even in awake patients, maintaining a comfortable environment for the patient.

One of the major intraoperative problems of LC under regional anaesthesia is right shoulder pain [45]. In a review and meta-analyses, Longo *et al*[46] showed that the pooled prevalence of shoulder pain during awake laparoscopy was 25% and required anaesthetic conversion in 3.4% of cases[46].

In our case, the pain was mild and disappeared in a short time with fentanyl injection.

Additionally, hypotension is a very frequent side effect of spinal anaesthesia[28,33] due to sympathetic blockage and the mechanical effect of pneumoperitoneum. In our case, it appeared at the beginning of the procedure, but it was easily managed with etilefrine chloride (2 mg) and norepinephrine infusion (0.05 gamma/kg/min) stopped at the end of the procedure.

Sinha *et al*[16] compared 3492 patients who underwent LC under spinal anaesthesia and 538 patients under general anaesthesia, demonstrating that the surgical aspects did not show any differences between the two groups. The use of spinal anaesthesia did not cause greater difficulties in technique,

Table 2 Indications for cholecystectomy under regional anaesthesia

No.	Indications
1	Gallbladder lithiasis
2	Cholecystitis
3	Biliary pancreatitis (previous MRCP to exclude choledocholithiasis)
4	Benign disease of gallbladder wall

MRCP: Magnetic resonance cholangiopancreatography.

longer operating times or complications. In addition, it has been shown that patients require less pain medication (61.57% *vs* 91.45%) and report less vomiting (2.29% *vs* 30.30%) and discomfort. In the same study, they also demonstrated how it was technically possible to perform the procedure even with pneumoperitoneum pressures between 8-10 mmHg[16].

Spinal anaesthesia is also associated with a low risk of complications and mortality rates compared with general anaesthesia and has numerous advantages.

Among the advantages are the patients being awake and oriented at the end of the procedure, less postoperative pain, and the ability to ambulate earlier than patients receiving general anaesthesia[22].

Turkstani *et al*[26] compared spinal and general anaesthesia in 50 patients who underwent LC under RA, demonstrating the occurrence of less pain in the postoperative period and focusing attention on the lower cost of spinal anaesthesia for the same patient outcomes[26].

During the postoperative period, our patient did not need painkilling therapy except for paracetamol.

Imbelloni *et al*[14] conducted a randomized, case-control study in healthy patients undergoing cholecystectomy to compare general and regional anaesthesia. The authors demonstrated that the use of regional anaesthesia, thereby maintaining low levels of abdominal pressure, can be a viable alternative to general anaesthesia, also providing a lower risk of thromboembolism, respiratory depression, myocardial infarction, and reduction of renal function[14].

Literature data show that awake LC is safe, feasible and could be advantageous to the whole population; however, at present, it is proposed to patients for whom total anaesthesia is particularly dangerous.

CONCLUSION

Unexpectedly, in the era of minimally invasive medicine, the use of regional anaesthesia in LC has not yet become widespread in clinical practice.

In fact, even if it is a safe and feasible procedure, the absence of numerous trials about the impact of RA, related outcomes and complications discourages surgeons and anaesthetists from proposing this procedure as the first choice of anaesthesia for LC unless the patient is not fit for general anaesthesia [47].

The possibility of using regional anaesthesia in our patient, with severe pulmonary disease and chronic respiratory failure, has allowed us to treat an invalidating pathology for the life of the subject in question, thereby reducing anaesthesiologic risks.

In conclusion, even though regional anaesthesia during LC is not a new technique, especially in patients with severe respiratory disease, new studies are certainly needed to standardize this technique and, above all, to clarify the guidelines about the indications for this procedure for all kinds of patients and to introduce this type of anaesthesia in routine clinical practice.

FOOTNOTES

Author contributions: All authors contributed equally to this work; All authors have read and approve the final manuscript.

Informed consent statement: The patient provided informed written consent prior to surgery.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Italy

ORCID number: Chiara Mazzone 0000-0002-4406-6592; Maria Sofia 0000-0002-5680-9939; Saverio Latteri 0000-0002-2759-4430.

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES

1 **Mouret P**. How I developed laparoscopic cholecystectomy. *Ann Acad Med Singap* 1996; **25**: 744-747 [PMID: 8924020]
2 **Overby DW**, Apelgren KN, Richardson W, Fanelli R; Society of American Gastrointestinal and Endoscopic Surgeons. SAGES guidelines for the clinical application of laparoscopic biliary tract surgery. *Surg Endosc* 2010; **24**: 2368-2386 [PMID: 20706739 DOI: 10.1007/s00464-010-1268-7]
3 **European Association for the Study of the Liver (EASL)**. EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones. *J Hepatol* 2016; **65**: 146-181 [PMID: 27085810 DOI: 10.1016/j.jhep.2016.03.005]
4 **Franklin ME Jr**, George J, Russek K. Needlescopic cholecystectomy. *Surg Technol Int* 2010; **20**: 109-113 [PMID: 21082554]
5 **Alexander HC**, Bartlett AS, Wells CI, Hannam JA, Moore MR, Poole GH, Merry AF. Reporting of complications after laparoscopic cholecystectomy: a systematic review. *HPB (Oxford)* 2018; **20**: 786-794 [PMID: 29650299 DOI: 10.1016/j.hpb.2018.03.004]
6 **Soper NJ**, Stockmann PT, Dunnegan DL, Ashley SW. Laparoscopic cholecystectomy. The new 'gold standard'? *Arch Surg* 1992; **127**: 917-21; discussion 921 [PMID: 1386505 DOI: 10.1001/archsurg.1992.01420080051008]
7 **Aerts R**, Penninckx F. The burden of gallstone disease in Europe. *Aliment Pharmacol Ther* 2003; **18** Suppl 3: 49-53 [PMID: 14531741 DOI: 10.1046/j.0953-0673.2003.01721.x]
8 **Azurin DJ**, Go LS, Cwik JC, Schuricht AL. The efficacy of epidural anesthesia for endoscopic preperitoneal herniorrhaphy: a prospective study. *J Laparoendosc Surg* 1996; **6**: 369-373 [PMID: 9025020 DOI: 10.1089/lps.1996.6.369]
9 **Pędziwiatr M**, Mavrikis J, Witowski J, Adamos A, Major P, Nowakowski M, Budzyński A. Current status of enhanced recovery after surgery (ERAS) protocol in gastrointestinal surgery. *Med Oncol* 2018; **35**: 95 [PMID: 29744679 DOI: 10.1007/s12032-018-1153-0]
10 **Bajwa SJ**, Kulshrestha A. Anaesthesia for laparoscopic surgery: General vs regional anaesthesia. *J Minim Access Surg* 2016; **12**: 4-9 [PMID: 26917912 DOI: 10.4103/0972-9941.169952]
11 **Skytioti M**, Elstad M, Søvik S. Internal Carotid Artery Blood Flow Response to Anesthesia, Pneumoperitoneum, and Head-up Tilt during Laparoscopic Cholecystectomy. *Anesthesiology* 2019; **131**: 512-520 [PMID: 31261258 DOI: 10.1097/ALN.0000000000002838]
12 **Kim BS**, Joo SH, Joh JH, Yi JW. Laparoscopic cholecystectomy in patients with anesthetic problems. *World J Gastroenterol* 2013; **19**: 4832-4835 [PMID: 23922485 DOI: 10.3748/wjg.v19.i29.4832]
13 **Hajong R**, Khariong PD, Baruah AJ, Anand M, Khongwar D. Laparoscopic cholecystectomy under epidural anesthesia: a feasibility study. *N Am J Med Sci* 2014; **6**: 566-569 [PMID: 25535604 DOI: 10.4103/1947-2714.145468]
14 **Imbelloni LE**, Fornasari M, Fialho JC, Sant'Anna R, Cordeiro JA. General anesthesia versus spinal anesthesia for laparoscopic cholecystectomy. *Rev Bras Anestesiol* 2010; **60**: 217-227 [PMID: 20682154 DOI: 10.1016/S0034-7094(10)70030-1]
15 **Pursnani KG**, Bazza Y, Calleja M, Mughal MM. Laparoscopic cholecystectomy under epidural anesthesia in patients with chronic respiratory disease. *Surg Endosc* 1998; **12**: 1082-1084 [PMID: 9685547 DOI: 10.1007/s004649900785]
16 **Sinha R**, Gurwara AK, Gupta SC. Laparoscopic cholecystectomy under spinal anesthesia: a study of 3492 patients. *J Laparoendosc Adv Surg Tech A* 2009; **19**: 323-327 [PMID: 19522659 DOI: 10.1089/lap.2008.0393]
17 **Mehta PJ**, Chavda HR, Wadhwana AP, Porecha MM. Comparative analysis of spinal versus general anesthesia for laparoscopic cholecystectomy: A controlled, prospective, randomized trial. *Anesth Essays Res* 2010; **4**: 91-95 [PMID: 25885237 DOI: 10.4103/0259-1162.73514]
18 **Kar M**, Kar JK, Debnath B. Experience of laparoscopic cholecystectomy under spinal anesthesia with low-pressure pneumoperitoneum--prospective study of 300 cases. *Saudi J Gastroenterol* 2011; **17**: 203-207 [PMID: 21546725 DOI: 10.4103/1319-3767.80385]
19 **Tiwari S**, Chauhan A, Chaterjee P, Alam MT. Laparoscopic cholecystectomy under spinal anaesthesia: A prospective, randomised study. *J Minim Access Surg* 2013; **9**: 65-71 [PMID: 23741111 DOI: 10.4103/0972-9941.110965]
20 **V K**, Pujari VS, R SM, Hiremath BV, Bevinaguddaiah Y. Laparoscopic Cholecystectomy Under Spinal Anaesthesia vs. General Anaesthesia: A Prospective Randomised Study. *J Clin Diagn Res* 2014; **8**: NC01-NC04 [PMID: 25302232 DOI: 10.7860/JCDR/2014/9829.4700]
21 **Gramatica L Jr**, Brasesco OE, Mercado Luna A, Martinessi V, Panebianco G, Labaque F, Rosin D, Rosenthal RJ, Gramatica L. Laparoscopic cholecystectomy performed under regional anesthesia in patients with chronic obstructive

pulmonary disease. *Surg Endosc* 2002; **16**: 472-475 [PMID: 11928031 DOI: 10.1007/s00464-001-8148-0]
22 **Imbelloni LE**. Spinal anesthesia for laparoscopic cholecystectomy: Thoracic vs. Lumbar Technique. *Saudi J Anaesth* 2014; **8**: 477-483 [PMID: 25422604 DOI: 10.4103/1658-354X.140853]
23 **Yuksek YN**, Akat AZ, Gozalan U, Daglar G, Pala Y, Canturk M, Tutuncu T, Kama NA. Laparoscopic cholecystectomy under spinal anesthesia. *Am J Surg* 2008; **195**: 533-536 [PMID: 18304510 DOI: 10.1016/j.amjsurg.2007.05.043]
24 **Bilgi M**, Alshair EE, Göksu H, Sevim O. Experience of Laparoscopic Cholecystectomy Under Thoracic Epidural Anaesthesia: Retrospective Analysis of 96 Patients. *Turk J Anaesthesiol Reanim* 2015; **43**: 29-34 [PMID: 27366461 DOI: 10.5152/TJAR.2014.68926]
25 **Donmez T**, Erdem VM, Uzman S, Yildirim D, Avaroglu H, Ferahman S, Sunamak O. Laparoscopic cholecystectomy under spinal-epidural anesthesia *vs*. general anaesthesia: a prospective randomised study. *Ann Surg Treat Res* 2017; **92**: 136-142 [PMID: 28289667 DOI: 10.4174/astr.2017.92.3.136]
26 **Turkstani A**, Ibraheim O, Khairy G, Alseif A, Khalil N. Spinal versus general anesthesia for laparoscopic cholecystectomy: a cost effectiveness and side effects study. *Anaesth Pain Intensive Care* 2009; **13.1**: 9-14
27 **Lee JH**, Huh J, Kim DK, Gil JR, Min SW, Han SS. Laparoscopic cholecystectomy under epidural anesthesia: a clinical feasibility study. *Korean J Anesthesiol* 2010; **59**: 383-388 [PMID: 21253374 DOI: 10.4097/kjae.2010.59.6.383]
28 **Hamad MA**, El-Khattary OA. Laparoscopic cholecystectomy under spinal anesthesia with nitrous oxide pneumoperitoneum: a feasibility study. *Surg Endosc* 2003; **17**: 1426-1428 [PMID: 12802665 DOI: 10.1007/s00464-002-8620-5]
29 **Bessa SS**, Katri KM, Abdel-Salam WN, El-Kayal el-SA, Tawfik TA. Spinal versus general anesthesia for day-case laparoscopic cholecystectomy: a prospective randomized study. *J Laparoendosc Adv Surg Tech A* 2012; **22**: 550-555 [PMID: 22686181 DOI: 10.1089/lap.2012.0110]
30 **Costantino GN**, Vincent GJ, Mukalian GG, Kliefoth WL Jr. Laparoscopic cholecystectomy in pregnancy. *J Laparoendosc Surg* 1994; **4**: 161-164 [PMID: 8043927 DOI: 10.1089/lps.1994.4.161]
31 **Edelman DS**. Alternative laparoscopic technique for cholecystectomy during pregnancy. *Surg Endosc* 1994; **8**: 794-796 [PMID: 7974110 DOI: 10.1007/BF00593444]
32 **van Zundert AA**, Stultiens G, Jakimowicz JJ, Peek D, van der Ham WG, Korsten HH, Wildsmith JA. Laparoscopic cholecystectomy under segmental thoracic spinal anaesthesia: a feasibility study. *Br J Anaesth* 2007; **98**: 682-686 [PMID: 17371777 DOI: 10.1093/bja/aem058]
33 **Tzovaras G**, Fafoulakis F, Pratsas K, Georgopoulou S, Stamatiou G, Hatzitheofilou C. Laparoscopic cholecystectomy under spinal anesthesia: a pilot study. *Surg Endosc* 2006; **20**: 580-582 [PMID: 16437265 DOI: 10.1007/s00464-005-0405-1]
34 **Kim Y**, Pomper J, Goldberg ME. Anesthetic management of the pregnant patient with carcinoma of the breast. *J Clin Anesth* 1993; **5**: 76-78 [PMID: 8382932 DOI: 10.1016/0952-8180(93)90094-u]
35 **Kim YI**, Lee JS, Jin HC, Chae WS, Kim SH. Thoracic epidural anesthesia for laparoscopic cholecystectomy in an elderly patient with severely impaired pulmonary function tests. *Acta Anaesthesiol Scand* 2007; **51**: 1394-1396 [PMID: 17944644 DOI: 10.1111/j.1399-6576.2007.01460.x]
36 **Hausman MS Jr**, Jewell ES, Engoren M. Regional versus general anesthesia in surgical patients with chronic obstructive pulmonary disease: does avoiding general anesthesia reduce the risk of postoperative complications? *Anesth Analg* 2015; **120**: 1405-1412 [PMID: 25526396 DOI: 10.1213/ANE.0000000000000574]
37 **Imbelloni LE**. Spinal anesthesia for laparoscopic cholecystectomy. *Glob J Anesthesiol* 2014; **1**: 101 [DOI: 10.17352/2455-3476.000001]
38 **van Zundert AA**, Stultiens G, Jakimowicz JJ, van den Borne BE, van der Ham WG, Wildsmith JA. Segmental spinal anaesthesia for cholecystectomy in a patient with severe lung disease. *Br J Anaesth* 2006; **96**: 464-466 [PMID: 16549626 DOI: 10.1093/bja/ael036]
39 **Sharp JR**, Pierson WP, Brady CE 3rd. Comparison of CO2- and N2O-induced discomfort during peritoneoscopy under local anesthesia. *Gastroenterology* 1982; **82**: 453-456 [PMID: 6459262]
40 **Jaffray B**. Minimally invasive surgery. *Arch Dis Child* 2005; **90**: 537-542 [PMID: 15851444 DOI: 10.1136/adc.2004.062760]
41 **Lindgren L**, Koivusalo AM, Kellokumpu I. Conventional pneumoperitoneum compared with abdominal wall lift for laparoscopic cholecystectomy. *Br J Anaesth* 1995; **75**: 567-572 [PMID: 7577282 DOI: 10.1093/bja/75.5.567]
42 **Aloia TA**, Járufe N, Javle M, Maithel SK, Roa JC, Adsay V, Coimbra FJ, Jarnagin WR. Gallbladder cancer: expert consensus statement. *HPB (Oxford)* 2015; **17**: 681-690 [PMID: 26172135 DOI: 10.1111/hpb.12444]
43 **Kietaibl S**, Ferrandis R, Godier A, Llau J, Lobo C, Macfarlane AJ, Schlimp CJ, Vandermeulen E, Volk T, von Heymann C, Wolmarans M, Afshari A. Regional anaesthesia in patients on antithrombotic drugs: Joint ESAIC/ESRA guidelines. *Eur J Anaesthesiol* 2022; **39**: 100-132 [PMID: 34980845 DOI: 10.1097/EJA.0000000000001600]
44 **Burns SM**, Cowan CM. Spinal anaesthesia for caesarean section: current clinical practice. *Hosp Med* 2000; **61**: 855-858 [PMID: 11211587 DOI: 10.12968/hosp.2000.61.12.1485]
45 **Kisa A**, Koruk S, Kocoglu H, Leblebici İM. Comparison of General Anesthesia with Spinal Anesthesia in Laparoscopic Cholecystectomy Operations. *Medeni Med J* 2019; **34**: 346-353 [PMID: 32821460 DOI: 10.5222/MMJ.2019.37929]
46 **Longo MA**, Cavalheiro BT, de Oliveira Filho GR. Laparoscopic cholecystectomy under neuraxial anesthesia compared with general anesthesia: Systematic review and meta-analyses. *J Clin Anesth* 2017; **41**: 48-54 [PMID: 28802605 DOI: 10.1016/j.jclinane.2017.06.005]
47 **Asaad P**, O'Connor A, Hajibandeh S. Meta-analysis and trial sequential analysis of randomized evidence comparing general anesthesia *vs* regional anesthesia for laparoscopic cholecystectomy. *World J Gastrointest Endosc* 2021; **13**: 137-154 [PMID: 34046151 DOI: 10.4253/wjge.v13.i5.137]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3010-3016

DOI: 10.12998/wjcc.v11.i13.3010

ISSN 2307-8960 (online)

CASE REPORT

Bilateral malignant glaucoma with bullous keratopathy: A case report

Ya-Bin Ma, Ya-Long Dang

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Tanabe S, Japan; Wang WW, China

Received: October 7, 2022
Peer-review started: October 7, 2022
First decision: December 26, 2022
Revised: January 22, 2023
Accepted: March 31, 2023
Article in press: March 31, 2023
Published online: May 6, 2023

Ya-Bin Ma, Ya-Long Dang, Department of Ophthalmology, Sanmenxia Central Hospital, Sanmenxia 472000, Henan Province, China

Corresponding author: Ya-Long Dang, MD, PhD, Associate Chief Physician, President, Surgeon, Department of Ophthalmology, Sanmenxia Central Hospital, Wenhua Street, Sanmenxia 472000, Henan Province, China. dangyalong@126.com

Abstract

BACKGROUND

Malignant glaucoma, caused by aqueous misdirection, is a challenging post-surgical complication presented with normal/high intraocular pressure and shallowing of the central and peripheral anterior chambers. Its incidence is about 0.6%-4.0%. It can be secondary to filtering surgeries, laser iridotomy, and cataract surgery. Short axial length and a history of angle closure glaucoma are its main risk factors. Here, we report a bilateral malignant glaucoma with bullous keratopathy in the patient's left eye.

CASE SUMMARY

We present a case of bilateral malignant glaucoma. The cause of malignant glaucoma for each eye of this patient was different. Hence, the management strategy and selection of surgical methods were also different. However, the normal anterior chamber was ultimately maintained, and maximum visual function was preserved. Even though the left eye received multiple surgeries and corneal endothelial decompensation occurred, the formation of a retroendothelial fibrous membrane partially compensated for the function of the corneal endothelium.

CONCLUSION

The formation of a retroendothelial fibrous membrane partially compensated for the function of the corneal endothelium.

Key Words: Malignant glaucoma; Corneal epithelial cell; Lens epithelial cell; Bullous keratopathy; Retroendothelial fibrous membrane; Case report

Core Tip: Malignant glaucoma, caused by aqueous misdirection, is a challenging post-surgical complication presented with normal/high intraocular pressure and shallowing of the central and peripheral anterior chambers. Its incidence is about 0.6%-4.0%. It can be secondary to filtering surgeries, laser iridotomy, and cataract surgery. Short axial length and a history of angle closure glaucoma are its main risk factors. Here, we report bilateral malignant glaucoma with bullous keratopathy in the patient's left eye. Interestingly, the best corrected visual acuity of the left eye improved to 20/70, and bullous keratopathy was relieved after the migration and implant of lens epithelial cells into the corneal endothelium.

Citation: Ma YB, Dang YL. Bilateral malignant glaucoma with bullous keratopathy: A case report. *World J Clin Cases* 2023; 11(13): 3010-3016
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3010.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3010

INTRODUCTION

Malignant glaucoma, caused by aqueous misdirection, is a challenging post-surgical complication presented with normal/high intraocular pressure (IOP) and shallowing of the central and peripheral anterior chambers. Its incidence is about 0.6%-4.0%[1-3]. It can be secondary to filtering surgeries, laser iridotomy, and cataract surgery. Short axial length and a history of angle closure glaucoma are its main risk factors[4,5]. Here, we reported bilateral malignant glaucoma with bullous keratopathy in the patient's left eye. Interestingly, the best corrected visual acuity (BCVA) of her left eye improved to 20/70, and bullous keratopathy was relieved after the migration and implant of lens epithelial cells into the corneal endothelium.

CASE PRESENTATION

Chief complaints

A 36-year-old woman complained of "blurred vision in both eyes" and was diagnosed with chronic angle-closure glaucoma.

History of present illness

She received bilateral laser peripheral iridotomy and was prescribed with timolol, brimonidine, and brinzolamide twice per day and latanoprost daily. Her IOP remained high (38 mmHg-45 mmHg), and visual field worsened.

History of past illness

The patient did not report any past illnesses.

Physical examination

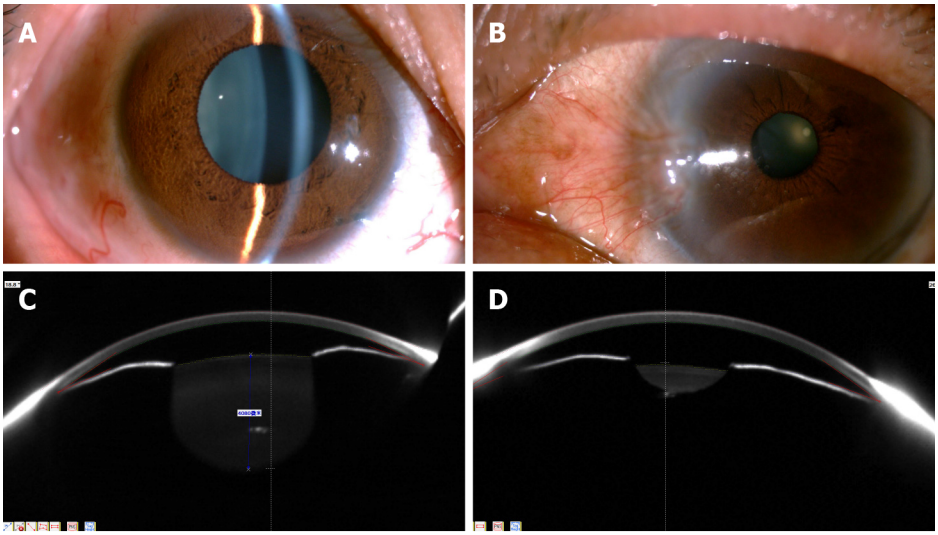
The BCVA of both eyes was 20/20. The central and peripheral anterior chambers were shallow. The anterior chamber angles were partially closed. The anterior chamber depth was 1.86 mm (OD) and 1.61 mm (OS). The pupil diameter was 6.5 mm (OD) and 2.8 mm (OS). The pupillary light reflex in her right eye was delayed (Figure 1). The lenses were transparent. Fundoscopy revealed that the right cup-disc ratio was 0.9, and the disc border was narrow. The left optic disc boundaries were clear and pale red in color. No apparent abnormalities were observed in either retina.

Laboratory examinations

The right eye showed a tubular visual field. The contrast sensitivity in the left eye was decreased and accompanied with a visual field defect. The central corneal thicknesses were 535 μm (OD) and 556 μm (OS), and the IOPs were 45 mmHg (OD) and 40 mmHg (OS). The axial lengths were 19.55 mm (OD) and 19.59 mm (OS). The corneal endothelial cell density was 2488/mm^2 (OD) and 2890/mm^2 (OS).

Imaging examinations

OCT revealed that the thickness of retinal nerve fiber layer in her right eye reduced (Figure 2A). No abnormality was observed in the left eye (Figure 2B).



DOI: 10.12998/wjcc.v11.i13.3010

Figure 1 Anterior segment photographs and pentacam analysis. A and B: Bilateral corneas show transparency. Pupil diameter: OD 6.5 mm and OS 2.8 mm. The hole of iridotomy was marked by a black arrow; B: Different perspectives; C and D: Central and peripheral anterior chambers were shallow, and partial angle closure was present in both eyes.

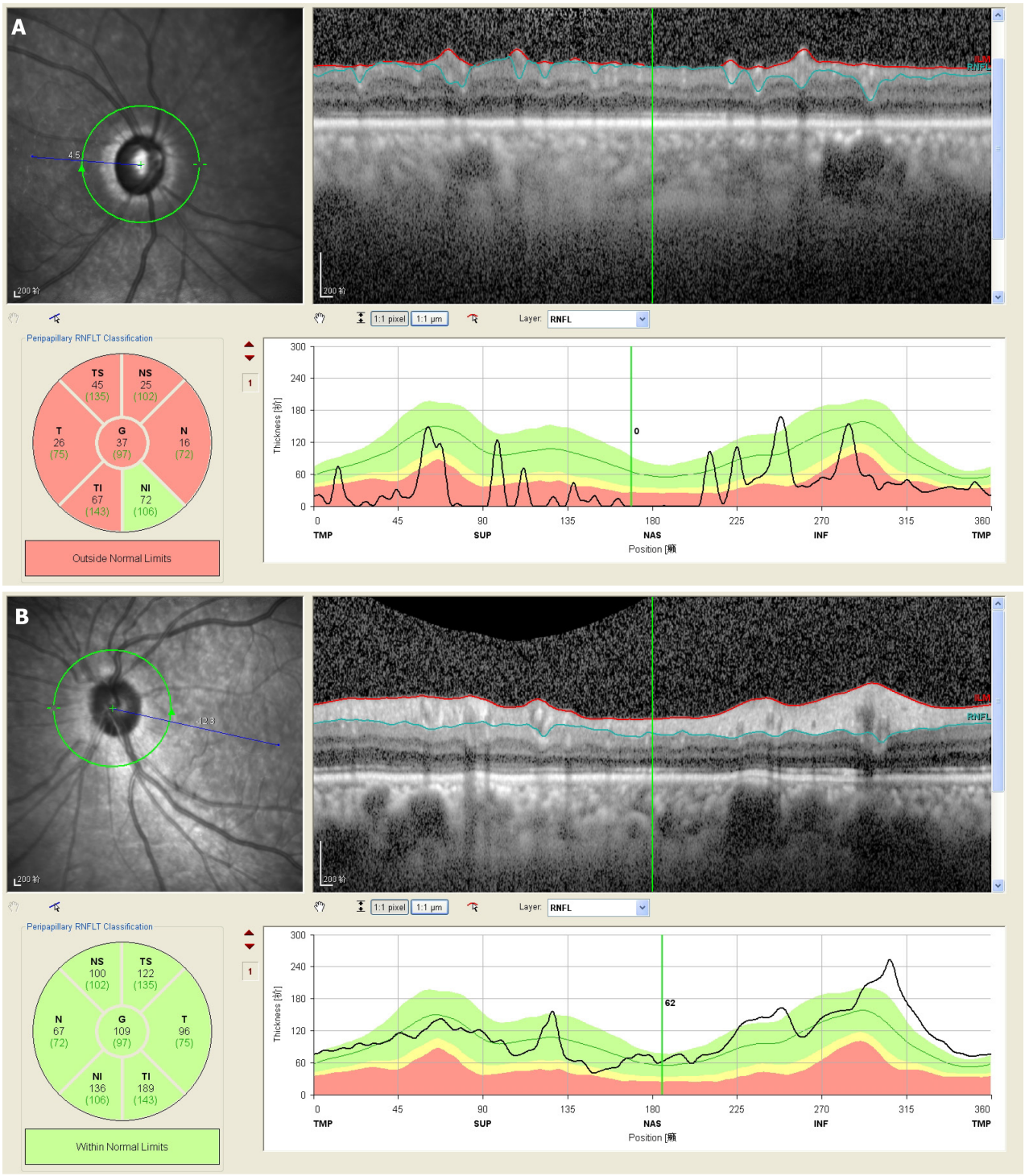
FINAL DIAGNOSIS

Bilateral chronic angle-closure glaucoma

TREATMENT

For her right eye, we performed cataract phacoemulsification combined with intraocular lens implantation. Postoperatively, the patient had a grade II shallow anterior chamber, intraocular lens protrusion, and IOP of 42 mmHg. We considered malignant glaucoma in her right eye. Therefore, periorbital injection of methylprednisolone and atropine mydriasis were continued for 3 d; however, there was no improvement. Subsequently, the patient underwent a capsulotomy and an anterior vitrectomy. Postsurgery, there was significant anterior chamber deepening with a central ACD of 2.89 mm and IOP fluctuating between 25 and 35 mmHg. Considering that this might be an instance of chronic angle closure in the right eye, we implanted an Ahmed drainage valve. Post-surgery, the IOP stabilized at 13 mmHg–19 mmHg, and BCVA was 20/25. The surgery had achieved the expected outcomes.

Due to the short axial length in her left eye and malignant glaucoma in her right eye, we performed cataract phacoemulsification and intraocular lens implantation, combined with anterior vitrectomy for her left eye. Post-surgery, the ACD was deepened at approximately 2.51 mm, but the IOP remained at 30 mmHg. One week later, considering the angle closure, we implanted an Ahmed valve. Postsurgery, the patient's anterior chamber gradually disappeared, and a grade III shallow anterior chamber was detected. There was significant corneal edema. IOP was 20 mmHg, and the Seidel test was negative. We considered the malignant glaucoma in her left eye. We administered periorbital injections of methylprednisolone and atropine eye drops twice per day. However, these treatments were ineffective. A viscoelastic agent was injected into the anterior chamber, and laser posterior capsulotomy was performed. However, a grade III shallow anterior chamber recurred. A peripheral iridectomy with zonulo-capsulo-hyaloidotomy was performed through the pars plana route. Tension sutures were used to reform the anterior chamber. On day 2 postsurgery, the ACD was significantly increased to 2.75 mm. The IOP was 15 mmHg. One-week post-surgery, corneal edema was still significant, and bullous changes could be seen in the epithelium (Figure 3A). The OCT and slit lamp examination suggested that nearly one-third of the cornea endothelial detached, and a translucent membrane attached and stretched the endothelial layer (Figures 3B and 4A and B). The slit lamp revealed a bundle of white fibers that proliferated behind the corneal endothelium near the pupillary limbus at the 10 o'clock position and were pulling on the intraocular lens surface. Yttrium-aluminum-garnet (YAG) laser was immediately carried out to remove the proliferative fibers. We saw that fiber bundles had high tension and significant rebound.

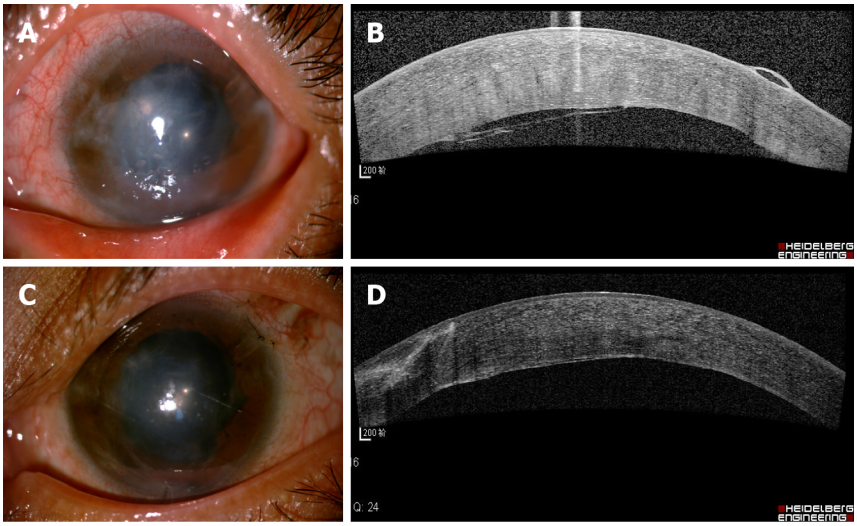


DOI: 10.12998/wjcc.v11.i13.3010

Figure 2 Optical coherence tomography of the optic nerve head. A: The retinal nerve fiber layer in various quadrants of the right eye appeared to have thinned; B: No apparent abnormalities were observed in the retinal nerve fiber layer of the left eye.

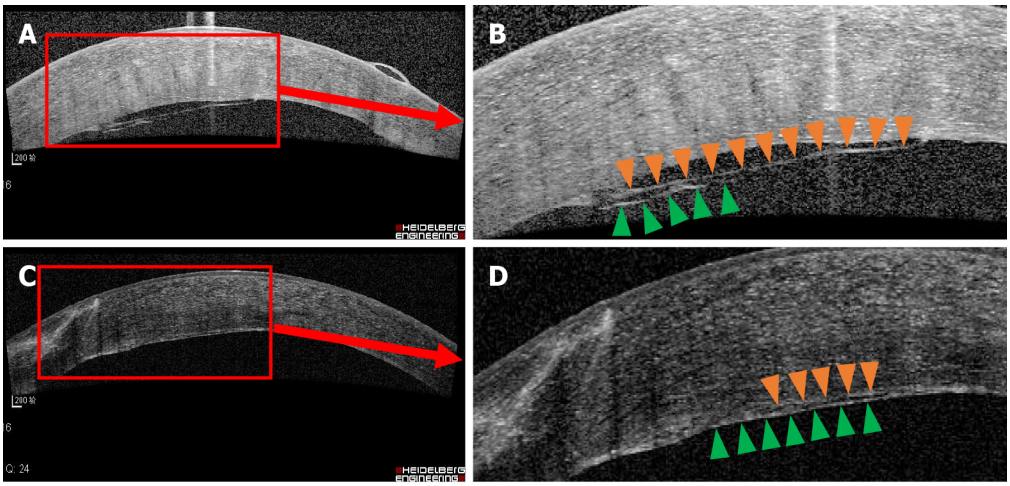
OUTCOME AND FOLLOW-UP

Two weeks after the YAG laser, the corneal edema had abated, the corneal bullae had disappeared, and the peripheral cornea was transparent (Figure 3C). The OCT revealed that the corneal endothelial detachment gradually resolved, and a highly reflective membranous mass attached to the medial endothelial layer (Figures 3D and 4C and D). At the 1-year follow-up, the IOP was 17 mmHg, and ACD was normal. The peripheral cornea was partially transparent. The corneal edema persisted (central corneal thickness: 756 μm), and a fibrous proliferative membrane could be seen in the epithelium. The corneal epithelial bullae disappeared, and BCVA was 20/70.



DOI: 10.12998/wjcc.v11.i13.3010 **Copyright** ©The Author(s) 2023.

Figure 3 Anterior segment photography and optical coherence tomography of the left eye. A: After peripheral iridectomy with zonulo-capsulo-hyaloidotomy and tension suture fixation, the anterior chamber was reconstructed. However, a significant corneal edema and bullous changes were seen; B: Optical coherence tomography showed that extensive corneal endothelial detachment involving approximately half of the cornea and a translucent membrane attached and stretched the endothelial layer; C: Two weeks after yttrium-aluminum-garnet laser, the corneal edema had abated, the corneal bullae had disappeared, and the peripheral cornea was transparent. D: Optical coherence tomography showed the corneal endothelial detachment gradually resolved. A highly reflective membranous mass attached to the medial endothelial layer.



DOI: 10.12998/wjcc.v11.i13.3010 **Copyright** ©The Author(s) 2023.

Figure 4 Enlarged figure of corneal optical coherence tomography. A and B: A corneal endothelial detachment (orange arrows) involving approximately half of the cornea and a translucent membrane (green arrows) attached and stretched the endothelial layer (orange arrows); B: Enlarged image; C and D: Two weeks after removal of the fibrous bundle, corneal endothelial detachment gradually disappeared. A highly reflective membranous mass (green arrows) was attached to the medial endothelial layer (orange arrows).

DISCUSSION

We presented a case of bilateral malignant glaucoma after phacoemulsification and intraocular lens implantation combined with anterior vitrectomy and Ahmed drainage valve implantation. The patient's right anterior chamber and IOP fully recovered after anterior vitrectomy. Although we realized that the incidence of malignant glaucoma in her left eye was extremely high and carried out anterior vitrectomy during stage I, grade III shallow anterior chamber and corneal lens contact still occurred, resulting in corneal endothelial decompensation. Fortunately, the anterior chamber reformed, and the IOP stabilized after peripheral iridectomy with zonulo-capsulo-hyaloidotomy and a tension suture fixation in the anterior chamber. It is worth noting that 1 wk after the left intraocular lens was disengaged from the cornea, a bundle of tense fiber formed between the lens surface and the corneal endothelium. This was suspected to be caused by epithelial cells migrating and transdifferentiating into myofibroblasts in the corneal endothelium. These myofibroblasts were attached to the surface of the corneal endothelium, blocking the entry of aqueous humor into the subcorneal epithelium and thereby preventing bullous

keratopathy.

Short axial length and anterior segment crowding are risk factors for malignant glaucoma[6]. Wang *et al*[6] analyzed 1183 patients with angle-closure glaucoma and found that the axial length and ACD of those patients were significantly lower than of those with primary angle-closure glaucoma (axial length: 21.44 ± 1.18 mm *vs* 22.17 ± 0.97 mm, ACD: 2.12 ± 0.41 mm *vs* 2.49 ± 0.48 mm). As malignant glaucoma often involves both eyes[7,8], we performed a three-step lens resection combined with vitrectomy on the patient's left eye[9]. First, the central vitreous was removed *via* the pars plana vitrectomy to relieve crowding of the anterior segment. Second, lens phacoemulsification, combined with intraocular lens implantation, was carried out. Finally, anterior vitrectomy was performed. Postsurgery, the anterior chamber was stable and deep, and aqueous misdirection did not occur. However, as the patient had chronic angle closure, the IOP remained high. Considering that trabeculectomy has poor results after vitrectomy, we opted for Ahmed drainage valve implantation[10].

Postsurgery, the patient had a grade III shallow anterior chamber and intraocular lens protrusion, with the intraocular lens coming into contact with the corneal endothelium. Although the IOP did not exceed 21 mmHg, aqueous misdirection had occurred. The diagnosis of malignant glaucoma was confirmed. The reasons for this were: (1) Excessive aqueous humor drainage after valve implantation; and (2) Postoperative inflammation promotes the proliferation, adhesion, and transformation of lens epithelial cells and ciliary body edema, resulting in a blockage of normal aqueous humor circulation [11]. Therefore, we carried out a peripheral iridectomy with zonulo-capsulo-hyaloidotomy at the 6 o'clock position, combined with tension suture fixation in the anterior chamber[12]. The postoperative anterior chamber reformation was good.

After the malignant glaucoma occurred, the patient's left eye developed a grade III shallow anterior chamber, the intraocular lens was in contact with the corneal endothelium, and there was moderate-severe inflammation[11]. Inflammatory responses can promote epithelial-mesenchymal transformation of the lens epithelial cell[13]. In this patient, a fibrous bundle could be seen between the corneal endothelium and surface of the intraocular lens at the 10 o'clock 1 wk after anterior chamber reformation had been successfully performed.

The fibrous bundle had tension between the corneal endothelium and the intraocular lens. It pulled the corneal endothelium, resulting in partial detachment. After the fibrous bundle was resected with YAG laser, the corneal endothelium and fibrous membrane gradually attached to the posterior surface of the cornea. Even though the density of corneal endothelial cells was low (797 cells/mm^2) and the function was poor (6A cells accounted for 20%), the corneal bullae gradually disappeared, together with the formation of the fibrous membrane behind the corneal endothelium. This suggests that fibrous membrane derived from lens epithelial transformation is somewhat impermeable to water.

CONCLUSION

We presented a case of bilateral malignant glaucoma. The cause of malignant glaucoma for each eye of this patient was different. Hence, the management strategy and selection of surgical methods were also different. However, the normal anterior chamber was ultimately maintained, and maximum visual function was preserved. Even though the left eye received multiple surgeries and corneal endothelial decompensation occurred, the formation of a retroendothelial fibrous membrane partially compensated for the function of the corneal endothelium.

FOOTNOTES

Author contributions: Dang YL contributed to conception of the study; Dang YL performed the surgery; Ma YB and Dang YL contributed significantly to analysis and manuscript preparation; all authors have read and approved the final manuscript.

Supported by The Central Guiding Local Science & Technology Projects, No. Z20221341047; The Major Scientific and Technological Project of Sanmenxia 2022, No. 2022001007

Informed consent statement: Written informed consent was obtained from the patient for the publication of this case report.

Conflict-of-interest statement: All authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Ya-Long Dang 0000-0003-2194-6375.

S-Editor: Liu GL
L-Editor: Filipodia
P-Editor: Liu GL

REFERENCES

1 **Chandler PA**, Simmons RJ, Grant WM. Malignant glaucoma. Medical and surgical treatment. *Am J Ophthalmol* 1968; **66**: 495-502 [PMID: 5676357 DOI: 10.1016/0002-9394(68)91535-3]
2 **Simmons RJ**. Malignant glaucoma. *Br J Ophthalmol* 1972; **56**: 263-272 [PMID: 5032764 DOI: 10.1136/bjo.56.3.263]
3 **Lowe RF**. Clinical types of primary angle closure glaucoma. *Aust N Z J Ophthalmol* 1988; **16**: 245-250 [PMID: 3179051 DOI: 10.1111/j.1442-9071.1988.tb01216.x]
4 **Jacoby B**, Reed JW, Cashwell LF. Malignant glaucoma in a patient with Down's syndrome and corneal hydrops. *Am J Ophthalmol* 1990; **110**: 434-435 [PMID: 2145771 DOI: 10.1016/s0002-9394(14)77033-3]
5 **Cohen RG**, Wu HK, Schuman JS. Glaucoma with inflammatory precipitates on the trabecular meshwork: a report of Grant's syndrome with ultrasound biomicroscopy of precipitates. *J Glaucoma* 1996; **5**: 266-270 [PMID: 8795772]
6 **Wang M**, Tan Q, Jiang H, Xia X, Wang P, Jiang J, Liu D. [Clinical analysis of malignant glaucoma after glaucoma surgery]. *Zhongnan Daxue Xuebao Yixueban* 2015; **40**: 543-548 [PMID: 26032082 DOI: 10.11817/j.issn.1672-7347.2015.05.015]
7 **Saunders PP**, Douglas GR, Feldman F, Stein RM. Bilateral malignant glaucoma. *Can J Ophthalmol* 1992; **27**: 19-21 [PMID: 1555130 DOI: 10.1001/archopht.1964.00970020601004]
8 **Stan C**. Glaucom malign bilateral--prezentare de caz. *Conexiuni Medicale* 2007; 45-47 [DOI: 10.33311/conmed.2007.3.3.10]
9 **Sharma A**, Sii F, Shah P, Kirkby GR. Vitrectomy-phacoemulsification-vitrectomy for the management of aqueous misdirection syndromes in phakic eyes. *Ophthalmology* 2006; **113**: 1968-1973 [PMID: 17074562 DOI: 10.1016/j.ophtha.2006.04.031]
10 **Wang MH**, Li QM, Dong HT, Dong SQ, Li Y, Zheng CY. Ahmed Valves *vs* Trabeculectomy Combined with Pans Plana Vitrectomy for Neovascular Glaucoma with Vitreous Hemorrhage. *Eur J Ophthalmol* 2017; **27**: 774-780 [PMID: 28430329 DOI: 10.5301/ejo.5000973]
11 **Martínez-de-la-Casa JM**, García-Feijoó J, Castillo A, Polo V, Larrosa JM, Pablo L, García-Sánchez J. Glaucoma maligno tras cirugía combinada de implante valvular de Ahmed y facoemulsificación en el tratamiento del glaucoma cró nico por cierre angular. *Arch Soc Esp Oftalmol* 2005; **80**: 11 [DOI: 10.4321/s0365-66912005001100009]
12 **Balekudaru S**, Choudhari NS, Rewri P, George R, Bhende PS, Bhende M, Lingam V, Lingam G. Surgical management of malignant glaucoma: a retrospective analysis of fifty eight eyes. *Eye (Lond)* 2017; **31**: 947-955 [PMID: 28257136 DOI: 10.1038/eye.2017.32]
13 **Gao L**, Zhou Y, Li N, Liu X, Cong F. Lens Epithelial Mesenchymal Transition and Long-Term Chronic Inflammation After Cataract Surgery. *Ocul Immunol Inflamm* 2022; 1-3 [PMID: 35708475 DOI: 10.1080/09273948.2022.2088567]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3017-3021

DOI: 10.12998/wjcc.v11.i13.3017

ISSN 2307-8960 (online)

CASE REPORT

Finger compartment syndrome due to a high-pressure washer injury: A case report

Jun Ho Choi, Seung Yeon Choi, Jae Ha Hwang, Kwang Seog Kim, Sam Yong Lee

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Jamaluddin J, Malaysia; Malik S, Pakistan

Received: November 9, 2022
Peer-review started: November 9, 2022
First decision: January 30, 2023
Revised: February 3, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 6, 2023

Jun Ho Choi, Seung Yeon Choi, Jae Ha Hwang, Kwang Seog Kim, Sam Yong Lee, Department of Plastic and Reconstructive Surgery, Chonnam National University Hospital Chonnam National University Medical School, Gwangju 61469, South Korea

Corresponding author: Jae Ha Hwang, MD, PhD, Professor, Surgeon, Department of Plastic and Reconstructive Surgery, Chonnam National University Hospital Chonnam National University Medical School, 42 Jebong-ro, Dong-gu, Gwangju 61469, South Korea. psjhhwang@daum.net

Abstract

BACKGROUND

Although the finger compartment syndrome is not common, it compresses the neurovascular bundles in a limited space and blocks blood flow to the fingers, causing necrosis of the fingertips. Finger fasciotomy through unilateral or bilateral midline release of the finger can achieve decompression of the finger compartment. Herein, we report a case of the compartment syndrome in a finger injury caused by a high-pressure water flow which is commonly used in car washing stations.

CASE SUMMARY

A 60-year-old man injured his right middle finger while using a high-pressure washer at a car washing station. The patient complained of severe pain in his middle finger and a 0.2 cm punctured open wound on the volar side of the distal phalangeal joint of the middle finger. The fingertip was pale, numb, and characterized by severe swelling and a limited range of motion. Finger radiography showed that there was no fracture in the finger. Digital decompression was performed through finger fasciotomy by bilateral midline incision. On the second day after surgery, the color of the fingertip returned to pink, swelling was resolved, and the range of motion returned to normal. The sensation of the fingertip was completely restored, and the capillary refill test and pinprick test were positive.

CONCLUSION

The fingertip compartment syndrome can be caused by a high-pressure water flow damage to the fingers when using high-pressure washers at a car washing station. To avoid finger necrosis, rapid diagnosis of the finger compartment syndrome and appropriate digital decompression are essential to better outcome.

Key Words: Compartment syndrome; Crush injuries; Fasciotomy; Finger injuries; Case

report

Core Tip: Though the fingertip compartment syndrome is not common, the digital decompression through finger fasciotomy with midlateral release is essential. In this case, compartment syndrome occurred in the middle finger without fracture due to a crushing injury caused by a common high-pressure washer. Fasciotomy was performed immediately. The patient was concerned about necrosis of the finger and demanded early amputation on the first day after operation. But the complete recovery was confirmed on the next day without significant complications. Therefore, we should avoid determining the recovery of finger circulation hastily and performing premature amputation of the fingertip.

Citation: Choi JH, Choi SY, Hwang JH, Kim KS, Lee SY. Finger compartment syndrome due to a high-pressure washer injury: A case report. *World J Clin Cases* 2023; 11(13): 3017-3021
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3017.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3017

INTRODUCTION

Compartment syndrome is a pathologic condition in which blood circulation to tissues is impaired due to increased pressure in the closed osteofascial compartment[1]. High pressure in the compartment leads to increased interstitial fluid pressure, capillary bed stenosis, decreased perfusion into tissues, and cell death[1]. This causes not only severe pain and swelling, but also tissue necrosis and functional morbidity. The most common cause of compartment syndrome is trauma, and other causes include burn, muscle overuse, infection and snake bites[1,2].

In the finger, two neurovascular bundles on the radial and ulnar sides of fingers are confined by the digital cutaneous ligament, Cleland's ligament, and Grayson's ligament[3]. Severe swelling of the finger compresses the neurovascular bundles in a limited space and blocks the blood flow of the fingers, causing necrosis of the fingertips. Although finger compartment syndrome is not common, finger fasciotomy through midlateral release of the finger can achieve decompression of the finger compartment[2]. Here, we report a case of compartment syndrome in a finger injury caused by a high-pressure water flow system commonly used at car washing stations.

CASE PRESENTATION

Chief complaints

A 60-year-old man injured his right middle finger while using a high-pressure washer at a car washing station.

History of present illness

The middle finger was penetrated by high-pressure stream from a 2 mm nozzle of a high-pressure washer. The patient complained of severe pain in his middle finger and was admitted to the emergency room four hours after the injury. There was a 0.2 cm puncture wound on the volar side of the distal phalangeal joint of the middle finger, and the fingertip was pale and numb (Figure 1A). The water flow pressure of the high-pressure washer was 140 bar.

History of past illness

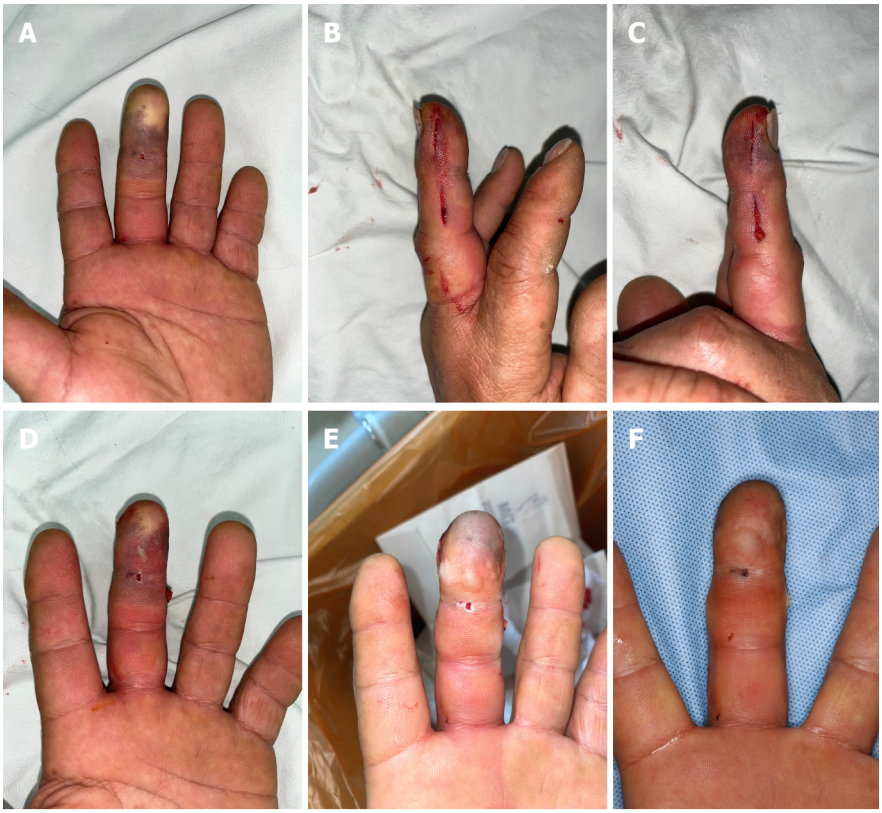
The patient had a 90-pack-year smoking history without other underlying diseases.

Personal and family history

The patient had no other relevant personal and family history.

Physical examination

Severe swelling and a limited range of motion were observed. Since the middle finger showed negative results in the capillary refill test and the pinprick test, finger fasciotomy was immediately performed (Figure 1B and C).



DOI: 10.12998/wjcc.v11.i13.3017 **Copyright** ©The Author(s) 2023.

Figure 1 Clinical course of finger compartment syndrome. A 60-year-old man was diagnosed with compartment syndrome in the right middle finger with an 0.2 cm penetrating wound on the distal phalangeal joint. A: Preoperative photograph showing the pale and tense distal phalanx in the middle finger; B and C: Finger fasciotomy on the radial and ulnar sides of the middle finger; D: Immediate postoperative photograph showing incomplete recovery of the fingertip; E: First-day postoperative photograph showing no further recovery at the middle fingertip; F: Third-day postoperative photograph showing complete recovery at the middle fingertip.

Laboratory examinations

No laboratory examinations were performed.

Imaging examinations

Finger radiography showed that there was no fracture in the finger.

FINAL DIAGNOSIS

The final diagnosis was the compartment syndrome in finger injury.

TREATMENT

Incisions were performed on both lateral midlines in the distal and middle phalanx, and digital compartment decompression was achieved. After fasciotomy, an improvement in capillary perfusion was observed in the fingertip, but without complete recovery (Figure 1D).

OUTCOME AND FOLLOW-UP

On the first day after surgery, the fingertip was still pale, swollen, and numb (Figure 1E). The capillary refill test and pinprick test were also negative and the patient requested amputation of the fingertip because he did not want the treatment period to be prolonged. However, we proposed delaying amputation for a few days because there was a possibility that the blood flow would improve after fasciotomy and the boundary of necrosis was not yet demarcated. On the second day after surgery, the color of the fingertip returned to pink, swelling was resolved, and the range of motion returned to

normal. The sensation of the fingertip was completely restored. The pinprick test was positive, and the capillary refill test time was normal (*i.e.*, within 2 s). The patient was discharged on the third day after surgery (Figure 1F). After two weeks, the patient recovered without complications, and the fasciotomy incision sites underwent wound healing by secondary intention.

DISCUSSION

Compartment syndrome is caused by increased interstitial tissue pressure due to intrinsic or extrinsic factors. This increased pressure causes progressive arteriole collapse and local tissue hypoxia. If this condition continues without appropriate treatment, it can lead to loss of function, limb, or life[2,4]. The most common cause of compartment syndrome is traumatic injury associated with crushing-type mechanisms[2]. However, few studies have investigated acute compartment syndrome of the fingers and presented data on its prevalence[5]. In this case, compartment syndrome occurred in the middle finger without fracture due to a crushing injury caused by a high-pressure washer.

Although the compartment pressure may be helpful for diagnosis, consensus on the threshold is still lacking. However, McQueen *et al*[6] reported that the difference between tissue pressure and perfusion pressure can be a useful clinical marker. Codding *et al*[7] recommended that the hand compartment be released when the tissue pressure is within 30 mmHg of the patient's diastolic blood pressure. The "5 P's" are often associated with compartment syndrome: Pain, paleness, paresthesia, lack of pulse, and paralysis. These 5 P's are used as a routine evaluation method as a clinical feature of compartment syndrome for diagnosis[2]. In our case, the patient's compartment syndrome symptoms were clear, but it would have been better to check the tissue pressure to obtain objective results.

Since digital neurovascular bundles are limited by the finger skin ligaments, Cleland's ligaments, and Grayson's ligaments, excessive finger swelling can constrict the neurovascular bundles in this space[3]. Cleland's ligaments are located dorsal to the digital blood vessels and nerves, and Grayson's ligaments are located volar to these structures[8]. These ligaments provide stability to the digits, and protect the digital blood vessels and nerves. However, these ligaments need to be released when finger compartment syndrome is diagnosed.

Digital decompression is an operation to release Cleland's ligament through a midaxial incision of the phalanx[4]. During operation, care must be taken with the skin incision to avoid iatrogenic injury to the neurovascular bundles. Ischemic damage in the muscle area can recover within 4 h, but irreversible damage remains if the interval until treatment exceeds 8 h. Therefore, for a better prognosis in treatment of compartment syndrome treatment, not delaying treatment is important[9]. In this case, fasciotomy was performed 4 h after the injury, but recovery was not clear until the first day after surgery. The patient was convinced of necrosis of the fingertip on the first day after surgery. Because the patient did not want to prolong the treatment period, he urged the medical staff to amputate the distal phalanx prematurely. However, complete recovery was observed on the second day.

The relationship between the degree of injury and recovery time has not been reported in fingertip compartment syndrome. However, in this case, proper digital decompression was performed, and complete recovery was confirmed on the second day after surgery. It would not be an appropriate judgement to hastily evaluate the recovery of finger circulation and perform premature amputation of the fingertip.

CONCLUSION

Fingertip compartment syndrome can be caused by high-pressure water flow damage to the fingers when using a high-pressure washer at a car washing station. To avoid finger necrosis, a rapid diagnosis of finger compartment syndrome and digital decompression are essential.

FOOTNOTES

Author contributions: Choi JH and Choi SY contributed to manuscript writing and data collection; Hwang JH and Kim KS contributed to editing and conceptualization; Lee SY contributed to supervision; All authors have read and approved the final manuscript.

Informed consent statement: Written informed consent was obtained from the patient for the publication of this case report.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: South Korea

ORCID number: Jun Ho Choi 0000-0002-4848-517X; Seung Yeon Choi 0000-0002-7829-0875; Jae Ha Hwang 0000-0001-6992-8067; Kwang Seog Kim 0000-0002-6766-4640; Sam Yong Lee 0000-0002-3185-2519.

S-Editor: Liu GL
L-Editor: A
P-Editor: Liu GL

REFERENCES

1 **Oak NR**, Abrams RA. Compartment Syndrome of the Hand. *Orthop Clin North Am* 2016; **47**: 609-616 [PMID: 27241383 DOI: 10.1016/j.ocl.2016.03.006]
2 **Leversedge FJ**, Moore TJ, Peterson BC, Seiler JG 3rd. Compartment syndrome of the upper extremity. *J Hand Surg Am* 2011; **36**: 544-59; quiz 560 [PMID: 21371631 DOI: 10.1016/j.jhsa.2010.12.008]
3 **Zwanenburg RL**, Werker PM, McGrouther DA. The anatomy and function of Cleland's ligaments. *J Hand Surg Eur Vol* 2014; **39**: 482-490 [PMID: 24305724 DOI: 10.1177/1753193413511944]
4 **Rubinstein AJ**, Ahmed IH, Vosbikian MM. Hand Compartment Syndrome. *Hand Clin* 2018; **34**: 41-52 [PMID: 29169596 DOI: 10.1016/j.hcl.2017.09.005]
5 **Schwartz-Fernandes F**, McDermott E, Culp J. Crush Injury-induced Finger Compartment Syndrome: A Case Report and Literature Review. *Cureus* 2020; **12**: e7509 [PMID: 32373412 DOI: 10.7759/cureus.7509]
6 **McQueen MM**, Gaston P, Court-Brown CM. Acute compartment syndrome. Who is at risk? *J Bone Joint Surg Br* 2000; **82**: 200-203 [PMID: 10755426]
7 **Codding JL**, Vosbikian MM, Ilyas AM. Acute compartment syndrome of the hand. *J Hand Surg Am* 2015; **40**: 1213-6; quiz 1216 [PMID: 25801580 DOI: 10.1016/j.jhsa.2015.01.034]
8 **de-Ary-Pires B**, Valdez CF, Shecaira AP, de Ary-Pires R, Ary Pires-Neto M. Cleland's and Grayson's ligaments of the hand: a morphometrical investigation. *Clin Anat* 2007; **20**: 68-76 [PMID: 17080463 DOI: 10.1002/ca.20241]
9 **Donaldson J**, Haddad B, Khan WS. The pathophysiology, diagnosis and current management of acute compartment syndrome. *Open Orthop J* 2014; **8**: 185-193 [PMID: 25067973 DOI: 10.2174/1874325001408010185]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3022-3028

DOI: 10.12998/wjcc.v11.i13.3022

ISSN 2307-8960 (online)

CASE REPORT

Primary dedifferentiated chondrosarcoma of the lung with a 4-year history of breast cancer: A case report

Huan Wen, Feng-Jie Gong, Jian-Min Xi

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ralic M, North Macedonia; Tangsuwanaruk T, Thailand

Received: November 7, 2022
Peer-review started: November 7, 2022
First decision: January 20, 2023
Revised: February 3, 2023
Accepted: March 31, 2023
Article in press: March 31, 2023
Published online: May 6, 2023

Huan Wen, Jian-Min Xi, Department of Pathology, Hunan Provincial Hospital of Integrated Traditional Chinese and Western Medicine, Changsha 410006, Hunan Province, China

Feng-Jie Gong, Department of Radiology, Hunan Provincial Hospital of Integrated Traditional Chinese and Western Medicine, Changsha 410006, Hunan Province, China

Corresponding author: Jian-Min Xi, MD, Associate Chief Physician, Department of Pathology, Hunan Provincial Hospital of Integrated Traditional Chinese and Western Medicine, No. 58 Lushan Road, Changsha 410006, Hunan Province, China. xijianmin@qq.com

Abstract

BACKGROUND

Primary dedifferentiated chondrosarcoma (DDCS) of the lung is extremely rare and has a poor prognosis, especially in patients with a history of carcinomas and related treatment. Herein, we report a case of primary DDCS of the lung in a patient with a 4-year history of breast cancer and related treatment.

CASE SUMMARY

A 49-year-old woman was admitted to our hospital with complaints of headache, dizziness, slurred speech, and dyskinesia in May 2021. Computed tomography (CT) examinations showed multiple nodules in the brain, vertebral body, and both lungs with multiple enlarged lymph nodes in the right hilum and mediastinum, which were considered metastases of breast cancer. No obvious mass was discovered in the right hilum. After several months of related administration, the patient's headache disappeared, and her condition improved. However, new problems of asthma, dyspnea, cough, and restricted activity appeared in late November 2021. Although the CT scan indicated that the lesions in the brain, lung, and vertebral body had shrunk or disappeared, a soft tissue density lesion appeared in her right hilum and blocked the bronchial lumen. To relieve her dyspnea, part of the mass was resected, and a stent was placed *via* fiberoptic bronchoscopy. Following a complete pathological examination of the tumor, it was confirmed to be a primary DDCS of the lung. The patient then received two rounds of systemic chemotherapy with a regimen of cisplatin + ifosfamide + doxorubicin hydrochloride liposome, palliative radiotherapy for the tumor in her right lung, and four cycles of systemic chemotherapy and targeted therapy with a regimen of temozolomide combined with bevacizumab successively. She was in stable condition after the completion of the systemic chemotherapy and targeted therapy but underwent rapid progression after lung

radiotherapy. The CT examinations showed multiple nodules in the brain and in both lungs, and the tumor in the right hilum was increased in size.

CONCLUSION
This case revealed a rare primary DDCS of the lung with a medical history of breast cancer, meaning a worse prognosis and making it more difficult to treat.

Key Words: Dedifferentiated chondrosarcoma; Lung; Chemotherapy; Radiotherapy; Breast cancer; Case report

Core Tip: Dedifferentiated chondrosarcoma (DDCS) is a rare and high-grade malignant tumor. Here, we report a case of primary DDCS of the lung with a 4-year history of breast cancer and related treatment, which is extremely rare and easily misdiagnosed. It lacks a specific clinical manifestation and a precise imaging diagnosis. Thus, an additional pathological examination is beneficial. In addition, we found that radiotherapy accelerates the progression of DDCS. Altogether, this case created a more comprehensive understanding of this tumor and will provide a reference for future diagnosis, treatment, and prognosis estimations.

Citation: Wen H, Gong FJ, Xi JM. Primary dedifferentiated chondrosarcoma of the lung with a 4-year history of breast cancer: A case report. *World J Clin Cases* 2023; 11(13): 3022-3028
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3022.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3022

INTRODUCTION

Dedifferentiated chondrosarcoma (DDCS) is a tumor with a high degree of malignancy, poor curative effect, easy recurrence, and metastasis. Further, it is insensitive to chemoradiotherapy[1,2]. It usually occurs in people aged 40–60 years and is more common in males. The most common locations of DDCS are the femur and pelvis. It mainly manifests as localized pain, limited activity, and rapid enlargement of the mass. DDCS occurring outside the bone is extremely rare. Although primary DDCSs outside the bone have been observed in the lung[1-5], orbit[6], pleura[7], and throat[8], they were individual cases, and there are only four cases of DDCS occurring in the lung. Here, we present a case of primary DDCS of the lung with a 4-year history of breast cancer and related treatment.

CASE PRESENTATION

Chief complaints

A 49-year-old woman was admitted to our hospital to be evaluated due to headaches, dizziness, slurred speech, and dyskinesia on May 7, 2021.

History of present illness

The patient's symptoms started approximately 2 wk ago.

History of past illness

The patient had a 4-year history of invasive ductal cancer of the left breast and underwent surgery, adjuvant chemoradiotherapy, and endocrine therapy. The specific circumstances are unclear. There is no additional remarkable past medical history about the patient.

Personal and family history

No specific cancer history was recorded on her pedigree.

Physical examination

During admission, she was pale, weak, and walking unsteadily. The other physical examinations were normal.

Laboratory examinations

Tumor-related biomarkers, including carcinoembryonic antigen, carbohydrate antigen (CA) 125, and CA199, were within the normal ranges. Other laboratory indicators were generally normal or slightly abnormal.

Imaging examinations

In May 2021, the computed tomography (CT) examinations showed multiple nodules in the brain, vertebral body, and both lungs, with multiple enlarged lymph nodes in the right hilum and mediastinum, which were considered metastases of breast cancer. No obvious mass was seen in the right hilum of the lung (Figure 1A and B). Subsequently, the patient was subjected to four cycles of systemic chemotherapy [Abraxane 260 mg/m^2 intravenously (IV) on day 1 of a 21-d cycle] combined with targeted therapy (Bevacizumab 15 mg/kg IV on day 1 of a 21-d cycle), endocrine therapy (oral Exemestane tablet 25 mg once a day), and palliative radiotherapy for the brain metastasis successively. After administration, the patient's headache disappeared, and her condition improved. However, she was admitted to our hospital again due to the occurrence of asthma, dyspnea, cough, and restricted activity in late November 2021. The CT scan indicated that the lesions in the patient's brain, lung, and vertebral body had shrunk or disappeared, but a soft tissue density lesion appeared at her right hilum of the lung and blocked the bronchial lumen (Figure 1C and D).

Histological findings

Since the patient presented symptoms of obvious dyspnea, a fiberoptic bronchoscopy was performed, part of the mass was resected, and a stent was placed. The collected specimen was sent for pathological examination. Histologically, the three pieces of gray and taupe tissue of the right lung (2.5 cm × 2 cm × 1.8 cm in size) showed two kinds of tumor components. One part was a well-differentiated chondrosarcoma—the tumor cells were round or oval, with mild atypia, a mitotic appearance, thin cytoplasm, and cartilaginous pits. The other part was a poorly differentiated sarcoma—the tumor cells were fusiform, large atypia, rich in tumor giant cells, and mitotic images. In addition, the two tumor components were well demarcated without transition and with hemorrhage and necrosis (Figure 2A–D). Immunohistochemistry staining showed that the tumor cells in both parts were positive for Vimentin, negative for Cytokeratin, and with a mutated p53 gene. S-100 tested positive in the chondrosarcoma, and h-Caldesmon, smooth muscle actin, cluster of differentiation antigen (CD) 99, and CD68 were partly positive in the dedifferentiated sarcoma (Figure 2E–H). The positive rate of Ki67 in the dedifferentiated sarcoma was approximately 30%.

FINAL DIAGNOSIS

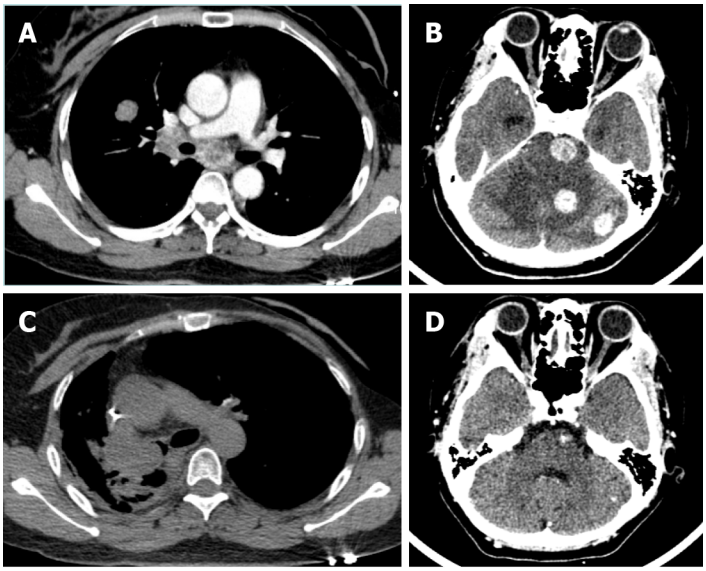
Since careful clinical and radiologic examinations showed no evidence of further bone tumor, the tumor was confirmed to be a primary DDCS of the lung after a complete histologic preparation and examination.

TREATMENT

The patient was diagnosed with DDCS of the lung in early December 2021. Subsequently, systemic chemotherapy was administrated for the patient with a regimen of cisplatin (75 mg/m^2 IV on day 1 of a 21-d cycle) + ifosfamide (2 g IV on day 1 to 3 of a 21-d cycle) + doxorubicin hydrochloride liposome (40 mg/m^2 IV on day 1 of a 21-d cycle) in December 2021 and January 2022. Since the patient continued to suffer from asthma, palliative radiotherapy for the tumor in her right lung was performed in February 2022. She recently underwent chemotherapy and targeted therapy with a regimen of temozolomide (150 mg/m^2 IV on days 1–5 of a 28-d cycle) combined with bevacizumab (7.5 mg/kg IV on day 1 of a 14-d cycle) from April to July 2022.

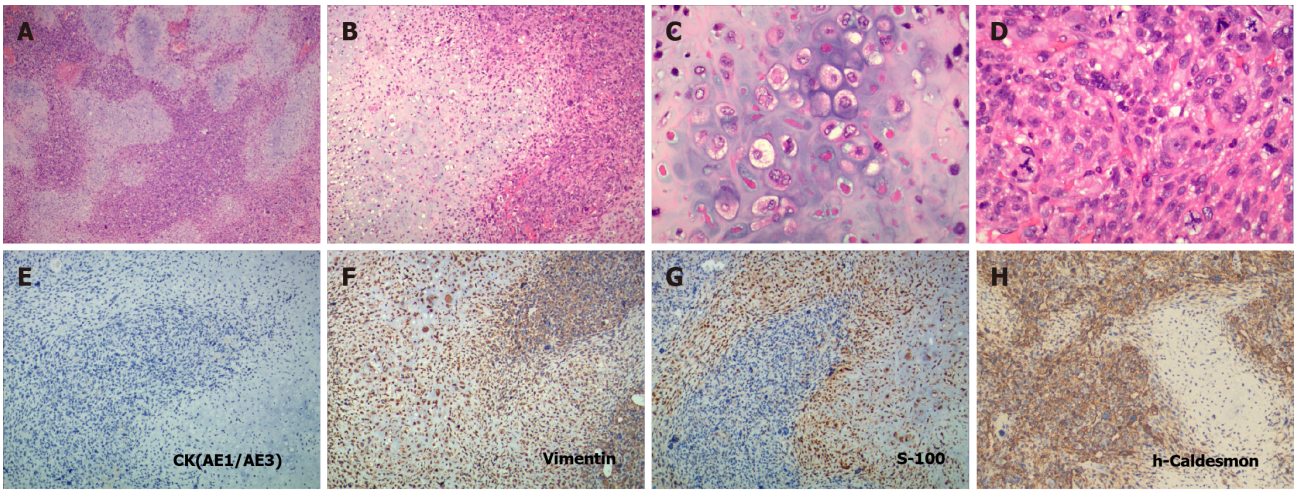
OUTCOME AND FOLLOW-UP

The patient was in a stable condition when two cycles of chemotherapy with a regimen of cisplatin + ifosfamide + doxorubicin hydrochloride liposome were completed. However, her condition significantly worsened after 30 sessions of radiation therapy for the tumor in her right lung. The CT examinations showed multiple nodules in the brain and both lungs, and the tumor in the right hilum of the lung was increased in size. It was considered a progressive disease based on the response evaluation criteria for solid tumors. Subsequently, she received four cycles of chemotherapy and targeted therapy with a regimen of temozolomide combined with bevacizumab. Her condition was stable, and the CT result of



DOI: 10.12998/wjcc.v11.i13.3022 **Copyright** ©The Author(s) 2023.

Figure 1 Computed tomography findings of the patient's lungs and brain. A: Computed tomography (CT) examination in May 2021 showed that there was a space-occupying lesion in the lung lobe, and no obvious mass was seen in the right hilum; B: CT examination in May 2021 showed three intracranial space-occupying lesions; C: CT examination in November 2021 showed a soft tissue mass in the right hilum, blocking the bronchial lumen; D: CT examination in November 2021 indicated that the nodules in the brain had shrunk or disappeared.



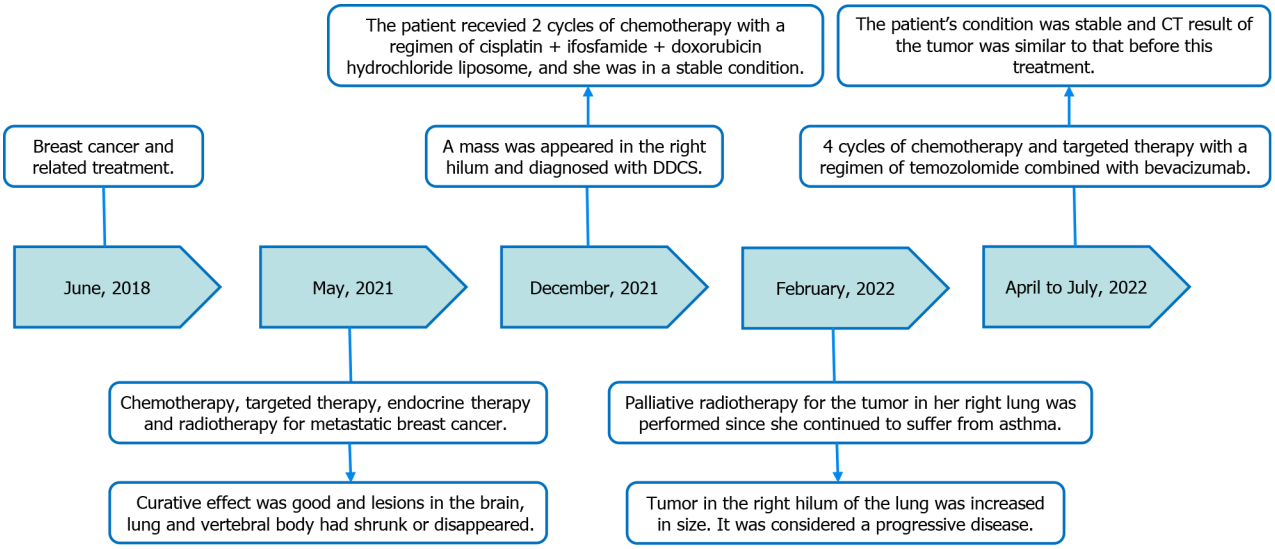
DOI: 10.12998/wjcc.v11.i13.3022 **Copyright** ©The Author(s) 2023.

Figure 2 Histopathologic and immunohistochemical observation of the right hilum mass. A and B: Dedifferentiated chondrosarcoma under low magnification and medium magnification, respectively, showed the tumors characterized by the following two distinct histopathologic components: a low-grade chondrosarcoma region sharply juxtaposed with a high-grade noncartilaginous sarcoma component; C: Typical low-grade chondrosarcoma region; D: Typical high-grade dedifferentiated sarcoma region; E: Negative expression of epithelial marker Cytokeratin in dedifferentiated chondrosarcoma (DDCS); F: Positive expression of mesenchymal marker Vimentin in DDCS; G: Positive expression of S-100 in low-grade chondrosarcoma region; H: Expression of h-Caldesmon in high-grade dedifferentiated sarcoma region, suggesting that the dedifferentiated sarcoma may have smooth muscle cell differentiation (A to D: Hematoxylin and eosin staining, A: × 40, B: × 100, C and D: × 400; E to H: Immunohistochemical staining, × 100).

the tumor was similar to that before this treatment. No additional follow-up information was obtained from the patient at the time of manuscript writing. The timeline summarizing the main treatment and outcome of this case report is shown in Figure 3.

DISCUSSION

Regarding the origin of DDCS, there are two theories. Most studies believe that DDCS is derived from the differentiation of a stem cell with multi-directional differentiation potential, while others hold that it is differentiated from two different types of tumor cells independently, which is controversial[9-11].



DOI: 10.12998/wjcc.v11.i13.3022

Figure 3 Timeline summarizing the main treatment and outcome of this case report. CT: Computed tomography; DDCS: Dedifferentiated chondrosarcoma.

Regarding molecular genetics, Yang *et al*[11] reported that isocitrate dehydrogenase (IDH) 1 and IDH2 were mutated in chondrosarcoma and had the same mutation in both components of DDCS, but there was no mutation in other mesenchymal tumors, which also supported that the tumor may originate from the same primary mesenchymal cells.

DDCS often presents a "biphasic sign" on CT, meaning it has the characteristics of soft tissue sarcoma and punctate and annular calcifications of chondrosarcoma in the same tumor. Histologically, the tumor is composed of the following two components: chondrosarcoma is usually grade I–II, and dedifferentiated sarcoma is high-grade spindle cell sarcoma with obvious atypia and frequent mitotic figures, which commonly include malignant fibrous histiocytoma, pleomorphic undifferentiated sarcoma, osteosarcoma, fibrosarcoma, rhabdomyosarcoma, *etc*. In terms of immunohistochemistry, chondrosarcoma components express the S-100 protein, and dedifferentiated components express corresponding sarcoma markers. In this case, the CT examination did not show punctate and annular calcifications, which are characteristic of chondrosarcoma, but instead, showed soft tissue density lesions. However, the pathological examination showed that the tumor is characterized by the following two distinct histopathologic components: A low-grade chondrosarcoma region sharply juxtaposed with a high-grade noncartilaginous sarcoma component, which correlated with the diagnosis of DDCS. Meanwhile, immunohistochemical expression of the tumor also supported this conclusion. Since the patient had a history of breast cancer and related treatment, if there were metaplastic cancer components in the breast tumor tissue, then the DDCS of the lung may have been transferred from the previous breast metaplastic carcinoma. Therefore, we reviewed her previous pathological sections of breast cancer but found no metaplastic cancer component and excluded the possibility of breast cancer metastasis. Furthermore, there was no evidence of further bone tumor according to the imaging examinations; therefore, we believe the tumor was a primary DDCS of the lung.

At present, surgical treatment remains the preferred choice for DDCS. Those who don't have the opportunity for surgery can be treated with radiotherapy and chemotherapy. However, most scholars believe that DDCS is radiation resistant, and radiotherapy often has no obvious effect. Some scholars even found that DDCS after radiotherapy reduces the stability of tumor cells and deletes the PTEN gene, which promotes the proliferation potential of tumor cells[12]. The use of chemotherapy in the treatment of DDCS remains controversial, but most scholars believe that it has no obvious effect[13]. However, some scholars believe that when the dedifferentiated components are sensitive to chemotherapy and the patient's physical condition is good, additional chemotherapy can be considered [14,15]. Recent research found that a combination of surgery and chemotherapy showed a trend toward higher overall survival in non-metastatic patients with DDCS[16]. Therefore, whether to perform chemotherapy or radiotherapy should be determined by the physicians according to the specific condition of the patient. In this case, the patient was considered to have metastatic breast cancer. She had undergone relevant chemoradiotherapy, targeted therapy, and endocrine therapy. This caused the masses in the brain, vertebral body, and the other lung to shrink and disappear, but the hilar mass appeared and grew rapidly. After a diagnostic confirmation of DDCS, the patient received two rounds of systemic chemotherapy with a regimen of cisplatin + ifosfamide + doxorubicin hydrochloride liposome and four rounds of chemotherapy and targeted therapy with a regimen of temozolomide combined with bevacizumab successively. Consequently, her condition remains stable. The therapies of

the patient in the present case were changed several times due to the diagnosis change and intolerance to chemotherapy; however, their effectiveness was unclear. Thus, whether the chemoradiotherapy suppressed the progression of DDCS is still unknown and must be investigated by further studies. These are the limitations of this rare case. The patient also underwent palliative radiotherapy for the tumor, which to the progression of the disease, meaning radiotherapy probably plays a negative role in the development of DDCS. Molecular targeted therapy for DDCS is still under study, and it has been reported that immunotherapy was effective for the tumor which is programmed death-ligand 1-positive [17].

The case of a primary DDCS of the lung with a 4-year history of breast cancer and related treatment is extremely rare. It lacks a specific clinical manifestation to distinguish it from other lung tumors, and the CT examination may not clearly show the "biphasic sign" characteristic. Moreover, when the tumor occurs in a patient who has a history of another malignant tumor, it is easily considered a recurrence or metastasis of the previous tumor by the oncologist, which results in misdiagnosis. Thus, clinical findings, image examination and pathological examination are indispensable to further confirm the DDCS and improve the recognition of this tumor.

CONCLUSION

In conclusion, DDCS is an extremely rare and high-grade malignant tumor. The tumor has a worse prognosis and more difficulties in treatment, especially in patients with a history of another carcinoma. Further, radiotherapy is likely to accelerate the progression of DDCS.

ACKNOWLEDGEMENTS

We thank the patient and her family for their support.

FOOTNOTES

Author contributions: Wen H contributed to manuscript writing, editing and data collection; Gong FJ contributed to data analysis; Xi JM contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

Informed consent statement: Written informed consent was obtained from the patient for the publication of this case report.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Huan Wen 0000-0001-6056-6979; Feng-Jie Gong 0000-0002-5092-862X; Jian-Min Xi 0000-0001-9657-7901.

S-Editor: Liu GL
L-Editor: A
P-Editor: Liu GL

REFERENCES

1 **Li XF**, Zhou HB, Zhao XL, Dai F, Li T, Wang L, Xu WM. [Primary dedifferentiated chondrosarcoma of lung: report of a case]. *Zhonghua Binglixue Zazhi* 2011; **40**: 127-128 [PMID: 21426817]

2 **Gusho CA**, Lee L, Zavras A, Seikel Z, Miller I, Colman MW, Gitelis S, Blank AT. Dedifferentiated Chondrosarcoma: A Case Series and Review of the Literature. *Orthop Rev (Pavia)* 2022; **14**: 35448 [PMID: 35769663 DOI: 10.52965/001c.35448]

3 **Boueiz A**, Abougergi MS, Noujeim C, Bousamra A, Sfeir P, Zaatari G, Bou-Khalil P. Primary dedifferentiated chondrosarcoma of the lung. *South Med J* 2009; **102**: 861-863 [PMID: 19593290 DOI: 10.1097/SMJ.0b013e3181ad6236]

4 **Steurer S**, Huber M, Lintner F. Dedifferentiated chondrosarcoma of the lung: case report and review of the literature. *Clin Lung Cancer* 2007; **8**: 439-442 [PMID: 17681099 DOI: 10.3816/CLC.2007.n.030]

5 **Kawano D**, Yoshino I, Shoji F, Ito K, Yano T, Maehara Y. Dedifferentiated chondrosarcoma of the lung: report of a case. *Surg Today* 2011; **41**: 251-254 [PMID: 21264763 DOI: 10.1007/s00595-009-4240-1]

6 **Qi XM**, Zhang RR. Orbital soft tissue dedifferentiated chondrosarcoma: a case report. *Zhonghua Yixue Zazhi* 2021; **101**: 667-668 [DOI: 10.3760/cma.j.cn112137-20200812-02358]

7 **Liu Y**, He CY, Liu J. Pleural dedifferentiate chondrosarcoma case. *Fangshexue Shijian* 2021; **4**: 279-280 [DOI: 10.13609/j.cnki.1000-0313.2021.02.026]

8 **Fidai SS**, Ginat DT, Langerman AJ, Cipriani NA. Dedifferentiated Chondrosarcoma of the Larynx. *Head Neck Pathol* 2016; **10**: 345-348 [PMID: 26718693 DOI: 10.1007/s12105-015-0676-3]

9 **Bovée JV**, Cleton-Jansen AM, Rosenberg C, Taminiau AH, Cornelisse CJ, Hogendoorn PC. Molecular genetic characterization of both components of a dedifferentiated chondrosarcoma, with implications for its histogenesis. *J Pathol* 1999; **189**: 454-462 [PMID: 10629543 DOI: 10.1002/(SICI)1096-9896(199912)189:4<454::AID-PATH467>3.0.CO;2-N]

10 **Meijer D**, de Jong D, Pansuriya TC, van den Akker BE, Picci P, Szuhai K, Bovée JV. Genetic characterization of mesenchymal, clear cell, and dedifferentiated chondrosarcoma. *Genes Chromosomes Cancer* 2012; **51**: 899-909 [PMID: 22674453 DOI: 10.1002/gcc.21974]

11 **Yang T**, Bai Y, Chen J, Sun K, Luo Y, Huang W, Zhang H. Clonality analysis and IDH1 and IDH2 mutation detection in both components of dedifferentiated chondrosarcoma, implicated its monoclonal origin. *J Bone Oncol* 2020; **22**: 100293 [PMID: 32742915 DOI: 10.1016/j.jbo.2020.100293]

12 **Gao L**, Hong X, Guo X, Cao D, Gao X, DeLaney TF, Gong X, Chen R, Ni J, Yao Y, Wang R, Chen X, Tian P, Xing B. Targeted next-generation sequencing of dedifferentiated chondrosarcoma in the skull base reveals combined TP53 and PTEN mutations with increased proliferation index, an implication for pathogenesis. *Oncotarget* 2016; **7**: 43557-43569 [PMID: 27248819 DOI: 10.18632/oncotarget.9618]

13 **Cranmer LD**, Chau B, Mantilla JG, Loggers ET, Pollack SM, Kim TS, Kim EY, Kane GM, Thompson MJ, Harwood JL, Wagner MJ. Is Chemotherapy Associated with Improved Overall Survival in Patients with Dedifferentiated Chondrosarcoma? *Clin Orthop Relat Res* 2022; **480**: 748-758 [PMID: 34648466 DOI: 10.1097/CORR.0000000000002011]

14 **Dhinsa BS**, DeLisa M, Pollock R, Flanagan AM, Whelan J, Gregory J. Dedifferentiated Chondrosarcoma Demonstrating Osteosarcomatous Differentiation. *Oncol Res Treat* 2018; **41**: 456-460 [PMID: 29902785 DOI: 10.1159/000487803]

15 **Mavrogenis AF**, Ruggieri P, Mercuri M, Papagelopoulos PJ. Dedifferentiated chondrosarcoma revisited. *J Surg Orthop Adv* 2011; **20**: 106-111 [PMID: 21838071]

16 **Gonzalez MR**, Bryce-Alberti M, Portmann-Baracco A, Inchaustegui ML, Castillo-Flores S, Pretell-Mazzini J. Appendicular dedifferentiated chondrosarcoma: A management and survival study from the SEER database. *J Bone Oncol* 2022; **37**: 100456 [PMID: 36246299 DOI: 10.1016/j.jbo.2022.100456]

17 **Singh A**, Thorpe SW, Darrow M, Carr-Ascher JR. Case report: Treatment of metastatic dedifferentiated chondrosarcoma with pembrolizumab yields sustained complete response. *Front Oncol* 2022; **12**: 991724 [PMID: 36465334 DOI: 10.3389/fonc.2022.991724]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3029-3037

DOI: 10.12998/wjcc.v11.i13.3029

ISSN 2307-8960 (online)

CASE REPORT

Importance of proper ventilator support and pulmonary rehabilitation in obese patients with heart failure: Two case reports

Eun-Hee Lim, Sung-Hee Park, Yu Hui Won

Specialty type: Rehabilitation

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Hasabo EA, Sudan

Received: November 15, 2022
Peer-review started: November 15, 2022
First decision: February 17, 2023
Revised: February 26, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 6, 2023

Eun-Hee Lim, Physical Medicine and Rehabilitation, Jeonbuk National University Medical School, Jeonju 54907, South Korea

Sung-Hee Park, Yu Hui Won, Department of Physical Medicine and Rehabilitation, Jeonbuk National University Medical School, Jeonju 54907, South Korea

Sung-Hee Park, Yu Hui Won, Research Institute of Clinical Medicine of Jeonbuk National University, Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju 54907, South Korea

Corresponding author: Yu Hui Won, MD, PhD, Professor, Department of Physical Medicine and Rehabilitation, Jeonbuk National University Medical School, 20 Geonjiro, Deokjin-gu, Jeonju, Jeonbuk 54907, South Korea. wonyh@jbnu.ac.kr

Abstract

BACKGROUND

The optimal treatment for heart failure (HF) is a combination of appropriate medications. Controlling the disease using only medical therapy is difficult in patients with HF, severe hypercapnia, and desaturation. These patients should first receive ventilator support followed by pulmonary rehabilitation (PR).

CASE SUMMARY

We report two cases in which arterial blood gas (ABG) improved and PR was possible with appropriate ventilator support. Two patients with extreme obesity complaining of worsening dyspnea–a 47-year-old woman and a 36-year-old man both diagnosed with HF–were hospitalized because of severe hypercapnia and hypoxia. Despite proper medical treatment, hypercapnia and desaturation resolved in neither case, and both patients were transferred to the rehabilitation department for PR. At the time of the first consultation, the patients were bedridden because of dyspnea. Oxygen demand was successfully reduced once noninvasive ventilation was initiated. As the patients' dyspnea gradually improved to the point where they could be weaned off the ventilator during the daytime, they started engaging in functional training and aerobic exercise. After 4 mo of follow-up, both patients were able to perform activities of daily living and maintain their lower body weight and normalized ABG levels.

CONCLUSION

Symptoms of patients with obesity and HF may improve once ABG levels are normalized through ventilator support and implementation of PR.

Key Words: Noninvasive ventilation; Heart failure; Obesity; Rehabilitation; Dyspnea; Case report

Core Tip: We describe two patients with heart failure (HF) and obesity who experienced respiratory failure, including hypercapnia and hypoxia. Neither patient demonstrated a significant response to pharmacological management; however, in both cases, symptoms improved with noninvasive ventilation, and they were able to return to their daily life. These findings suggest that in patients with obesity and HF who developed pulmonary hypertension and cor pulmonale may need to be treated for obesity hypoventilation and sleep apnea. The symptoms of these comorbidities may improve when arterial blood gas levels are normalized with appropriate ventilator support and pulmonary rehabilitation.

Citation: Lim EH, Park SH, Won YH. Importance of proper ventilator support and pulmonary rehabilitation in obese patients with heart failure: Two case reports. *World J Clin Cases* 2023; 11(13): 3029-3037
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3029.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3029

INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by shortness of breath, extreme fatigue, limb, and ankle swelling that are often accompanied by signs, including respiratory distress, gallop rhythm, and pulmonary edema. HF is most commonly caused by a structural or functional abnormality of the heart, resulting in increased intracardiac pressure and/or insufficient cardiac output at rest or during exercise [1]. HF may be classified as either acute or chronic depending on the time and speed of occurrence[2]. Acute HF refers to the rapid or gradual onset of symptoms and/or signs of HF that are sufficiently severe for the patient to seek urgent medical attention, leading to unplanned hospital admissions or emergency department visits[3,4]. Acute HF has a 1-year mortality rate of 20%–30% and an additional risk of hospitalization[5].

Pharmacological management is considered the optimal treatment for patients with acute HF[1]. However, in patients with HF and severe hypercapnia and desaturation, controlling the disease with medication alone is difficult. Appropriate ventilator support followed by pulmonary rehabilitation (PR) should be considered in such patients. Herein, we describe two patients with HF whose symptoms improved after arterial blood gas (ABG) levels normalized with the aid of noninvasive ventilation (NIV) without intubation, which was administered after medication and oxygen supply treatment proved ineffective due to severe hypercapnia.

CASE PRESENTATION

Chief complaints

Case 1: A 47-year-old woman with extreme obesity was admitted to the emergency department because of worsening dyspnea.

Case 2: A 36-year-old man with extreme obesity and chronic HF was admitted to the cardiology outpatient department because of worsening dyspnea.

History of present illness

Case 1: The patient visited the emergency room due to worsening dyspnea that had started 1 wk earlier, and systemic edema had worsened during the last 3 d. She was diagnosed with HF and admitted to the Department of Cardiology. Edema management was initiated because respiratory failure was suspected owing to the deterioration of her pulmonary edema. However, despite medical treatment, her hypercapnia and desaturation could not be reversed, and the patient was referred to the rehabilitation department for PR.

Case 2: The patient visited the emergency room because of worsening dyspnea, which had begun 2 wk earlier, and systemic edema. He was diagnosed with HF and admitted to the Department of Cardiology. He was alert at the time of hospitalization; however, he suddenly lost consciousness and was moved to the intensive care unit (ICU), where he was intubated and treated with mechanical ventilation. Therefore, edema management was initiated. However, despite medical treatment, an attempt to wean

him off the ventilator failed, his hypercapnia could not be reversed, and he was referred to our department for PR.

History of past illness

Case 1: The patient had a history of diabetes mellitus, hypertension (HTN), and chronic kidney disease (Table 1). She was also diagnosed with asthma, chronic HF, and pulmonary HTN within the previous year.

Case 2: The patient had a history of diabetes mellitus and HTN and had been diagnosed with HF approximately 6 mo prior to admission (Table 1).

Personal and family history

Case 1: The patient had no remarkable family history.

Case 2: The patient had no remarkable family history.

Physical examination

Case 1: On admission, the patient weighed 130 kg [body mass index (BMI): 48.63 kg/m^2). She was alert at the time of the first consultation, although her oxygen demand was high (15 L/min *via* an oxygen mask), and she was bedridden owing to dyspnea (Table 2).

Case 2: On admission, the patient's weight was 167.1 kg (BMI: 56.48 kg/m^2). The patient was alert at the time of the first consultation. He had undergone extubation 2 days earlier. His oxygen demand was high (10 L/min *via* a T-piece), and he was bedridden because of dyspnea (Table 2).

Laboratory examinations

Case 1: When the patient arrived at the emergency room, the ABG analysis (ABGA) results indicated severe hypercapnia: pH 7.307; pCO_2 97.1 mmHg; pO_2 73.3 mmHg; and SaO_2 93.2%. At the time of the consultation, her ABG levels still indicated hypercapnia: pH, 7.354; pCO_2 96.7 mmHg; pO_2 63.8 mmHg; and SaO_2 88.6% (Table 2).

Case 2: On ICU admission, his ABGA results indicated severe hypercapnia and hypoxemia: pH 7.148; pCO_2 110 mmHg; pO_2 79 mmHg; and SaO_2 91.7% (Table 2). At the time of the consultation, the patient's ABG levels still indicated hypercapnia: pH 7.351; pCO_2 74.9 mmHg; pO_2 103 mmHg, and SaO_2 97.5% (Table 2).

Imaging examinations

Case 1: Upon arrival at the emergency room, a chest radiograph indicated cardiomegaly (Figure 1A), and chest computed tomography (CT) revealed mosaic attenuation in both lungs and mild pericardial and pleural effusion. Transthoracic echocardiography (TTE) revealed a D-shaped left ventricle (LV) with normal LV systolic function (ejection fraction, 56%) and right ventricle (RV) dysfunction with severe tricuspid regurgitation due to coaptation failure, severe resting pulmonary HTN, RV dilatation (44 mm), right atrial enlargement, and a dilated main pulmonary artery (33 mm). These findings indicated resting pulmonary HTN deterioration compared to the TTE results that the patient had received 3 mo earlier (severe tricuspid regurgitation with moderate resting pulmonary HTN, RV dilatation (43 mm), right atrial enlargement).

Case 2: On ICU admission, chest radiography indicated cardiomegaly, pericardial effusion, and pulmonary interstitial edema with bilateral pleural effusion (Figure 1B). TTE revealed concentric LV hypertrophy, global hypokinesia with mild LV systolic dysfunction (ejection fraction, 47%), left atrial enlargement (48 mm), RV dysfunction with resting pulmonary HTN, diastolic dysfunction (grade 1), and mild pericardial effusion without hemodynamic significance. These findings indicated an aggravation of LV ejection fraction (57% → 47%), newly developed RV dysfunction with mild resting pulmonary HTN, and a decrease in LV end-diastolic pressure (15 → 11) compared to the TTE results that the patient had received 7 mo earlier. Chest CT revealed patchy consolidation with decreasing lung volume in the dependent portion of both lungs, an increase in heart size, and mild pericardial effusion. Therefore, the patient was diagnosed with aspiration pneumonia and cardiomegaly with a small pericardial effusion.

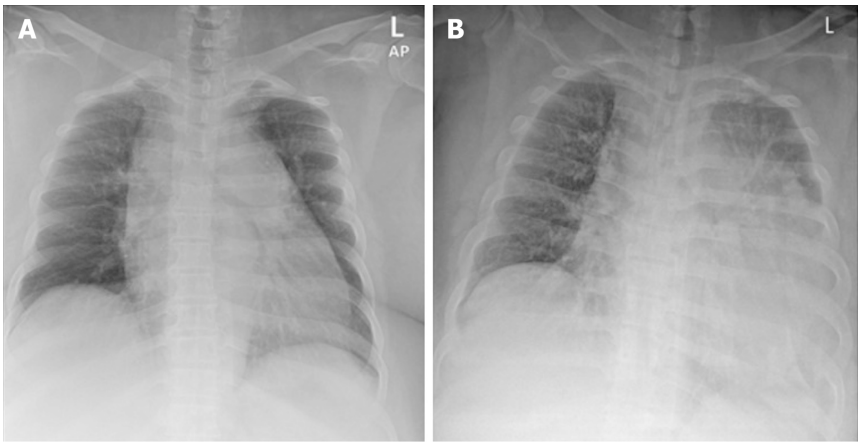
FINAL DIAGNOSIS

Both patients were diagnosed with HF and respiratory failure.

Table 1 Demographic data

	Case 1	Case 2
Age	47	36
Gender	F	M
Height (cm)	163.5	172
Weight (kg)	130	167.1
Body mass index (kg/m^2)	48.93	56.48
Past medical history		
Hypertension	O	O
Diabetes mellitus	O	O
Heart failure	O	O
Pulmonary hypertension	O	O
Cor pulmonale	O	×
Chronic kidney disease	O	×
Bronchial asthma	O	×

F: Female; M: Male.



DOI: 10.12998/wjcc.v11.i13.3029

Figure 1 Chest X-ray at admission. A: Patient 1, cardiomegaly; B: Patient 2, cardiomegaly, pericardial effusion, and pulmonary interstitial edema with pleural effusion on both sides.

TREATMENT

Case 1

NIV was initiated, and oxygen demand was gradually reduced (O_2 1–2 L). As the patient's dyspnea and hypercapnia/hypoxia gradually improved to the point where she could be weaned off the ventilator during the day, she began engaging in aerobic exercise and functional training. In the early stages, evaluation using a pulmonary function test was not possible because of the patient's severe dyspnea. When her status improved with the ventilation treatment, the pulmonary function test was finally performed and yielded a forced vital capacity (FVC) of 2.27 L (75% of predicted maximum) and a forced expiratory volume in the first second (FEV1) of 1.71 L (66% of predicted maximum), resulting to an FEV1/FVC of 75%.

Case 2

We changed the patient's treatment from mechanical ventilation to NIV because we expected long-term ventilator use after extubation. NIV was started immediately, and his oxygen demand was gradually reduced. At the time of discharge from the ICU, he was still bedridden because of dyspnea and required oxygen at a rate of 5 L/min (administered *via* a nasal prong) during the day; NIV was continued during

Table 2 Comparison of admission and discharge results

	Patient 1				Patient 2			
	Adm	RM consult	Discharge	F/U (4 mo)	Adm	RM consult	Discharge	F/U (4 mo)
Height (cm)	163.5	163.5	163.5	163.5	172	172	172	172
Weight (kg)	130	105.5	98.2	88	167.1	138.4	135.7	138
BMI	48.63	39.47	36.73	32.92	56.48	46.78	45.87	46.65
Noninvasive ventilation								
Mode			iVAPS	iVAPS			PCV	PCV
Setting			Target Va 8	Target Va 8			IPAP 19	IPAP 19
			PS 2-14	PS 2-14			EPAP 5	EPAP 5
			EPAP 4-10	EPAP 4-10				
O_2			4 L/min	4 L/min			4 L/min	4 L/min
Apply time			9 pm-7 am	9 pm-7 am			10 pm-6 am	10 pm-6 am
Daytime O_2	15 L/min	15 L/min	1.5L/min	None	10 L/min	10 L/min	None	None
(reserve mask)								
ABG test[1]								
pH	↓7.307	7.354	7.39	-	↓7.148	7.351	7.406	-
PCO_2 (mmHg)	↑97.1	↑96.7	↑51.7	-	↑110	↑74.9	37.7	-
PO_2 (mmHg)	↓73.3	↓63.8	↓72.3	-	↓79	103	97.3	-
SaO_2 (%)	93.2	88.6	94.3	-	91.7	97.5	98	-
Pulmonary function test								
PCF (L/min)	NT	NT	260	-	NT	340	370	510
FVC (L)	NT	NT	2.27	3.21	NT	NT	4.72 (102%)	4.64 (101%)
			-0.75	-0.95				
FEV_1 (L)	NT	NT	1.71	2.39	NT	NT	3.46 (101%)	2.76
			-0.66	-0.93				-0.81
FEV_1/FVC (%)	NT	NT	75	75	NT	NT	73	59
PEF (%)	NT	NT	72	-	NT	NT	84	56
6MWT	NT	NT	234 m	376 m	NT	389 m	480 m	549 m
AHI[2]	Not done						78.1/h	

[1]Measured in the morning (reflecting respiration values during sleep).
[2]Measured value use of polysomnography.
RM: Rehabilitation medicine; F/U: Follow up; BMI: Body mass index; NIV: Non-invasive ventilation; ABGA: Arterial blood gas analysis; PFT: Pulmonary function test; NT: Not testable; PCF: Peak cough flow; FVC: Forced vital capacity; FEV1: Forced expiratory volume in the first second; PEF: Peak expiratory flow; 6MWT: 6-minute walking test; AHI: Apnea/hypopnea index.

the night.

OUTCOME AND FOLLOW-UP

Case 1

At the time of discharge, the patient could move around with the aid of a walking device and only needed oxygen at a rate of 1.5 L/min during the day; ventilation continued, but only during the night. On the day of discharge, she performed a 6-minute walking test (6MWT), which yielded a 6MWT distance of 234 m; her weight at that point was 98.2 kg (BMI: 36.73 kg/m^2). The ABGA results indicated

hypercapnia, although her levels (pH 7.390; pCO_2 51.7 mmHg; pO_2 72.3 mmHg; and SaO_2 94.3%) improved compared to those at the last assessment. The patient was discharged and prescribed home ventilation and O_2 therapy.

The patient visited the outpatient department. She still relied on NIV during the night but did not need O_2 supply during the day. Her O_2 saturation in room air was ≥ 93%. The patient reported a subjective improvement in dyspnea, and the pulmonary function test also indicated improvements, with an FVC of 3.21 L (95% of predicted maximum), an FEV_1 of 2.39 L (93% of the predicted maximum), and an FEV_1/FVC ratio of 75%. The 6MWT distance measured at this visit was 376 m, and her weight was 88 kg (BMI: 32.92 kg/m^2). After 4 mo of follow-up, the patient returned to work while performing activities of daily living independently, maintaining her body weight with aerobic exercises, and relying on NIV only during the night.

Case 2

As the patient's dyspnea gradually improved, he started engaging in aerobic exercises. In the early stages, a pulmonary function test could not be performed because of severe dyspnea. When his respiratory function had improved, he finally underwent the test, which yielded an FCV of 4.72 L (102% of predicted maximum), an FEV_1 of 3.46 L (101% of predicted maximum), and thus an FEV_1/FVC of 73%. The patient expressed an interest in active rehabilitation treatment and was therefore transferred to our department. At the time of transfer to the rehabilitation department, he did not rely on additional oxygen during the day and used NIV only at night.

Polysomnography was performed because we observed desaturation during sleep, and the use of NIV was maintained during sleep because of the patient's severe obstructive sleep apnea (AHI 78.1/h). He engaged in aerobic exercises on an ergometer and treadmill, and gait training using a walking device. He also exercised to strengthen his muscles as his lower extremities were weak after he had been bedridden for approximately a month. When he was discharged from the hospital, the ABGA results and 6MWT demonstrated improvements, and the patient could move around independently using a walking device. The 6MWT yielded a distance of 480 m, and his weight was 135.7 kg (BMI: 45.87 kg/m^2), indicating a reduction compared to his weight at admission (167.1 kg). When the patient was dis-charged, his ABGA results were within the normal range as follows: pH, 7.406; pCO_2 37.7 mmHg; pO_2 97.3 mmHg; and SaO_2 98.0%.

The patient visited the outpatient department. He still relied on NIV at night and breathing normal room air during the day. He reported subjective improvement in his dyspnea. The pulmonary function test results were similar to those at the last assessment, and yielded an FVC of 4.64 L (101% of predicted maximum), an FEV_1 of 2.76 L (81% of the predicted maximum), and an FEV_1/FVC of 59%. His 6MWT distance improved compared to the previous test (510 m), and his weight was similar at 138 kg (BMI: 46.65 kg/m^2). After 4 mo of follow-up, the patient returned to work while performing activities of daily living independently, maintaining his body weight with aerobic exercises, and relying on NIV only during the night.

DISCUSSION

These cases demonstrate that appropriate ventilator application and PR in patients with obesity and HF complaining of dyspnea caused by severe hypercapnia can improve symptoms and help patients return to daily life. Because dyspnea is a major barrier for patients with HF in performing activities of daily living, controlling its symptoms is especially important. HF causes complications, such as arrhythmia, thromboembolism, respiratory muscle weakness, and pulmonary HTN[6]. Obesity can also occur because of reduced physical activity[7] and is associated with mortality and various complications, including diabetes mellitus, heart problems, dementia, and cancer[8]. Therefore, treating HF is important and generally involves pharmacological management, such as diuretic therapy, in acute HF. Furthermore, whether the patient's HF is caused by hypoventilation needs to be considered.

Previous studies have demonstrated that NIV is more effective than conventional oxygen therapy, improves dyspnea, and decreases intubation rates for acute cardiogenic pulmonary edema and acute HF associated with pulmonary disease[9,10]. By contrast, large randomized trials have reported that NIV application does not lead to a reduction in intubation rates; however, this observation might have been attributed to the relatively low intubation rates in the study patient population[11]. Additionally, NIV support is recommended as adjuvant therapy in patients with acute cardiogenic pulmonary edema with severe dyspnea or when medication treatment is ineffective because it has been proven to improve dyspnea and metabolic abnormalities in a faster and safer way than standard oxygen therapy[11,12]. Our two patients who did not significantly benefit from pharmacological management demonstrated symptom improvement and were able to return to their daily lives with the aid of appropriate NIV.

Obesity may occur in response to decreased physical activity in patients with HF or may cause HF by contributing to cardiac hemodynamics, endothelial dysfunction, insulin resistance, vascular changes, and metabolic disorders, including cardiac lipotoxicity[13]. Therefore, obesity should be carefully monitored in patients with HF. Previous studies have also reported independent associations between

obesity and pulmonary HTN and between obesity and mortality in the presence of pulmonary HTN [14]. Obesity, insulin resistance, and sleep apnea cause pulmonary HTN, which impairs endothelial function[15]. Moreover, patients with obesity hypoventilation syndrome may experience daytime hypoventilation, chronic hypoxemia, polycythemia, pulmonary HTN, and cor pulmonale[16], which increases the likelihood that these patients will require invasive mechanical ventilation or ICU admission[17].

Dyspnea exacerbation can contribute to functional disabilities that degrade the quality of life of patients with HF, progress over time, and are associated with poor prognosis[18]. Exercise-based cardiac rehabilitation (CR) for all patients with HF has been proven to be safe and effective in improving heart and body functions, reducing readmission rates, and improving quality of life[19,20]. Chronic HF management guidelines in some countries specifically list exercise-based CR as a category I recommendation[21,22]. The two patients presented here were bedridden when rehabilitation was initiated, were able to improve their dyspnea symptoms through NIV until they were able to engage in gait training, and improved further with the aid of breathing education and aerobic exercises until they could resume performing activities of daily living. These two cases demonstrate that respiratory assistance should be prioritized at the start of rehabilitation to facilitate training thereafter.

CONCLUSION

Patients with obesity and HF who develop pulmonary HTN and cor pulmonale need to be assessed and potentially treated for obesity hypoventilation and sleep apnea, in addition to receiving medication for HF. The two reported cases suggest that the symptoms of these comorbidities may improve once ABG levels are normalized through appropriate ventilator support and PR.

ACKNOWLEDGEMENTS

The authors thank all the members of the Department of Physical Medicine & Rehabilitation, Jeonbuk National University Hospital.

FOOTNOTES

Author contributions: Lim EH drafted the manuscript; Won YH and Park SH performed the data analysis; all authors contributed to the final diagnoses; Won YH and Park SH interpreted the data, wrote and revised the manuscript; all authors reviewed the manuscript before submission.

Supported by The "Research Base Construction Fund Support Program" funded by Jeonbuk National University in 2021.

Informed consent statement: Informed written consent was obtained from both patients for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare no competing interests.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: South Korea

ORCID number: Eun-Hee Lim 0000-0003-4339-5260; Sung-Hee Park 0000-0002-4743-2551; Yu Hui Won 0000-0003-2007-9652.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Zhang YL

REFERENCES

1 **Authors/Task Force Members**, McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022; **24**: 4-131 [PMID: 35083827 DOI: 10.1002/ejhf.2333]

2 **Ponikowski P**, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. [2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure]. *Kardiol Pol* 2016; **74**: 1037-1147 [PMID: 27748494 DOI: 10.5603/KP.2016.0141]

3 **Kurmani S**, Squire I. Acute Heart Failure: Definition, Classification and Epidemiology. *Curr Heart Fail Rep* 2017; **14**: 385-392 [PMID: 28785969 DOI: 10.1007/s11897-017-0351-y]

4 **Maggioni AP**. Epidemiology of Heart Failure in Europe. *Heart Fail Clin* 2015; **11**: 625-635 [PMID: 26462102 DOI: 10.1016/j.hfc.2015.07.015]

5 **Orso D**, Tavazzi G, Corradi F, Mearelli F, Federici N, Peric D, D'Andrea N, Santori G, Mojoli F, Forfori F, Vetrugno L, Bove T. Comparison of diuretic strategies in diuretic-resistant acute heart failure: a systematic review and network meta-analysis. *Eur Rev Med Pharmacol Sci* 2021; **25**: 2971-2980 [PMID: 33877660 DOI: 10.26355/eurrev_202104_25550]

6 **Watson RD**, Gibbs CR, Lip GY. ABC of heart failure. Clinical features and complications. *BMJ* 2000; **320**: 236-239 [PMID: 10642237 DOI: 10.1136/bmj.320.7229.236]

7 **Reddy YNV**, Rikhi A, Obokata M, Shah SJ, Lewis GD, AbouEzzedine OF, Dunlay S, McNulty S, Chakraborty H, Stevenson LW, Redfield MM, Borlaug BA. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. *Eur J Heart Fail* 2020; **22**: 1009-1018 [PMID: 32150314 DOI: 10.1002/ejhf.1788]

8 **Kinlen D**, Cody D, O'Shea D. Complications of obesity. *QJM* 2018; **111**: 437-443 [PMID: 29025162 DOI: 10.1093/qjmed/hcx152]

9 **Masip J**, Peacock WF, Price S, Cullen L, Martin-Sanchez FJ, Seferovic P, Maisel AS, Miro O, Filippatos G, Vrints C, Christ M, Cowie M, Platz E, McMurray J, DiSomma S, Zeymer U, Bueno H, Gale CP, Lettino M, Tavares M, Ruschitzka F, Mebazaa A, Harjola VP, Mueller C; Acute Heart Failure Study Group of the Acute Cardiovascular Care Association and the Committee on Acute Heart Failure of the Heart Failure Association of the European Society of Cardiology. Indications and practical approach to non-invasive ventilation in acute heart failure. *Eur Heart J* 2018; **39**: 17-25 [PMID: 29186485 DOI: 10.1093/eurheartj/ehx580]

10 **Masip J**. Noninvasive Ventilation in Acute Heart Failure. *Curr Heart Fail Rep* 2019; **16**: 89-97 [PMID: 31147960 DOI: 10.1007/s11897-019-00429-y]

11 **Gray A**, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J; 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med* 2008; **359**: 142-151 [PMID: 18614781 DOI: 10.1056/NEJMoa0707992]

12 **Weng CL**, Zhao YT, Liu QH, Fu CJ, Sun F, Ma YL, Chen YW, He QY. Meta-analysis: Noninvasive ventilation in acute cardiogenic pulmonary edema. *Ann Intern Med* 2010; **152**: 590-600 [PMID: 20439577 DOI: 10.7326/0003-4819-152-9-201005040-00009]

13 **Ebong IA**, Goff DC Jr, Rodriguez CJ, Chen H, Bertoni AG. Mechanisms of heart failure in obesity. *Obes Res Clin Pract* 2014; **8**: e540-e548 [PMID: 25434909 DOI: 10.1016/j.orcp.2013.12.005]

14 **Frank RC**, Min J, Abdelghany M, Paniagua S, Bhattacharya R, Bhambhani V, Pomerantsev E, Ho JE. Obesity Is Associated With Pulmonary Hypertension and Modifies Outcomes. *J Am Heart Assoc* 2020; **9**: e014195 [PMID: 32079475 DOI: 10.1161/JAHA.119.014195]

15 **Zamanian RT**, Hansmann G, Snook S, Lilienfeld D, Rappaport KM, Reaven GM, Rabinovitch M, Doyle RL. Insulin resistance in pulmonary arterial hypertension. *Eur Respir J* 2009; **33**: 318-324 [PMID: 19047320 DOI: 10.1183/09031936.00000508]

16 **Olson AL**, Zwillich C. The obesity hypoventilation syndrome. *Am J Med* 2005; **118**: 948-956 [PMID: 16164877 DOI: 10.1016/j.amjmed.2005.03.042]

17 **Nowbar S**, Burkart KM, Gonzales R, Fedorowicz A, Gozansky WS, Gaudio JC, Taylor MR, Zwillich CW. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. *Am J Med* 2004; **116**: 1-7 [PMID: 14706658 DOI: 10.1016/j.amjmed.2003.08.022]

18 **Dunlay SM**, Manemann SM, Chamberlain AM, Cheville AL, Jiang R, Weston SA, Roger VL. Activities of daily living and outcomes in heart failure. *Circ Heart Fail* 2015; **8**: 261-267 [PMID: 25717059 DOI: 10.1161/CIRCHEARTFAILURE.114.001542]

19 **Taylor RS**, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, Lough F, Rees K, Singh S. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2014; **2014**: CD003331 [PMID: 24771460 DOI: 10.1002/14651858.CD003331.pub4]

20 **Leggio M**, Fusco A, Loreti C, Limongelli G, Bendini MG, Mazza A, Coraci D, Padua L. Effects of exercise training in heart failure with preserved ejection fraction: an updated systematic literature review. *Heart Fail Rev* 2020; **25**: 703-711 [PMID: 31399956 DOI: 10.1007/s10741-019-09841-x]

21 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017; **70**: 776-803 [PMID: 28461007 DOI: 10.1016/j.jacc.2017.04.025]

22 **Pelliccia A**, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, Collet JP, Corrado D, Drezner JA, Halle M, Hansen D, Heidbuchel H, Myers J, Niebauer J, Papadakis M, Piepoli MF, Prescott E, Roos-Hesselink JW, Graham Stuart A, Taylor RS, Thompson PD, Tiberi M, Vanhees L, Wilhelm M; ESC Scientific Document Group. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2021; **42**: 17-96 [PMID: 32860412 DOI: 10.1093/eurheartj/ehaa605]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3038-3044

DOI: 10.12998/wjcc.v11.i13.3038

ISSN 2307-8960 (online)

CASE REPORT

Multiple flexor tendon ruptures due to osteochondroma of the hamate: A case report

Tae Young Kwon, Young-Keun Lee

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Modi N, India

Received: November 16, 2022
Peer-review started: November 16, 2022
First decision: February 14, 2023
Revised: February 19, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 6, 2023

Tae Young Kwon, Department of Orthopedics, Jeonbuk National University Hospital, Jeonju-si 54907, South Korea

Young-Keun Lee, Department of Orthopedic Surgery, Research Institute of Clinical Medicine of Jeonbuk National University – Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju 54896, South Korea

Corresponding author: Young-Keun Lee, MD, PhD, Associate Professor, Doctor, Department of Orthopedic Surgery, Research Institute of Clinical Medicine of Jeonbuk National University – Biomedical Research Institute of Jeonbuk National University Hospital, No. 567 Baekje-daero, Deokjin-gu, Republic of Korea, Jeonju 54896, South Korea. trueyklee@naver.com

Abstract

BACKGROUND

Closed rupture of the little and ring finger flexor tendons caused by the hamate is mostly associated with a fracture or nonunion of the hamate hook. Only one case of a closed rupture of the finger flexor tendon caused by osteochondroma in the hamate has been reported. Here, we present a case study to highlight the possibility of hamate osteochondroma as a rare cause of finger closed flexor tendon rupture based on our clinical experience and literature review.

CASE SUMMARY

A 48-year-old man who had been a rice-field farmer for 7–8 h a day for the past 30 years visited our clinic due to the loss of right little finger and ring finger flexion involving both the proximal and distal interphalangeal joints. The patient was diagnosed with a complete rupture of the ring and little finger flexors because of the hamate and was pathologically diagnosed with an osteochondroma. Exploratory surgery was performed, and a complete rupture of the ring and little finger flexors due to an osteophyte-like lesion of the hamate was observed, which was pathologically diagnosed as an osteochondroma.

CONCLUSION

One should consider that osteochondroma in the hamate may be the cause of closed tendon ruptures.

Key Words: Flexor tendon; Finger; Closed tendon rupture; Hamate; Osteochondroma; Case report

Core Tip: It is not easy to diagnose osteochondroma in the hamate. Therefore, osteochondroma in the hamate should be considered as a cause when dealing with patients with closed ruptures of the finger flexor tendon. Based on our experience, we also suggest that the surgical treatment of these patients requires careful pre-operative planning and preparation.

Citation: Kwon TY, Lee YK. Multiple flexor tendon ruptures due to osteochondroma of the hamate: A case report. *World J Clin Cases* 2023; 11(13): 3038-3044
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3038.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3038

INTRODUCTION

Closed ruptures of the flexor tendons other than in nonrheumatic patients are uncommon. These ruptures are frequently caused by intrinsic tendon pathology or structural deformities[1]. Closed rupture of the finger flexor tendons caused by the hamate is mostly associated with a fracture or nonunion of the hamate hook[2,3]. Only one case of a closed rupture of the finger flexor tendon caused by osteochondroma in the hamate has been reported[4]. An osteochondroma is a tumor that arises mainly from the metaphyses of long bones and is the most common form of primary benign bone tumor. However, it is rarely found in carpal bones[5-8]. In this report, we present a case study to highlight the possibility of hamate osteochondroma as a rare cause of finger closed flexor tendon rupture based on our clinical experience and literature review.

CASE PRESENTATION

Chief complaints

A 48-year-old man complained of the inability to flex his right ring finger (RRF) and right small finger (RSF).

History of present illness

The patient was unable to perform active flexion of the RSF for about 2 wk and active flexion of the RRF for about one week. The condition occurred without pain or a definite episode of trauma.

History of past illness

He had been a rice-field farmer for 7−8 h a day for the past 30 years.

Personal and family history

There was no history or evidence of rheumatoid or other inflammatory arthritis conditions.

Physical examination

Physical examination revealed no swelling or tenderness of the palm. However, he could not actively flex either the proximal or distal interphalangeal joint of the RRF and RSF (Figure 1A and B).

Laboratory examinations

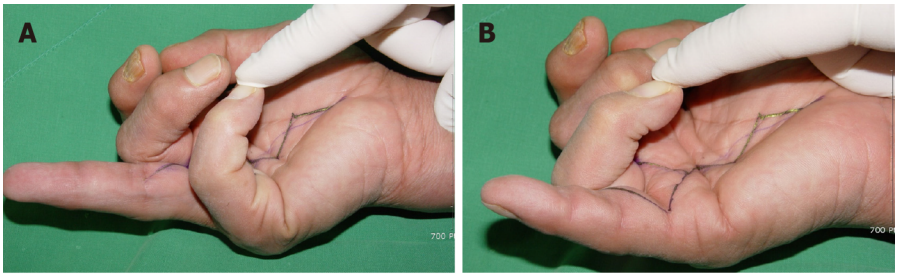
The patient's rheumatoid serology results were normal.

Imaging examinations

The radiologist reported no specific findings on preoperative magnetic resonance imaging (MRI) other than ring finger and small finger flexor tendon ruptures (Figure 2).

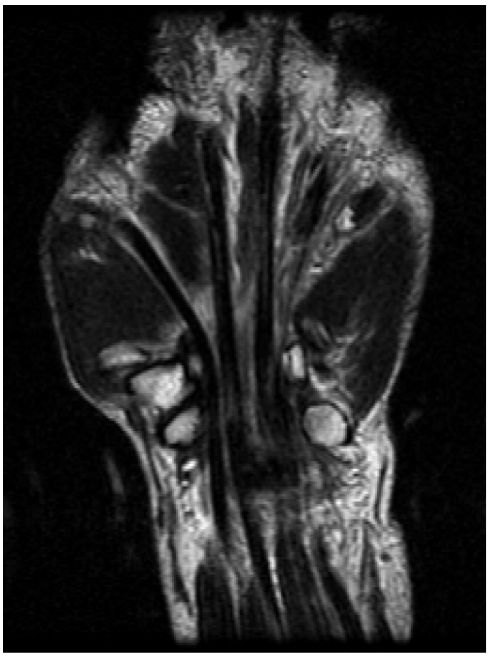
Further diagnostic work-up

The flexor tendons were explored under regional anesthesia through a volar zig-zag incision. During surgery, the flexor digitorum profundus (FDP) and flexor digitorum superficialis (FDS) tendons of the RRF and RSF were found to be completely ruptured (Figure 3A and B). Additionally, the flexor tendons of the long finger were attenuated and frayed. On the side of the hamate in the carpal tunnel, a protruding bony structure like an osteophyte was identified, which was covered by cartilage



DOI: 10.12998/wjcc.v11.i13.3038 **Copyright** ©The Author(s) 2023.

Figure 1 Preoperative physical examination. A: The loss of the ring finger flexion involving both proximal and distal interphalangeal joints; B: The loss of the little finger flexion involving both proximal and distal interphalangeal joints.



DOI: 10.12998/wjcc.v11.i13.3038 **Copyright** ©The Author(s) 2023.

Figure 2 Flexor tendon continuity of the ring finger and the small finger is not visible in the carpal tunnel on T1 coronal magnetic resonance imaging.

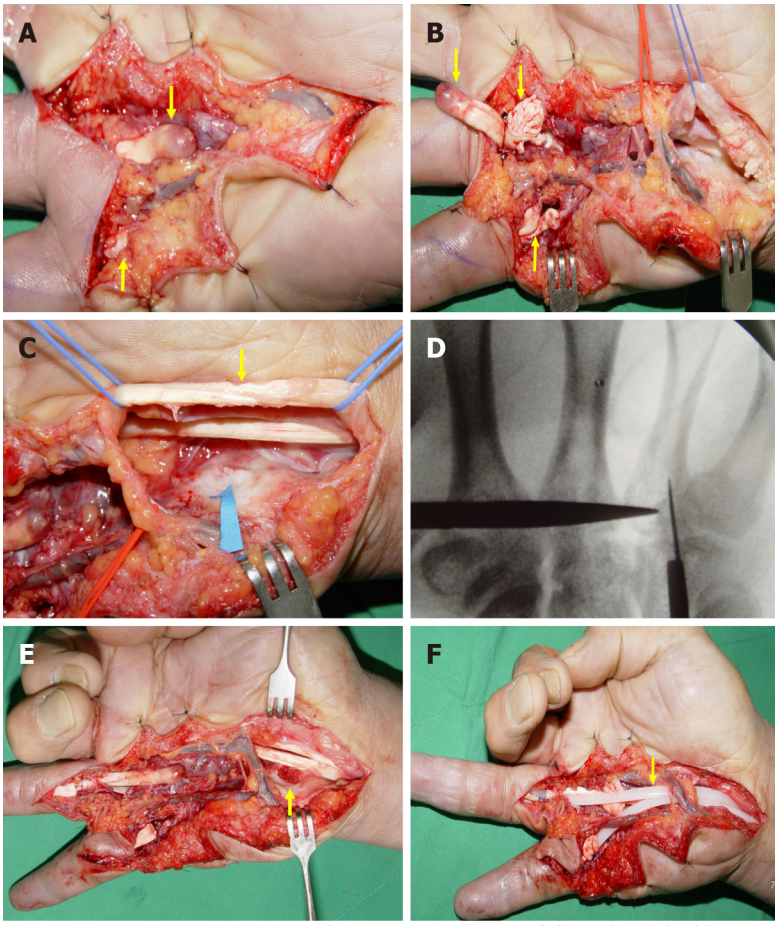
(Figure 3C). The flexor tendons were determined to be worn and ruptured by this structure. We used a C-arm image intensifier to identify this area during surgery (Figure 3D). It was excised and sent for histological examination (Figure 3E). Although we knew that primary reconstruction through tendon transfer or a free tendon graft was the best treatment for ruptured flexor tendons, we decided to perform staged tendon reconstruction after considering various factors. The ruptured flexor tendons were debrided, and Hunter rods (Wright Medical Technology, Inc., Arlington, TN, USA) were inserted (Figure 3F).

FINAL DIAGNOSIS

The final diagnosis was multiple flexor tendon ruptures due to osteochondroma of the hamate

TREATMENT

Postoperatively, the wrist was immobilized with dorsal block short arm splint for 2 wk.



DOI: 10.12998/wjcc.v11.i13.3038

Figure 3 Intraoperative photographs. A and B: Complete rupture of the right ring finger and right small finger flexor tendons (yellow arrows); C: A protruding bony structure like an osteophyte is identified on the side of the hamate in the carpal tunnel, and is covered by cartilage (blue arrow). There is a partial rupture of the right long finger flexor tendon (yellow arrow); D: The intra operative C-arm image shows a bony lesion protruding into the carpal tunnel; E: Excisional biopsy was performed for the bony lesion (yellow arrow); F: Hunter rods were inserted (yellow arrow).

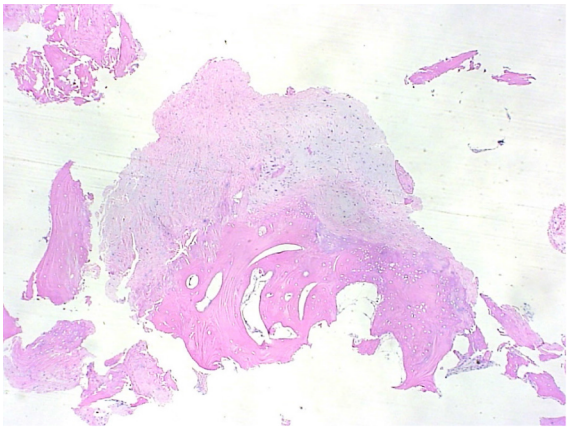
OUTCOME AND FOLLOW-UP

The histopathological examination revealed osteochondroma of the hamate with no malignant changes (Figure 4). However, tendon reconstruction could not be performed because the patient did not return to the hospital as he was busy with work.

DISCUSSION

An osteochondroma is a common tumor that accounts for 30% of benign bone tumors and 10%−15% of all bone tumors[9]. Since most cases are asymptomatic, they are often detected incidentally on radiographs and are commonly found around the knee area. Carpal osteochondroma is very rare and only three cases involving the hamate have been reported[4,6,8]. Only one case of carpal osteochondroma associated with a partial rupture of the finger flexor tendon has been reported[4]. The low incidence of osteochondromas in carpal bones might be related to the total area of the periosteal surface, which is small in carpal bones compared to long bones or larger tarsal bones[5]. In most cases of isolated osteochondromas, conservative treatment with regular follow-up monitoring is conducted[9]. However, surgical excision is performed if the tumor size presents an aesthetic problem, pathological fractures or symptoms of nerve or vascular compression appear, limitations in joint movement occur, or tumor exacerbation is suspected[10]. Our case involved closed tendon rupture due to a hamate osteochondroma. However, the occurrence of osteochondroma in carpal bones is very rare, and the diagnosis can be very difficult because of its usual occurrence in a long bone and other atypical radiological findings. Similarly, in our case, the size was too small to be detected even on MRI before surgery, but it was found during surgery.

Closed injuries to the flexor tendon are rare and, therefore, can be easily missed initially. The causes of closed rupture of the flexor tendons reported in previous papers were distal radius fractures,



DOI: 10.12998/wjcc.v11.i13.3038

Figure 4 Histopathologic analysis of the hamate bony lesion shows thick cartilaginous tissue, such as the typical cartilaginous cap seen in the common osteochondroma with no malignant changes (hematoxylin-eosin stain, original magnification x 100).

nonunions of the scaphoid, tendolipomatosis, dislocations of the lunate, Kienböck's disease, osteoarthritis of the pisotriquetral joint, and fractures or nonunions of the hamate hook[2,3,11-15]. Sometimes, closed ruptures of the flexor tendon occur without any underlying pathological conditions. Although the etiology of closed ruptures is unclear, these injuries likely depend on the interplay of several factors, including vascular alterations, repetitive microtrauma, local anatomic features, tendon anomalies, and genetic or other endogenous influences[16].

Closed ruptures of the flexor tendons are usually treated with primary reconstruction through tendon graft interposition or tendon transfer[17]. In addition, since osteochondroma is a benign and slow-growing tumor, it has been reported that there is no problem with primary treatment has been reported, even if accompanied by tendon rupture[7]. However, we have limited hand surgery experience at the time of this case. Initially, we planned primary tendon reconstruction *via* tendon transfer from the third FDS. However, since the third FDS tendon was also frayed and attenuated, tendon transfer could not be performed. As an alternative treatment method, we considered reconstruction using free tendon graft interposition. Two palmaris longus tendons should be harvested to ensure the success of this treatment, but we found this option unsuitable since surgery on this patient was not performed under general anesthesia. Moreover, if the grafted tendon passes through the osteochondroma removal site, there is a possibility of re-rupture due to wear of the tendon. Thus, we performed a Hunter rod insertion instead. However, this was done because of our lack of both experience and thorough preoperative preparation, which would have discovered the osteochondroma before surgery. In this regard, we suggest that careful planning and preparation are needed before surgery for patients with closed ruptures of the flexor tendon.

Rice-field farmers frequently work in small-scale agricultural settings using hand hoes and small sickles. Repetitive movements of the wrist are required to use these tools, and there is full wrist flexion with ulnar deviation. Thus, the FDP tendons of the ulnar digits deviate to an acute angle at the hamate in the carpal tunnel. Moreover, repetition of these movements can produce friction between the flexor tendon and the surface of the hamate, leading to attrition of both the tendon and the surface of the hamate[18]. Our patient had been a rice-field farmer for the past 30 years. Long-term repeated movements led to the attrition of both the tendon and the surface of the hamate. Moreover, microtrauma of the hamate because of its irregularity due to an osteochondroma was the main cause of flexor tendon rupture.

One limitation of this case report is that secondary tendon reconstruction could not be performed because the patient did not return to the hospital as he was busy with work. Therefore, we could not show the final result of his reconstructed fingers, and there was no final follow-up to determine whether the hamate osteochondroma recurred.

CONCLUSION

In the present case, repetitive friction between the flexor tendons and osteochondroma of the hamate may have caused tendon rupture. However, given that it is not easy to diagnose osteochondroma in the hamate, osteochondroma in the hamate should be considered as the cause when dealing with patients with closed ruptures of the finger flexor tendon. Based on our experience, we also suggest that surgical treatment requires careful pre-operative planning and preparation.

FOOTNOTES

Author contributions: Kwon TY and Lee YK were the patient's orthopedic surgeons; Kwon TY and Lee YK contributed to manuscript writing, editing, data collection, data analysis, conceptualization and supervision; All authors have read and approved the final manuscript.

Informed consent statement: Written informed consent was obtained from the patient for the publication of this case report.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: South Korea

ORCID number: Tae Young Kwon 0000-0002-3532-7156; Young-Keun Lee 0000-0001-8749-4135.

S-Editor: Liu GL
L-Editor: A
P-Editor: Liu GL

REFERENCES

1 **De Smet L**, Baeten Y. Closed rupture of both flexor tendons of the fifth finger due to a calcium hydroxyapatite deposit in the carpal tunnel. *Acta Orthop Belg* 1998; **64**: 336-338 [PMID: 9828484]
2 **Yamazaki H**, Kato H, Nakatsuchi Y, Murakami N, Hata Y. Closed rupture of the flexor tendons of the little finger secondary to non-union of fractures of the hook of the hamate. *J Hand Surg Br* 2006; **31**: 337-341 [PMID: 16580104 DOI: 10.1016/j.jhsb.2005.12.015]
3 **Stark HH**, Chao EK, Zemel NP, Rickard TA, Ashworth CR. Fracture of the hook of the hamate. *J Bone Joint Surg Am* 1989; **71**: 1202-1207 [PMID: 2777848]
4 **Motomiya M**, Sakazaki T, Iwasaki N. Atypical osteochondroma of the hamate that presented clinically as carpal tunnel syndrome: report of an extremely rare case and literature review. *BMC Musculoskelet Disord* 2020; **21**: 231 [PMID: 32284050 DOI: 10.1186/s12891-020-03272-8]
5 **Malhotra R**, Maheshwari J, Dinda AK. A solitary osteochondroma of the capitate bone: a case report. *J Hand Surg Am* 1992; **17**: 1082-1083 [PMID: 1430943 DOI: 10.1016/s0363-5023(09)91067-x]
6 **Koti M**, Honakeri SP, Thomas A. A multilobed osteochondroma of the hamate: case report. *J Hand Surg Am* 2009; **34**: 1515-1517 [PMID: 19695798 DOI: 10.1016/j.jhsa.2009.04.029]
7 **Shah NR**, Wilczynski M, Gelberman R. Osteochondroma of the capitate causing rupture of the extensor digiti minimi: case report. *J Hand Surg Am* 2009; **34**: 46-48 [PMID: 19121729 DOI: 10.1016/j.jhsa.2008.08.004]
8 **Cha SM**, Shin HD, Kim DY. A solitary unilobed osteochondroma of the hamate: a case report. *J Pediatr Orthop B* 2017; **26**: 274-276 [PMID: 26569429 DOI: 10.1097/BPB.0000000000000247]
9 **Kitsoulis P**, Galani V, Stefanaki K, Paraskevas G, Karatzias G, Agnantis NJ, Bai M. Osteochondromas: review of the clinical, radiological and pathological features. *In Vivo* 2008; **22**: 633-646 [PMID: 18853760]
10 **Göçmen S**, Topuz AK, Atabey C, Şimşek H, Keklikçi K, Rodop O. Peripheral nerve injuries due to osteochondromas: analysis of 20 cases and review of the literature. *J Neurosurg* 2014; **120**: 1105-1112 [PMID: 24405073 DOI: 10.3171/2013.11.JNS13310]
11 **Takami H**, Takahashi S, Ando M. Attritional flexor tendon ruptures after a malunited intra-articular fracture of the distal radius. *Arch Orthop Trauma Surg* 1997; **116**: 507-509 [PMID: 9352050 DOI: 10.1007/BF00387589]
12 **Johnston GH**, Bowen CV. Attritional flexor tendon ruptures by an old lunate dislocation. *J Hand Surg Am* 1988; **13**: 701-703 [PMID: 3241040 DOI: 10.1016/s0363-5023(88)80128-x]
13 **Inoué G**. Attritional rupture of the extensor tendon due to longstanding Kienböck's disease. *Ann Chir Main Memb Super* 1994; **13**: 135-138 [PMID: 7521659 DOI: 10.1016/s0753-9053(05)80386-2]
14 **Crosby EB**, Linscheid RL. Rupture of the flexor profundus tendon of the ring finger secondary to ancient fracture of the hook of the hamate. Review of the literature and report of two cases. *J Bone Joint Surg Am* 1974; **56**: 1076-1078 [PMID: 4847234]
15 **Lee YK**, Lee M. Spontaneous rupture of flexor pollicis longus tendon by tendolipomatosis in proximal phalanx: A case report. *Medicine (Baltimore)* 2018; **97**: e12157 [PMID: 30212941 DOI: 10.1097/MD.0000000000012157]
16 **Bois AJ**, Johnston G, Classen D. Spontaneous flexor tendon ruptures of the hand: case series and review of the literature. *J Hand Surg Am* 2007; **32**: 1061-1071 [PMID: 17826564 DOI: 10.1016/j.jhsa.2007.06.012]

17 **Netscher DT**, Badal JJ. Closed flexor tendon ruptures. *J Hand Surg Am* 2014; **39**: 2315-23; quiz 2323 [PMID: 25442746 DOI: 10.1016/j.jhsa.2014.04.005]

18 **Lee GJ**, Kwak S, Kim HK, Ha SH, Lee HJ, Baek GH. Spontaneous Zone III rupture of the flexor tendons of the ulnar three digits in elderly Korean farmers. *J Hand Surg Eur Vol* 2015; **40**: 281-286 [PMID: 25005564 DOI: 10.1177/1753193414541221]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3045-3051

DOI: 10.12998/wjcc.v11.i13.3045

ISSN 2307-8960 (online)

CASE REPORT

Fractional flow reserve measured *via* left internal mammary artery after coronary artery bypass grafting: Two case reports

Li-Ying Zhang, Yi-Rong Gan, Yan-Zhen Wang, Ding-Xiong Xie, Zong-Ke Kou, Xiao-Qing Kou, Yun-Long Zhang, Bing Li, Rui Mao, Tian-Xiang Liang, Jing Xie, Jian-Jian Jin, Jin-Mei Yang

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Dabla PK, India; He YH, China

Received: November 16, 2022
Peer-review started: November 16, 2022
First decision: January 12, 2023
Revised: February 15, 2023
Accepted: March 21, 2023
Article in press: March 21, 2023
Published online: May 6, 2023

Li-Ying Zhang, Yi-Rong Gan, Yan-Zhen Wang, Ding-Xiong Xie, Zong-Ke Kou, Xiao-Qing Kou, Yun-Long Zhang, Bing Li, Rui Mao, Tian-Xiang Liang, Gansu Institute of Cardiovascular Diseases, Lanzhou 730050, Gansu Province, China

Li-Ying Zhang, Provincial Level Key Laboratory for Molecular Medicine of Major Diseases and Prevention and Treatment with Traditional Chinese Medicine Research in Gansu Colleges and Universities, Gansu University of Chinese Medicine, Lanzhou 730000, Gansu Province, China

Jing Xie, Jin-Mei Yang, Department of Functional, Lanzhou First People's Hospital, Lanzhou 730050, Gansu Province, China

Jian-Jian Jin, Department of Cardiology, The First Hospital of Lanzhou University, Lanzhou 730000, Gansu Province, China

Corresponding author: Jin-Mei Yang, MBBS, Associate Chief Physician, Department of Functional, Lanzhou First People's Hospital, No. 1 Wujiayuan, Qilihe District, Lanzhou 730050, Gansu Province, China. 503490860@qq.com

Abstract

BACKGROUND

The fractional flow reserve (FFR) has made the treatment of coronary heart disease more precise. However, there are few reports on the measurement of FFR *via* the left internal mammary artery (LIMA). Herein, we described the determination of further treatments by measuring FFR *via* the LIMA in 2 cases after coronary artery bypass grafting (CABG).

CASE SUMMARY

Case 1 was a 66-year-old male who was admitted due to "chest tightness after CABG." The patient underwent CABG 7 years prior due to coronary heart disease. Coronary artery angiography showed complete occlusion of the left anterior descending artery (LAD), and subtotal occlusion of the third segment of the right coronary artery. On arterial angiography, there was 85% stenosis at the distal end of the anastomosis of the LIMA-LAD graft. FFR *via* LIMA was determined at 0.75. Thus, balloon dilation was performed in Case 1. FFR after balloon dilation was 0.94. Case 2 was a 60-year-old male who was admitted due to "chest tightness after CABG." The patient underwent CABG 6 years prior due to coronary heart disease. There was 60% segmental stenosis in the middle segment of LAD and 75% anastomotic stenosis. FFR measured *via* LIMA was 0.83

(negative); thus the intervention was not performed. Case 2 was given drug treatments. At the 3-mo follow-up, there was no recurrence of chest tightness or shortness of breath in both cases. They are currently under continual follow-up.

CONCLUSION
We provided evidence that FFR measurement *via* grafted blood vessels, especially LIMA, after CABG is a good method to determine the intervention course.

Key Words: Left internal mammary artery; Fractional flow reserve; Coronary artery bypass; Intervention; Case report

Core Tip: We reported the determination of intervention by fractional flow reserve value measured *via* the left internal mammary artery after coronary artery bypass grafting in 2 cases. We provided evidence that fractional flow reserve measurement *via* grafted blood vessels, especially the left internal mammary artery, after coronary artery bypass grafting is a good method to determine whether to intervene.

Citation: Zhang LY, Gan YR, Wang YZ, Xie DX, Kou ZK, Kou XQ, Zhang YL, Li B, Mao R, Liang TX, Xie J, Jin JJ, Yang JM. Fractional flow reserve measured *via* left internal mammary artery after coronary artery bypass grafting: Two case reports. *World J Clin Cases* 2023; 11(13): 3045-3051
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3045.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3045

INTRODUCTION

Coronary angiography can only perform anatomical evaluation of the stenosis degree and cannot functionally evaluate the effect of the stenosis on the distal blood flow or identify the extent of myocardial ischemia. This causes overestimation or underestimation of the lesion severity and results in over-treatment or under-treatment of lesions[1]. Fractional flow reserve (FFR), which was first proposed in 1993[2], is an index for estimating coronary blood flow by pressure measurement. In recent years, the wide application of FFR has enabled patients with coronary heart disease to receive precise treatment[3, 4]. The left internal mammary artery (LIMA) has an excellent long-term patency rate and is the preferred vessel for coronary artery bypass grafting (CABG)[5]. However, the measurement of FFR *via* the LIMA is rarely reported. Herein, we reported the determination of further treatments in 2 patients by measuring FFR through the LIMA. These patients received CABG for coronary heart disease and had graft occlusion after CABG.

CASE PRESENTATION

Chief complaints

Case 1: A 66-year-old male was admitted to Gansu Institute of Cardiovascular Diseases due to "chest tightness after CABG."

Case 2: A 60-year-old male was admitted to Gansu Institute of Cardiovascular Diseases because of "chest tightness after CABG."

History of present illness

Case 1: The patient experienced intermittent chest tightness and shortness of breath in the prior 3 years. The symptoms worsened in the 3 mo prior to admission.

Case 2: The patient suffered from chest tightness and shortness of breath in the week prior to admission.

History of past illness

Case 1: The patient underwent CABG 7 years prior due to coronary heart disease. The coronary artery bypass grafts included the graft from LIMA to the left anterior descending artery (LAD), the graft from the ascending aorta (AO) to the right posterior descending coronary artery and the graft from the AO to the first diagonal branch of the left coronary artery.

Case 2: The patient received CABG 6 years prior due to coronary heart disease. The coronary artery bypass grafts included the LIMA-LAD graft and the saphenous vein-obtuse marginal branch graft.

Personal and family history

Case 1: The patient denied any family history of heart disease or genetic disease. The patient had a smoking history of 30 years (3 cigarettes a day).

Case 2: The patient denied any family history of heart disease or genetic disease. The patient had a smoking history of 30 years (20 cigarettes a day).

Physical examination

Case 1: Physical examination showed blood pressure of 152/93 mmHg and heart rate of 61 beats/min. There was no arrhythmia or pathological murmur.

Case 2: Physical examination showed blood pressure of 135/85 mmHg and heart rate of 77 beats/min. No arrhythmia or pathological murmur was observed.

Laboratory examinations

Case 1: Laboratory examinations showed that low density lipoprotein was 3.80 mmol/L, and total cholesterol was 5.70 mmol/L. No obvious abnormality was observed in other blood biochemical indicators.

Case 2: Laboratory examinations showed that low density lipoprotein was 2.06 mmol/L, and total cholesterol was 3.59 mmol/L. There was no obvious abnormality in other blood biochemical indicators.

Imaging examinations

Case 1: Coronary artery angiography showed complete occlusion of LAD and subtotal occlusion of the third segment of the right coronary artery (RCA). The angiography also showed that the AO-first diagonal branch of the left coronary artery and the AO-posterior descending coronary artery grafts had smooth blood flow and had no anastomotic stenosis. On the arterial angiography, it was observed that the LIMA-LAD graft had smooth blood flow and had no anastomotic stenosis. However, there was 85% stenosis at the distal end of the anastomosis of the LIMA-LAD graft (Figure 1A). Cardiac ultrasound showed that the left ventricular ejection fraction was 54%.

Case 2: Coronary artery angiography observed that the left coronary artery was dominant. There was no abnormality in the left main coronary artery. However, there was 60% segmental stenosis in the middle segment of LAD and chronic occlusion of the RCA from the opening with visible collateral circulation. The LIMA-LAD graft was unobstructed. However, there was 75% anastomotic stenosis (Figure 2A). Additionally, the saphenous vein-obtuse marginal branch graft was unobstructed. On cardiac ultrasound, the left ventricular ejection fraction was 50%, consistent with the changes of old myocardial infarction at the inferior and posterior heart walls.

Further diagnostic work-up

Case 1: The pressure measuring guide wire was inserted into the stenotic segment of LAD through the LIMA, and the FFR value was measured to be 0.75 (positive) (Figure 1B).

Case 2: The FFR measured from the LIMA to the distal end of the anastomosis was 0.83 (negative) (Figure 2B).

FINAL DIAGNOSIS

Case 1

The final diagnosis was stenosis at the distal end of the anastomosis of the LIMA-LAD graft.

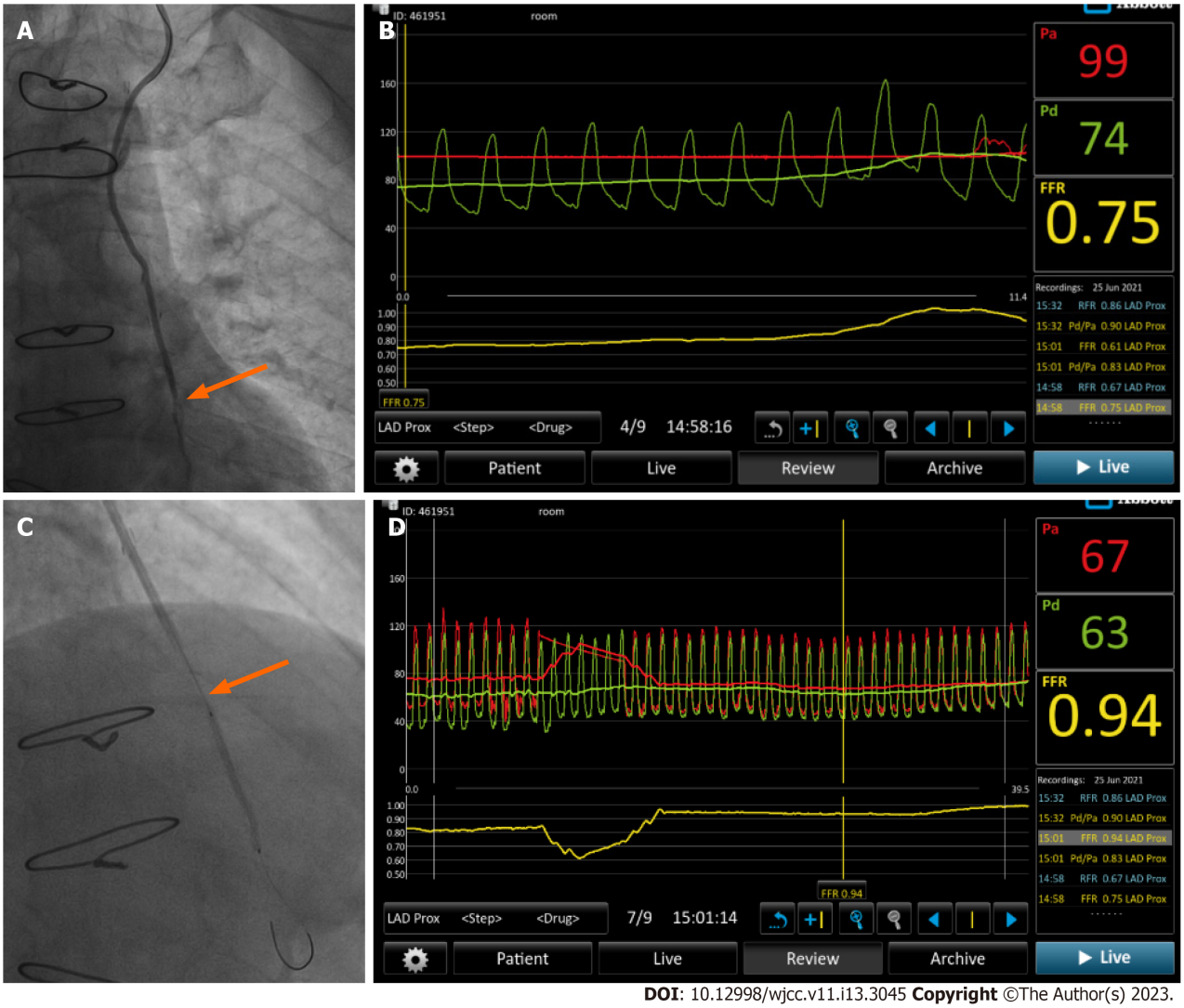
Case 2

The final diagnosis was segmental stenosis in the middle segment of LAD, chronic occlusion of the RCA and anastomotic stenosis.

TREATMENT

Case 1

Based on the positive FFR value, intervention was performed. In detail, dilation with a 2.0 mm × 31.0



DOI: 10.12998/wjcc.v11.i13.3045 **Copyright** ©The Author(s) 2023.

Figure 1 Images of case 1. A: Angiography showed 85% stenosis at the distal end of the anastomosis of the left internal mammary artery (LIMA)-left anterior descending artery graft (orange arrow); B: Before intervention, the fractional flow reserve measured *via* the LIMA was 0.75 (positive); C: Dilation with a 2.0 mm × 31.0 mm drug containing balloon was performed at the stenotic segment of the left anterior descending artery *via* the LIMA (orange arrow); D: After balloon dilation, remeasurement of pressure showed that the fractional flow reserve was 0.94.

mm balloon containing drugs was performed at the stenotic segment of the LAD *via* the LIMA (Figure 1C).

Case 2

Based on the negative FFR value, the intervention was not performed. The patient was given drug treatments according to traditional Chinese medicine and Western medicine.

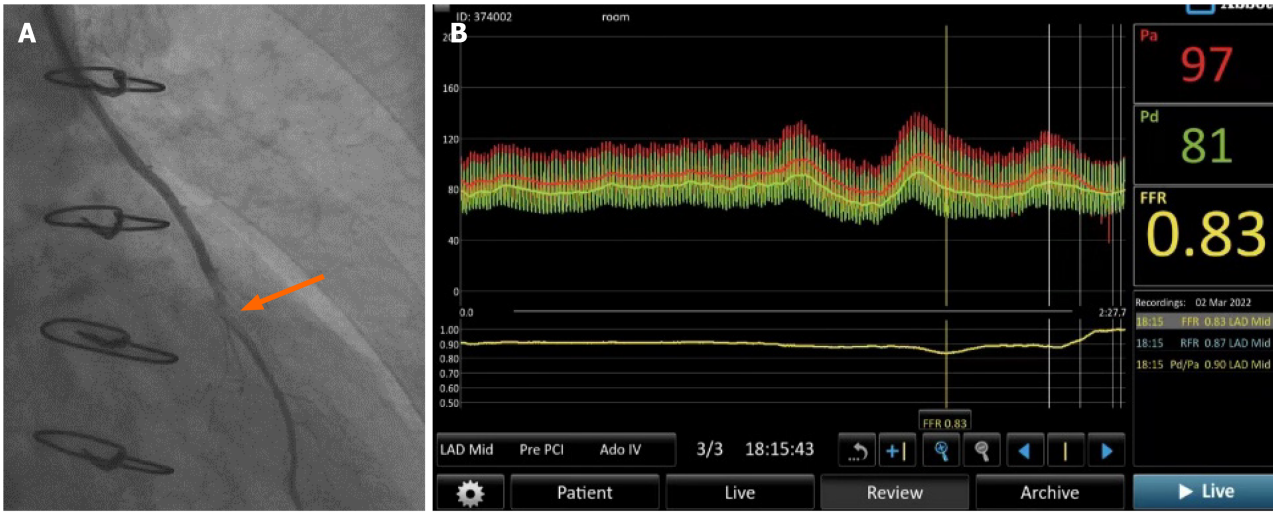
OUTCOME AND FOLLOW-UP

Case 1

Remeasurement of pressure showed that the FFR after balloon dilation was 0.94 (Figure 1D). There was no residual stenosis as shown on coronary angiography. Three days after intervention, the symptoms of chest tightness were significantly relieved, and the patient was discharged. At the 3-mo follow-up, the patient had no recurrence of chest tightness or shortness of breath. The patient is currently under continual follow-up.

Case 2

One week after drug treatment, the symptoms of chest tightness and shortness of breath were significantly relieved and the patient was discharged. At the 3-mo follow-up, there was no recurrence of chest tightness or shortness of breath. The patient is currently under continual follow-up.



DOI: 10.12998/wjcc.v11.i13.3045

Figure 2 Images of case 2. A: Angiography indicated 75% anastomotic stenosis (orange arrow); B: The fractional flow reserve measured from the left internal mammary artery to the distal end of the anastomosis was 0.83 (negative).

DISCUSSION

LIMA is a commonly used vessel for CABG. Its advantages[6] are as follows: (1) The pedicled LIMA can regulate blood flow according to physiological needs; (2) The LIMA can produce prostaglandins, which can dilate blood vessels and resist platelet aggregation; and (3) The LIMA has less possibility of atherosclerosis, ensuring a high long-term patency rate. The 2 patients in this report had occlusion in the proximal segment of the anterior descending artery and occlusion in the middle segment of the anterior descending artery. The blood supply of the anterior myocardium mainly came from the LIMA graft. Thus, intervention may be performed through the LIMA. However, re-intervention therapy should be performed with caution after recurrence. It is shown that nearly 25% of patients with coronary angiography stenosis above 70% do not have myocardial ischemia[7]. For these patients, stenting or coronary bypass based on the results of coronary angiography alone will not only have no effect but also increase the financial and psychological burden of patients, leading to over-treatment.

FFR can objectively and accurately evaluate coronary function, thus providing evidence for interventional therapy and assisting in making precise treatment plans during interventional therapy[8,9]. A multicenter clinical trial[7] showed that compared with traditional percutaneous coronary intervention using FFR as the gold standard to guide patients with coronary artery diseases for revascularization intervention significantly improved the prognosis of patients and significantly reduced the incidence of adverse events. The 3-year follow-up results from the Compare-Acute study showed that FFR-guided complete revascularization in patients with ST-segment elevation myocardial infarction and multivessel disease could significantly reduce costs[10]. FFR measurement is currently the optimal method to confirm whether coronary stenosis is complicated with myocardial ischemia. The latest international views believe that coronary angiography + FFR measurement is the "gold standard" for the diagnosis and treatment of coronary heart disease[11]. Clinically, an FFR value greater than 0.8 indicates no myocardial ischemia, and an FFR value less than 0.8 indicates myocardial ischemia[12]. Under this gold standard, the precise treatment of coronary heart disease by stenting or bypass grafting can be achieved [13].

In patients with chest tightness and shortness of breath after CABG, it should be first considered whether there is a problem with the grafted blood vessels, especially the LIMA-LAD graft. There may be factors such as atherosclerotic stenosis in LIMA, anastomotic stenosis and stenosis in LAD at the distal end of the anastomosis[14]. Previously, intervention was determined by the stenosis degree assessed by the angiography of LIMA. However, angiography cannot determine whether there is ischemia in the distal myocardium. Thus, the intervention may have some blindness to a certain extent [7]. The measurement of FFR enables the quantitative evaluation of the degree of myocardial ischemia at the distal end of the anastomosis and can more accurately determine whether to intervene.

In this report, Case 1 had 85% stenosis in the LAD at the distal end of the anastomosis of the LIMA-LAD graft. The measured FFR value was 0.75 (positive), and then balloon dilation was performed. The measured FFR value after drug balloon dilation was 0.94 (negative). The patient's symptoms were significantly relieved after intervention. In Case 2, although there was 75% stenosis at the anastomosis between the LIMA and the LAD, the FFR value was 0.83 (negative). This indicated that there may be no myocardial ischemia. Thus, intervention was not performed in Case 2, avoiding over-treatment. Case 2 was discharged after drug therapy.

Notably, this report is limited in that the measurement of FFR *via* LIMA was invasive and that we did not compare the FFR measured *via* LIMA with that measured by cardiac color Doppler.

CONCLUSION

In conclusion, we provided evidence that FFR measurement of grafted blood vessels, especially LIMA grafts, after CABG is a good method to determine the intervention course.

FOOTNOTES

Author contributions: Zhang LY, Gan YR and Wang YZ contributed equally to the study; Zhang LY, and Gan YR collected the cases and wrote the paper; Kou ZK and Kou XQ were responsible for surgical intervention; Zhang YL and Li B collected the data; Mao R was responsible for patient care; Liang TX was responsible for cardiopulmonary bypass; Xie J was responsible for clinical examination; Jin JJ analyzed the data; Xie DX, Wang YZ and Yang JM supervised the process, provided the financial support and revised the paper; All authors have read and approved the manuscript.

Supported by China Postdoctoral Science Foundation, No. 2021M693794; Health Key Science and Technology Development Project of Lanzhou, No. 2021006; Lanzhou Talent Innovation and Entrepreneurship Project, No. 2022-RC-51; and Gansu Province Double First-Class Scientific Research Key Project, No. GSSYLXM-05.

Informed consent statement: Informed written consents were obtained from the patients for publication of these two reports and any accompanying images.

Conflict-of-interest statement: All authors report having no relevant conflicts of interest for this article. The funders played no role in the study.

CARE Checklist (2016) statement: The authors have read CARE Checklist (2016), and the manuscript was prepared and revised according to CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Li-Ying Zhang 0000-0002-2667-659X; Yan-Zhen Wang 0000-0002-3627-5108; Jin-Mei Yang 0000-0003-0684-0548.

S-Editor: Li L
L-Editor: Filipodia
P-Editor: Yu HG

REFERENCES

1 **Song CX**, Dou KF. [Research progress of coronary function diagnosis]. *Zhongguo Xunhuan Zazhi* 2017; **32**: 403-405 [DOI: 10.3969/j.issn.1000-3614.2017.04.021]
2 **Pijls NH**, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation* 1993; **87**: 1354-1367 [PMID: 8462157 DOI: 10.1161/01.cir.87.4.1354]
3 **De Bruyne B**, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nüesch E, Jüni P; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014; **371**: 1208-1217 [PMID: 25176289 DOI: 10.1056/NEJMoa1408758]
4 **Driessen RS**, Danad I, Stuijfzand WJ, Raijmakers PG, Schumacher SP, van Diemen PA, Leipsic JA, Knuuti J, Underwood SR, van de Ven PM, van Rossum AC, Taylor CA, Knaapen P. Comparison of Coronary Computed Tomography Angiography, Fractional Flow Reserve, and Perfusion Imaging for Ischemia Diagnosis. *J Am Coll Cardiol* 2019; **73**: 161-173 [PMID: 30654888 DOI: 10.1016/j.jacc.2018.10.056]
5 **Zhao Q**, Yang Y, Zhu YP. [The state of the art for arterial coronary artery bypass grafting]. *Zhonghua Waike Zazhi* 2020; **58**: 337-340 [DOI: 10.3760/cma.j.cn112139-20200131-00050]

6 **Harky A**, Sankaranarayanan V, Kong QG. Internal mammary artery: the primary conduit for surgical revascularization. *Coron Artery Dis* 2021; **32**: 64-72 [PMID: 32310849 DOI: 10.1097/MCA.0000000000000895]

7 **Tonino PA**, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; **360**: 213-224 [PMID: 19144937 DOI: 10.1056/NEJMoa0807611]

8 **Chen J**, Wetzel LH, Pope KL, Meek LJ, Rosamond T, Walker CM. FFR(CT): Current Status. *AJR Am J Roentgenol* 2021; **216**: 640-648 [PMID: 33377794 DOI: 10.2214/AJR.20.23332]

9 **Mangiacapra F**, Bressi E, Sticchi A, Morisco C, Barbato E. Fractional flow reserve (FFR) as a guide to treat coronary artery disease. *Expert Rev Cardiovasc Ther* 2018; **16**: 465-477 [PMID: 29923434 DOI: 10.1080/14779072.2018.1489236]

10 **Smits PC**, Laforgia PL, Abdel-Wahab M, Neumann FJ, Richardt G, Boxma-de Klerk B, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Frederix GW, Omerovic E. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction: three-year follow-up with cost benefit analysis of the Compare-Acute trial. *EuroIntervention* 2020; **16**: 225-232 [PMID: 32250250 DOI: 10.4244/EIJ-D-20-00012]

11 **Tonino PA**, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 2010; **55**: 2816-2821 [PMID: 20579537 DOI: 10.1016/j.jacc.2009.11.096]

12 **Muller O**, Mangiacapra F, Ntalianis A, Verhamme KM, Trana C, Hamilos M, Bartunek J, Vanderheyden M, Wyffels E, Heyndrickx GR, van Rooij FJ, Witteman JC, Hofman A, Wijns W, Barbato E, De Bruyne B. Long-term follow-up after fractional flow reserve-guided treatment strategy in patients with an isolated proximal left anterior descending coronary artery stenosis. *JACC Cardiovasc Interv* 2011; **4**: 1175-1182 [PMID: 22035875 DOI: 10.1016/j.jcin.2011.09.007]

13 **Wardziak Ł**, Kruk M, Pleban W, Demkow M, Rużyłło W, Dzielińska Z, Kępka C. Coronary CTA enhanced with CTA based FFR analysis provides higher diagnostic value than invasive coronary angiography in patients with intermediate coronary stenosis. *J Cardiovasc Comput Tomogr* 2019; **13**: 62-67 [PMID: 30309764 DOI: 10.1016/j.jcct.2018.10.004]

14 **Higami T**, Yamashita T, Nohara H, Iwahashi K, Shida T, Ogawa K. Early results of coronary grafting using ultrasonically skeletonized internal thoracic arteries. *Ann Thorac Surg* 2001; **71**: 1224-1228 [PMID: 11308164 DOI: 10.1016/s0003-4975(00)02660-6]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3052-3061

DOI: 10.12998/wjcc.v11.i13.3052

ISSN 2307-8960 (online)

CASE REPORT

Uterine artery embolization combined with percutaneous microwave ablation for the treatment of prolapsed uterine submucosal leiomyoma: A case report

Hui-Li Zhang, Song-Yuan Yu, Chuan-Wu Cao, Jing-E Zhu, Jia-Xin Li, Li-Ping Sun, Hui-Xiong Xu

Specialty type: Obstetrics and gynecology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Di Meglio L, Italy

Received: December 3, 2022
Peer-review started: December 3, 2022
First decision: February 17, 2023
Revised: February 24, 2023
Accepted: March 31, 2023
Article in press: March 31, 2023
Published online: May 6, 2023

Hui-Li Zhang, Song-Yuan Yu, Jing-E Zhu, Jia-Xin Li, Li-Ping Sun, Department of Medical Ultrasound, Center of Minimally Invasive Treatment for Tumor, Shanghai Tenth People's Hospital, Shanghai 200072, China

Chuan-Wu Cao, Department of Interventional and Vascular Surgery, Shanghai Tenth People's Hospital, Shanghai 200072, China

Hui-Xiong Xu, Department of Ultrasound, Zhongshan Hospital, Shanghai 200032, China

Corresponding author: Hui-Xiong Xu, PhD, Professor, Department of Ultrasound, Zhongshan Hospital, No. 180 Fenglin Road, Xu Hui District, Shanghai 200032, China.
xuhuixiong2022@126.com

Abstract

BACKGROUND

Vaginal myomectomy is the most common form of radical treatment for prolapsed submucosal leiomyoma and is typically performed under general anesthesia. However, an alternative treatment approach is needed for patients who cannot tolerate general anesthesia. We describe a case with such a patient who was successfully treated *via* a minimally invasive method under local anesthesia.

CASE SUMMARY

A 46-year-old female suffered from abnormal uterine bleeding, severe anemia, and a reduced quality of life attributed to a massive prolapsed submucosal leiomyoma. She could not tolerate general anesthesia due to a congenital thoracic malformation and cardiopulmonary insufficiency. A new individualized combined treatment, consisting uterine artery embolization (UAE), percutaneous microwave ablation (PMWA) of the pedicle and the endometrium, and transvaginal removal of the leiomyoma by twisting, was performed. The lesion was completely removed successfully under local anesthesia without any major complications. The postoperative follow-up showed complete symptom relief and a significant improvement in the quality of life.

CONCLUSION

UAE combined with PMWA can be performed under local anesthesia and is a promising alternative treatment for patients who cannot tolerate general

anesthesia.

Key Words: Submucous leiomyoma; Percutaneous microwave ablation; Uterine artery embolism; Transvaginal myomectomy; Case report

Core Tip: Uterine leiomyoma is a clinically common and benign tumor. The mainstream treatment for prolapsed leiomyoma is myomectomy. General anesthesia is usually needed when resecting large lesions. However, for patients with severe systematic disease who cannot tolerate general anesthesia, radical treatment is not feasible. We report a patient who was treated successfully *via* a minimally invasive method under local anesthesia. A large prolapsed leiomyoma was removed after a combination of uterine artery embolism and percutaneous microwave ablation treatment. This is a good example of the use of minimally invasive interventional technology for treating special patients.

Citation: Zhang HL, Yu SY, Cao CW, Zhu JE, Li JX, Sun LP, Xu HX. Uterine artery embolization combined with percutaneous microwave ablation for the treatment of prolapsed uterine submucosal leiomyoma: A case report. *World J Clin Cases* 2023; 11(13): 3052-3061
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3052.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3052

INTRODUCTION

Uterine leiomyomas are the most common benign pelvic tumor in reproductive-aged women, with an incidence between 25% and 80% in the literature[1,2]. Submucosal leiomyomas can cause uterine cavity deformation, which usually leads to abnormal uterine bleeding (AUB), even if the lesion is small. Without effective treatment, leiomyomas may eventually protrude through the cervical canal and prolapse into the vagina, in which case they are classified as FIGO type 0[3]. For isolated prolapsed pedunculated submucosal leiomyomas, transvaginal myomectomy is the mainstream radical treatment, performed by twisting, ligation, or excision. For large lesions with a thick pedicle that cannot be removed by twisting alone, ligation or excision followed by hysteroscopic electrocoagulation under general or epidural anesthesia is usually indicated[4,5]. However, an alternative treatment is needed for patients with severe systemic disease who cannot tolerate hysteroscopic surgery or hysterectomy. Herein, we present a case of a large prolapsed pedunculated submucosal leiomyoma impacted in the cervical canal that was successfully treated with a new method, uterine artery embolization (UAE) combined with percutaneous microwave ablation (PMWA).

CASE PRESENTATION

Chief complaints

A 46-year-old female complained of prolonged menses, heavy menstrual bleeding (HMB) and severe anemia for 2 years, which led to a severely reduced quality of life.

History of present illness

In July 2019, the patient presented with intermenstrual bleeding and was diagnosed with a 2 cm submucosal leiomyoma in a local hospital but received no treatment. Half a year later, the patient began to experience HMB (sanitary towel changed every 1-2 h), prolonged menses (20 d), and severe anemia (minimal serum hemoglobin level 4.2 g/dL). Blood transfusion and iron supplementation were required on the heaviest days. Unfortunately, her cardiopulmonary function was not amenable to general anesthesia for hysteroscopic surgery. Therefore, the regimen was switched to medical therapy. Between July 2020 and June 2021, the patient underwent intramuscular injections of goserelin acetate 36 mg every three months, but the efficacy was unsatisfactory. Her menstrual length was 10-15 d, the pictorial blood-loss assessment chart (PBAC) scale score was 810, and the secondary anemia had not been corrected. In July 2022, the patient sought help at our clinic. The symptom severity score (SSS) and health-related quality of life (HRQOL) score were 75 and 12.07, respectively, according to the uterine fibroid symptoms and quality of life questionnaire[6]. Considering the patient's strong willingness to undergo radical treatment, we proposed a new plan: (1) Correct the anemia with pseudomenopausal therapy with combined oral contraceptive pills (COCs); and (2) determine a way to remove the prolapsed

myoma under local anesthesia to permanently eliminate the source of the AUB. After taking COCs for 3 mo, the patient's serum hemoglobin (Hb) level increased to 8.9 g/dL. Then, she was admitted to our hospital for further treatment.

History of past illness

Her medical history mainly included congenital scoliosis and thoracic deformity, pulmonary insufficiency, and pulmonary heart disease. The heart function stabilized to New York Heart Association Cardiac Function Classification I or II while on long-term cardiotonic (ivabradine hydrochloride tablet bid 5 mg) and diuretic medication (spironolactone bid 20 mg and hydrochlorothiazide bid 25 mg).

Personal and family history

No family history of AUB or other tumors was identified.

Physical examination

Vaginal examination revealed a 6 cm, dark red mass prolapsed into the vagina without significant mobility. The patient refused bimanual examination.

Laboratory examinations

Laboratory tests revealed mild anemia with an Hb of 9.2 g/dL and an estradiol level below 18.35 U/L, consistent with previous hormonal therapy. Pregnancy tests, vaginal bacteriology, cervical cytology, and tumor biomarkers were all negative. Studies for systemic coagulation disorders, von Willebrand disease, and thyroid dysfunction were also performed, but the results were unremarkable.

Imaging examinations

Chest X-ray showed that the patient's bilateral thorax was asymmetric, with severe scoliosis and increased and thickened bilateral lung markings (Figure 1). Electrocardiography revealed sinus tachycardia, and Doppler echocardiography showed mild pulmonary hypertension and mild regurgitation of the aortic, mitral, and tricuspid valves. Transabdominal ultrasound (TAUS) imaging revealed a mass prolapsing into the cervical canal (Figure 2A) with a large blood vessel embedded in the pedicle (Figure 2B). Contrast-enhanced ultrasound imaging (CEUS) showed that the two arteries in the pedicle were the main blood supply sources of the lesion (Figure 2C), one measuring 2.7 mm and the other 3 mm in diameter. Pelvic magnetic resonance imaging (MRI) demonstrated that the pedicle was attached to the posterior uterine inner wall (Figure 3A and B), and no evidence of malignancy was found on T2-weighted imaging or enhanced T1-weighted imaging.

CHIEF COMPLAINTS

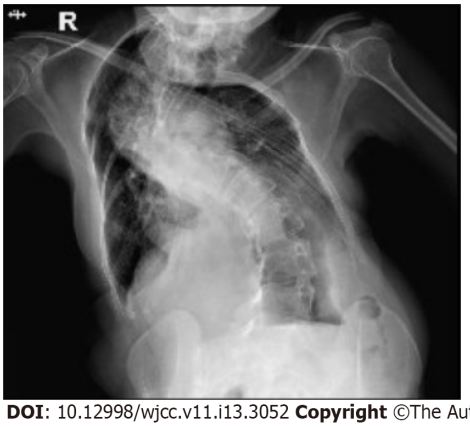
A 46-year-old female complained of prolonged menses, HMB and severe anemia for 2 years, which led to a severely reduced quality of life.

MULTIDISCIPLINARY EXPERT CONSULTATION

After systematic evaluation of the patient, a case discussion was conducted by a multidisciplinary collaborative group, which consisted of gynecologists, radiologists, and US interventionists, to formulate an optimal radical treatment protocol. Then, a new combined sequential two-session treatment plan was developed. Session one UAE involved blocking of the feeding arteries to reduce the risk of massive intraoperative intrauterine bleeding. Session two PMWA involved ablation of the pedicle, followed by removal of the lesion by twisting; the pedicle stump (to prevent intrauterine bleeding) and the endometrium (to eliminate potential concurrent endometrial hyperplasia, which might also contribute to heavy menstrual bleeding[7]) should be ablated at the same time.

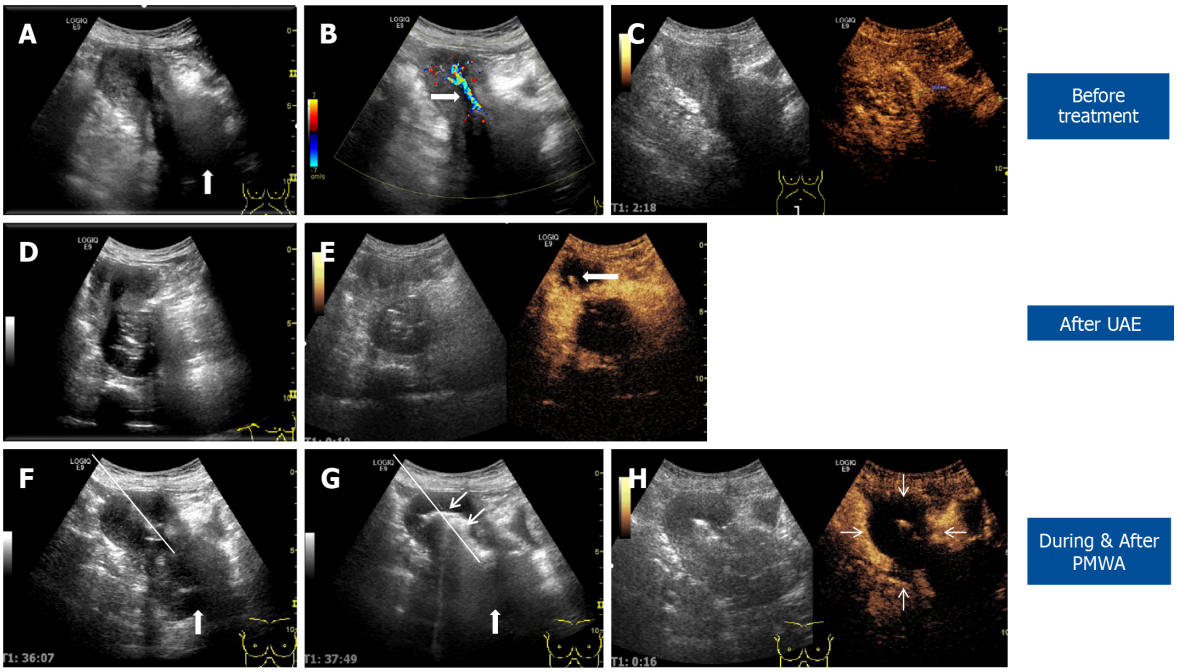
FINAL DIAGNOSIS

The diagnosis of this patient was defined clearly as a prolapsed pedicled submucous myoma, as its imaging manifestations were very typical. This could be proven by histopathological examination after lesion resection. The final diagnosis was uterine leiomyoma, as shown in the histopathological results (Figure 4).



DOI: 10.12998/wjcc.v11.i13.3052 **Copyright** ©The Author(s) 2023.

Figure 1 Chest X-ray examination after admission. Chest X-ray reveals severe scoliosis, thoracic deformity, and thickened lung markings.

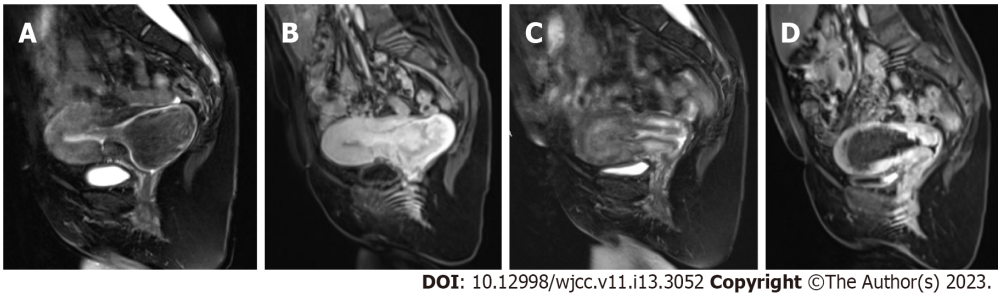


DOI: 10.12998/wjcc.v11.i13.3052 **Copyright** ©The Author(s) 2023.

Figure 2 Ultrasound imaging before, during and after treatment. A: B-mode ultrasound imaging (longitudinal section) demonstrates a homogeneous hypoechoic mass (TextTitle arrow) prolapsing into the cervical canal; B: Color Doppler flow imaging reveals a large blood vessel (TextTitle arrow) in the pedicle supplying the whole myoma; C: contrast-enhanced ultrasound imaging shows high enhancement in the pedicle, suggesting that it is the main blood supply source of the prolapsed lesion; D: Two days after UAE, both the uterus and myoma show slight atrophy; E: The upper segment of the pedicle shows enhancement on contrast-enhanced ultrasound imaging (TextTitle arrow), indicating partial recanalization of the feeding arteries; F: During the PMWA procedure, the microwave antenna (white line) was inserted into the pedicle precisely under real-time TAUS guidance; G: After thorough ablation of both the pedicle stump and the endometrium, a hyperechoic cloud covering the whole uterine cavity (arrows) is observed; H: Intraoperative contrast-enhanced ultrasound imaging shows no enhancement in the pedicle stump or the inner myometrium (arrows). UAE: Uterine artery embolism; PMWA: Percutaneous microwave ablation.

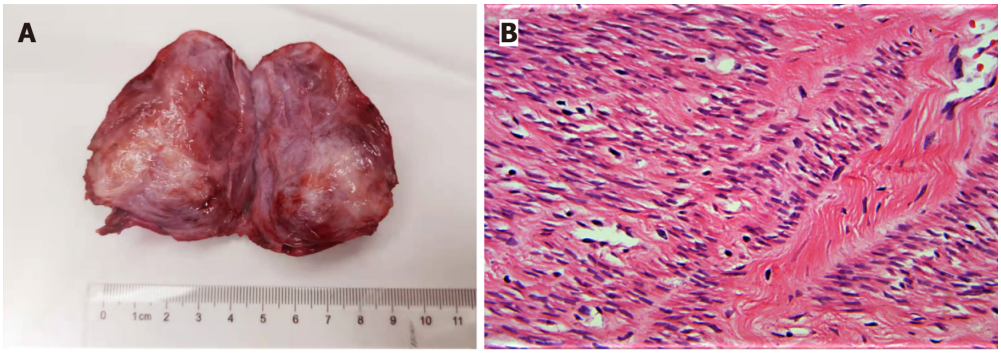
TREATMENT

After achieving consensus with the patient in terms of the therapeutic purposes and methods, the individualized therapy was implemented step by step. In session one, a standard UAE procedure was performed by a senior radiology interventional doctor. An angiographic imaging system (Siemens, Berlin, Germany) was used to perform pelvic digital subtraction angiography. Iopromide at 300 mg iodine/mL (Ultravist 240, Bayer Schering Pharma, Brussels, Belgium) was used to image the blood supply network, and 300-500 μm diameter, nonabsorbable polyvinyl alcohol (PVA) particles (Contour; Boston Scientific, Natick, Massachusetts, United States) were used to embolize the vascular network of the myoma. Before embolism, aortography revealed that the left uterine artery and two radial arteries downstream, which delivered nutrition to the pedicle in the early phase, were dilated (Figure 5A), while the bilateral uterine arteries supplied blood to the myoma in the late phase (Figure 5B). After the location of the opening of the uterine artery was identified with iodinated contrast media injection,



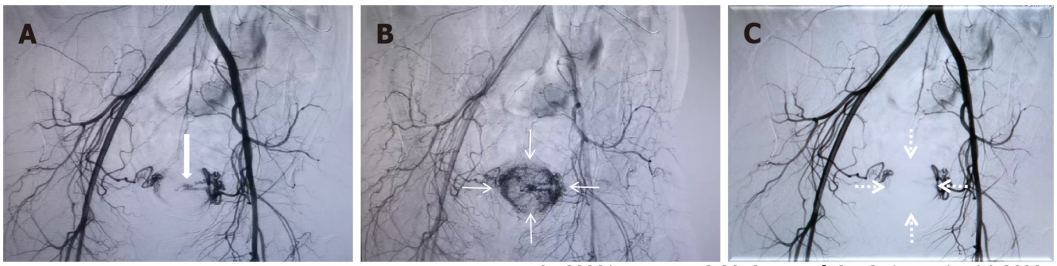
DOI: 10.12998/wjcc.v11.i13.3052 **Copyright** ©The Author(s) 2023.

Figure 3 Preoperative and postoperative magnetic resonance imaging demonstrations. A: Preoperative T2WI demonstrates a well-defined pedunculated submucosal myoma prolapsed into the cervical canal; B: Preoperative CE-T1WI shows enhancement of the pedicle and the myoma; C: Postoperative T2WI shows slight edema in the ablated inner myometrium and no damage to the outer myometrium or the surrounding organs; D: Postoperative CE-T1WI confirms no enhancement in the inner myometrium or tumor pedicle stump.



DOI: 10.12998/wjcc.v11.i13.3052 **Copyright** ©The Author(s) 2023.

Figure 4 Gross specimen and hematoxylin and eosin-stained image. A: Sectioned view of the resected specimen reveals a braided parenchymal mass without any significant degeneration; B: Hematoxylin and eosin-stained image shows abundant spindle smooth muscle cells and fibrous connective tissue with cellular heteromorphism.



DOI: 10.12998/wjcc.v11.i13.3052 **Copyright** ©The Author(s) 2023.

Figure 5 Findings for the blood supply of the myoma before and after uterine artery embolism. A: Aortography demonstrates a dilated left arcuate artery and two downstream radial arteries supplying the pedicle of the myoma; B: Bilateral uterine arteries contribute to the blood supply of the myoma; C: After complete occlusion of the radial arteries, no perfusion of the pedicle or myometrium is observed.

sufficient amounts of PVA particles were slowly injected into the feeding artery through a 3F catheter. Postembolism aortography confirmed that most of the radical arteries were blocked successfully (Figure 5C). The puncture site was locally pressurized with a pressure fixator, and the right lower extremity was immobilized for 6 h. The patient presented with fever, lower abdominal pain, and fatigue within 24 h, indicating postembolization syndrome. However, it was relieved after symptomatic treatment.

Two days after UAE, CEUS revealed significant lesion volume reduction (Figure 2D). Furthermore, significant perfusion was observed in part of the outer myometrium and the upper segment of the pedicle (Figure 2E), indicating collateral recanalization. Thus, session two of the treatment was scheduled on the same day and conducted smoothly under conscious sedation and analgesia. For preoperative analgesia, 40 μg dexmedetomidine (1 μg/kg) was diluted in normal saline to a concentration of 4 μg/mL and slowly pumped into the peripheral vein for the first 10 minutes; after that, injection of the drug was maintained at 0.2 μg/kg/h *via* a pump. For intraoperative analgesia, 30 mg of ketorolac tromethamine was injected as a slow bolus (> 15 s) *via* the peripheral vein. A monopolar

water-cooling MWA system (MTI-5A; 2450 MHz, Great Wall Medical Equipment Co. Ltd., Nanjing, China) equipped with a 14-gauge, 18 cm-long monopolar MWA antenna (XR-A2018W; Great Wall Medical Equipment Co. Ltd.) with a 1 cm active tip was used to carry out the PMWA procedure. The output power was set at 50-60 W. After local infiltration anesthesia with 0.1 g lidocaine hydrochloride, the microwave antenna was inserted into the pedicle under real-time TAUS guidance (Figure 2F). Then, the pedicle was ablated from deep to shallow with the "moving-shot" technique until the entire pedicle was covered by a hyperechoic cloud. After intraoperative CEUS confirmed no enhancement throughout the pedicle, the myoma was clamped with oval forceps and removed by twisting. Finally, the pedicle stump and the endometrium of the upper and middle uterine cavity were ablated. The PMWA procedure was considered complete after B-mode US imaging revealed that the whole uterine cavity was covered by a hyperechoic cloud (Figure 2G). Then, CEUS was performed again, and the results showed no signs of intrauterine bleeding (Figure 2H).

Two days later, postoperative MRI revealed that the anatomy of the uterus had returned to normal (Figure 3C), and half of the outer myometrium had regained perfusion (Figure 3D). The postoperative course was uneventful, and the patient was discharged 3 days later.

OUTCOME AND FOLLOW-UP

After the treatment, the patient achieved complete symptom relief. As we expected, the patient developed amenorrhea between 2 and 5 mo after treatment, and her Hb increased to normal levels at 3 mo (Figure 6A). During this period, the patient had mild lower abdominal pain for a week, which was relieved after traditional Chinese medical treatment. At the 6-month follow-up, the patient's weight increased from 37 kg to 42 kg (Figure 6B), the menstrual length decreased to 6 days (Figure 6C), PBAC score decreased from 810 to 38 (Figure 6D), the SSS score decreased from 75 to 0 (Figure 6E), and the HRQOL score increased from 12.07 to 92.24 (Figure 6F). No major complications were recorded.

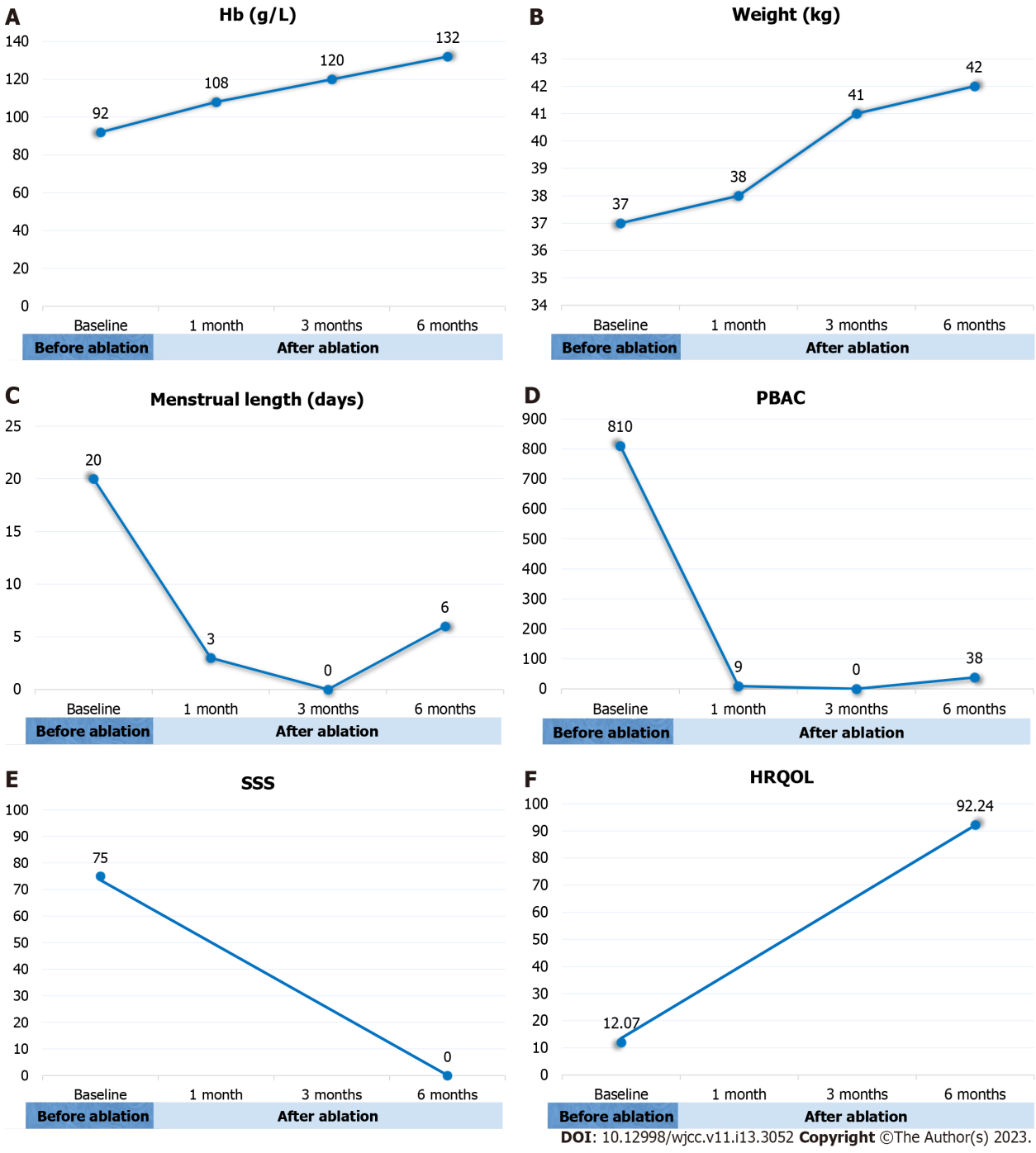
DISCUSSION

Most international guidelines agree that hysteroscopic myomectomy should be used as the first-line treatment for the management of symptomatic submucosal leiomyomas[8,9]. As surgeons accumulate sufficient skills and experience in this field, the clinical indications for hysteroscopic myomectomy are also gradually expanding to almost all submucosal leiomyomas[8,10,11], with success rates of 95% in the literature[12]. For women with a submucosal leiomyoma who have completed childbearing, endometrial ablation can be combined with hysteroscopic myomectomy for increased efficacy[7,13]. However, for the special case we described, the history of systemic disease limited the spectrum of available treatment options, and the traditional radical treatment through hysteroscopic myomectomy was considered unsuitable. As the efficacy of conservative drug treatment was not satisfactory, an alternative treatment was needed.

Several alternative, minimally invasive treatments have been developed for treating uterine leiomyomas in the past 20 years, including transcatheter UAE, MR or ultrasound (US)-guided high-intensity focused ultrasound (HIFU), US-guided MWA and radiofrequency ablation (RFA)[14-16]. With the exception of HIFU, which was not feasible in our case due to depth limitations, the other methods were all candidates for further treatment[17,18]. Their mechanisms are similar in that all can destroy the lesion blood supply network, indirectly or directly leading to coagulation and necrosis as well as tumor volume reduction several months after treatment. They are all promising methods for alleviating the symptoms of AUB, but naturally, they are associated with certain risks of complications[15]. For UAE, posttreatment complications mainly include pain, postembolism syndrome, pelvic infection, amenorrhea, and occasional embolism of the ovarian artery[19]. Minor complications after US-guided in situ thermal ablation (MWA or RFA) are similar and include pain, fever, pelvic infection, and vaginal discharge of necrotic tissue[20,21]. However, our patient had a strong desire to remove the leiomyoma during one hospitalization, which could not be achieved by applying any of the above technologies alone. Our idea to solve this problem was to leverage each technique and invent a new hybrid method mimicking the standard procedure for transcervical myoma removal.

In this new hybrid method, real-time US imaging was used to guide and monitor the surgery instead of hysteroscopy; UAE followed by PMWA was adopted to devascularize and dissect the pedicle, achieve intrauterine hemostasis, and perform endometrial ablation. To our knowledge, this method has not yet been reported.

When direct hysteroscopy guidance is not available, real-time US imaging becomes the best choice for guided treatment. Contrast-enhanced MRI and CEUS both play an important role in preoperative evaluation and local response evaluation after nonsurgical interventional treatment of uterine benign diseases[22]. In this case, with CEUS assessment before treatment, we preliminarily characterized the blood supply of the lesions, which provided a basis for assessing the bleeding risk and formulating the radical treatment plan. The second day after UAE, we observed partial vascular recanalization in the



DOI: 10.12998/wjcc.v11.i13.3052

Figure 6 Changes in weight, hemoglobin level and clinical scores. A: The Hb level increased to normal range 3 mo after treatment; B: The patient had gained weight gradually after ablation; C: Menstrual length was 6 mo for each cycle 6 mo after treatment; D: The patient had a transient amenorrhea from 3 to 5 mo after treatment, and returned to normal mense 6 mo after treatment with a PBAC score < 100; E: SSS score decreased from 75 to 0 after treatment, indicating complete relief of symptoms; F: HRQOL score increased from 12.07 to 92.24 at 6 mo after treatment, indicating huge improvement of the life quality. Hb: Hemoglobin; PBAC: Pictorial blood-loss assessment chart; SSS: Symptom severity scale; HRQOL: Health-related quality of life.

pedicle through CEUS examination, which indirectly confirmed the opening of some collateral branches of the uterine arteries, providing a basis for determining the optimal time for subsequent PMWA treatment. Finally, during the PMWA session, CEUS was used to detect potential intrauterine hemorrhage and evaluate the local response following thermal coagulation of the pedicle stump and the endometrium instead of hysteroscopy. This could inspire future PMWA treatments for patients with AUB caused by leiomyoma or adenomyosis.

The reasons why we used PMWA to assist in the dissection of the thick pedicle in this case were as follows. Electronic energy has been widely used to stop bleeding by inducing thermal coagulation and to cut tissue and seal vasculature with high power[23-25]. With different outpower settings and working durations of the electronic surgical instruments, protein denaturation, tissue necrosis, and even explosive vaporization of cells can be induced. Therefore, we used electronic surgical devices to cut

tissue, achieve intraoperative hemostasis, and directly seal the vasculature. US-guided PMWA with 60 W output power can quickly increase the tissue temperature within the electromagnetic field to 60-100°C, which is sufficient to induce tissue necrosis and small vessel occlusion[20,21,26]. Therefore, if the microwave antenna was pointed for a long enough duration in the direction perpendicular to the long axis of the pedicle, it could also be used to cut tissues. Li *et al*[27] reported that RFA of 80-90 W output power effectively blocked the feeding artery of a liver tumor with a diameter ≤ 3 mm with a success rate of 100%. Unfortunately, there is no clinical evidence that US-guided in situ thermal ablations could be used to block the feeding artery of a prolapsed submucosal leiomyoma, and further study is needed. Therefore, there was a potential risk of massive intraoperative bleeding when using the PMWA technique alone to block the feeding artery. As UAE has unique advantages in achieving hemostasis, it is often used in combination with surgery to treat large submucosal myomas with a high risk of intraoperative bleeding[28]. UAE is recommended by several guidelines as an alternative treatment for symptomatic uterine leiomyomas, including submucosal myomas[19,29,30]. Therefore, UAE was preoperatively performed to create a safe condition for the ultimate radical treatment. The planned sequential treatments were carried out successfully, and the patient was eventually cured.

CONCLUSION

This case demonstrates a new combined minimally invasive treatment for large prolapsed submucosal leiomyomas with a thick pedicle that can be performed under local anesthesia. This new method has potential as an alternative treatment for patients who cannot tolerate general anesthesia.

ACKNOWLEDGEMENTS

I would like to express my gratitude to all those who helped me during the writing of this paper. I gratefully acknowledge the help of Prof. Xu for his professional instruction and Prof. Yu who offered me valuable suggestions in the exploration of new clinical treatment methods. I would also like to thank Prof. Cao for his professional help and cooperation in the sequential treatment of this patient.

FOOTNOTES

Author contributions: Zhang HL contributed to manuscript writing and editing and data collection; Cao CW and Yu SY contributed to session one and session two of the treatment procedure; Li JX, Zhu JE, and Sun LP contributed to the evaluation and treatment of the patient; Xu HX contributed to the conceptualization and supervision of the study; all authors have read and approved the final manuscript.

Supported by Science and Technology Commission of Shanghai Municipality, China, No. 19DZ2251100; Shanghai Municipal Health Commission, China, No. SHSLCZDZK 03502; National Natural Science Foundation of China, No. 81725008.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Hui-Li Zhang 0000-0003-3509-9963; Song-Yuan Yu 0000-0003-3563-1884; Chuan-Wu Cao 0009-0003-4149-1803; Jing-E Zhu 0000-0003-2841-0733; Jia-Xin Li 0000-0002-5370-2634; Li-Ping Sun 0000-0002-4301-4520; Hui-Xiong Xu 0000-0002-8699-854X.

S-Editor: Ma YJ
L-Editor: A

P-Editor: Zhao S

REFERENCES

1 **Giuliani E**, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. *Int J Gynaecol Obstet* 2020; **149**: 3-9 [PMID: 31960950 DOI: 10.1002/ijgo.13102]

2 **Stewart EA**, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. *BJOG* 2017; **124**: 1501-1512 [PMID: 28296146 DOI: 10.1111/1471-0528.14640]

3 **Munro MG**, Critchley HO, Broder MS, Fraser IS; FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. *Int J Gynaecol Obstet* 2011; **113**: 3-13 [PMID: 21345435 DOI: 10.1016/j.ijgo.2010.11.011]

4 **Keizer AL**, Jacobs BL, Thurkow AL, de Lange ME, Radder CM, van Kesteren PJM, Hanstede MMF, Huirne JAF, Hehenkamp WJK. The effect of transcervical resection of submucous fibroids on menstrual blood loss: A prospective cohort study. *Eur J Obstet Gynecol Reprod Biol* 2022; **274**: 128-135 [PMID: 35640441 DOI: 10.1016/j.ejogrb.2022.05.019]

5 **van Wessel S**, van Vliet HAAM, Schoot BC, Weyers S, Hamerlynck TWO. Hysteroscopic morcellation versus bipolar resection for removal of type 0 and 1 submucous myomas: A randomized trial. *Eur J Obstet Gynecol Reprod Biol* 2021; **259**: 32-37 [PMID: 33571839 DOI: 10.1016/j.ejogrb.2021.01.050]

6 **Spies JB**, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. *Obstet Gynecol* 2002; **99**: 290-300 [PMID: 11814511 DOI: 10.1016/s0029-7844(01)01702-1]

7 **Stewart EA**. Clinical practice. Uterine fibroids. *N Engl J Med* 2015; **372**: 1646-1655 [PMID: 25901428 DOI: 10.1056/NEJMcp1411029]

8 **Amoah A**, Joseph N, Reap S, Quinn SD. Appraisal of national and international uterine fibroid management guidelines: a systematic review. *BJOG* 2022; **129**: 356-364 [PMID: 34532956 DOI: 10.1111/1471-0528.16928]

9 **Loddo A**, Djokovic D, Drizi A, De Vree BP, Sedrati A, van Herendael BJ. Hysteroscopic myomectomy: The guidelines of the International Society for Gynecologic Endoscopy (ISGE). *Eur J Obstet Gynecol Reprod Biol* 2022; **268**: 121-128 [PMID: 34902749 DOI: 10.1016/j.ejogrb.2021.11.434]

10 **Brito LG**, Magnani PS, de Azevedo Trapp AE, Sabino-de-Freitas MM. Giant prolapsed submucous leiomyoma: a surgical challenge for gynecologists. *Clin Exp Obstet Gynecol* 2011; **38**: 299-300 [PMID: 21995173]

11 **CRezk A**, Kahn J, Singh M. Fertility sparing management in uterine fibroids. Treasure Island (FL): StatPearls Publishing, 2022

12 **Rolli R**, Favilli A, Acanfora MM, Scuderi G, Di Renzo GC, Gerli S. Vaginal myomectomy is a safe and feasible procedure: a retrospective study of 46 cases. *J Obstet Gynaecol Res* 2012; **38**: 1201-1205 [PMID: 22563644 DOI: 10.1111/j.1447-0756.2012.01852.x]

13 **Brun JL**, Plu-Bureau G, Huchon C, Ah-Kit X, Barral M, Chauvet P, Cornelis F, Cortet M, Crochet P, Delporte V, Dubernard G, Giraudet G, Gosset A, Graesslin O, Hugon-Rodin J, Lecointre L, Legendre G, Maitrot-Mantelet L, Marcellin L, Miquel L, Le Mitouard M, Proust C, Roquette A, Rousset P, Sangnier E, Sapoval M, Thubert T, Torre A, Trémollières F, Vernhet-Kovacsik H, Vidal F, Marret H. [Management of women with abnormal uterine bleeding: Clinical practice guidelines of the French National College of Gynecologists and Obstetricians (CNGOF)]. *Gynecol Obstet Fertil Senol* 2022; **50**: 345-373 [PMID: 35248756 DOI: 10.1016/j.gofs.2022.02.078]

14 **Wang Y**, Zhang S, Li C, Li B, Ouyang L. Minimally invasive surgery for uterine fibroids. *Ginekol Pol* 2020; **91**: 149-157 [PMID: 32266956 DOI: 10.5603/GP.2020.0032]

15 **Ierardi AM**, Savasi V, Angileri SA, Petrillo M, Sbaraini S, Pinto A, Hanozet F, Marconi AM, Carrafiello G. Percutaneous High Frequency Microwave Ablation of Uterine Fibroids: Systematic Review. *Biomed Res Int* 2018; **2018**: 2360107 [PMID: 29511672 DOI: 10.1155/2018/2360107]

16 **Yang Y**, Zhang J, Han ZY, Yu MA, Ma X, Zhou HY, Hao YL, Zhao L, Dong XJ, Ge HL. Ultrasound-guided percutaneous microwave ablation for submucosal uterine fibroids. *J Minim Invasive Gynecol* 2014; **21**: 436-441 [PMID: 24316137 DOI: 10.1016/j.jmig.2013.11.012]

17 **Fan HJ**, Cun JP, Zhao W, Huang JQ, Yi GF, Yao RH, Gao BL, Li XH. Factors affecting effects of ultrasound guided high intensity focused ultrasound for single uterine fibroids: a retrospective analysis. *Int J Hyperthermia* 2018; **35**: 534-540 [PMID: 30428735 DOI: 10.1080/02656736.2018.1511837]

18 **Anneveldt KJ**, Verpalen IM, Nijholt IM, Dijkstra JR, van den Hoed RD, Van't Veer-Ten Kate M, de Boer E, van Osch JAC, Heijman E, Naber HR, Ista E, Franx A, Veersema S, Huirne JAF, Schutte JM, Boomsma MF. Lessons learned during implementation of MR-guided High-Intensity Focused Ultrasound treatment of uterine fibroids. *Insights Imaging* 2021; **12**: 188 [PMID: 34921657 DOI: 10.1186/s13244-021-01128-w]

19 **Lang JH**, Chen CL, Xiang Y. [Expert consensus of uterine artery embolization in the management of uterine fibroids and adenomysis]. *Zhonghua Fu Chan Ke Za Zhi* 2018; **53**: 289-293 [PMID: 29804344 DOI: 10.3760/CMA.j.issn.0529-567x.2018.05.001]

20 **Zhang J**, Guan Z, Qian LX, Sheng L, Zhang W, Li XH, Li CG, Jiang H. [The guideline and recommendations of the clinical application of ultrasound-guided percutaneous microwave/radiofrequency ablation in the treatment of uterine fibroids]. *Zhonghua Yixue Chaosheng Zazhi* 2015; **12** (5): 353-356 [DOI: 10.3877/CMA.j.issn.1672-6448.2015.05.004]

21 **Li QY**, Li XL, Deng EY, Yu SY, Sun LP, Zhang HL, Zhu JE, Li JX, Xu HX. Ultrasound-guided percutaneous microwave ablation for uterine fibroids: mid-term local treatment efficiency and associated influencing factors. *Br J Radiol* 2022; **95**: 20220039 [PMID: 35762323 DOI: 10.1259/bjr.20220039]

22 **Sidhu PS**, Cantisani V, Dietrich CF, Gilja OH, Saftoiu A, Bartels E, Bertolotto M, Calliada F, Clevert DA, Cosgrove D,

Deganello A, D'Onofrio M, Drudi FM, Freeman S, Harvey C, Jenssen C, Jung EM, Klauser AS, Lassau N, Meloni MF, Leen E, Nicolau C, Nolsoe C, Piscaglia F, Prada F, Prosch H, Radzina M, Savelli L, Weskott HP, Wijkstra H. The EFSUMB Guidelines and Recommendations for the Clinical Practice of Contrast-Enhanced Ultrasound (CEUS) in Non-Hepatic Applications: Update 2017 (Long Version). *Ultraschall Med* 2018; **39**: e2-e44 [PMID: 29510439 DOI: 10.1055/a-0586-1107]

23 **Tani T**, Naka S, Tani S, Shiomi H, Murakami K, Yamada A, Khiem DT. The invention of microwave surgical scissors for seamless coagulation and cutting. *Surg Today* 2018; **48**: 856-864 [PMID: 29748826 DOI: 10.1007/s00595-018-1662-7]

24 **Dang KT**, Naka S, Nguyen VQ, Yamada A, Tani T. Functional Evaluation of a Novel Microwave Surgical Device in a Canine Splenectomy Model. *J Invest Surg* 2021; **34**: 164-171 [PMID: 31179802 DOI: 10.1080/08941939.2019.1619884]

25 **Beisenova A**, Issatayeva A, Ashikbayeva Z, Jelbuldina M, Aitkulov A, Inglezakis V, Blanc W, Saccomandi P, Molardi C, Tosi D. Distributed Sensing Network Enabled by High-Scattering MgO-Doped Optical Fibers for 3D Temperature Monitoring of Thermal Ablation in Liver Phantom. *Sensors (Basel)* 2021; **21** [PMID: 33513666 DOI: 10.3390/s21030828]

26 **Zhang H**, Yu S, Xu H. Ultrasound-guided microwave ablation for symptomatic adenomyosis: More areas of concern for more uniform and promising outcomes. *J Interv Med* 2022; **5**: 122-126 [PMID: 36317146 DOI: 10.1016/j.jimed.2022.06.001]

27 **Li X**, Xu M, Liu M, Tan Y, Zhuang B, Lin M, Kuang M, Xie X. Contrast-enhanced ultrasound-guided feeding artery ablation as add-on to percutaneous radiofrequency ablation for hypervascular hepatocellular carcinoma with a modified ablative technique and tumor perfusion evaluation. *Int J Hyperthermia* 2020; **37**: 1016-1026 [PMID: 32865050 DOI: 10.1080/02656736.2020.1811902]

28 **Namkung J**, Kang SY, Chung YJ, Cho HH, Kim JH, Kim MR. Multidisciplinary Approach in Large-sized Submucosal Myoma: Hysteroscopic Myomectomy after Uterine Artery Embolization. *J Minim Invasive Gynecol* 2019; **26**: 643-647 [PMID: 29969685 DOI: 10.1016/j.jmig.2018.06.016]

29 **American College of Obstetricians and Gynecologists**. ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas. *Obstet Gynecol* 2008; **112**: 387-400 [PMID: 18669742]

30 **Kim MD**. Uterine Artery Embolization for Leiomyomas and Adenomyosis: A Pictorial Essay Based on Our Experience from 1300 Cases. *Korean J Radiol* 2019; **20**: 1462-1473 [PMID: 31544371 DOI: 10.3348/kjr.2019.0205]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3062-3069

DOI: 10.12998/wjcc.v11.i13.3062

ISSN 2307-8960 (online)

CASE REPORT

Metachronous urothelial carcinoma in the renal pelvis, bladder, and urethra: A case report

Jian-Qing Zhang, Yu Duan, Kun Wang, Xiao-Li Zhang, Ke-Hua Jiang

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Morozov S, Russia; Mao YM, China

Received: November 28, 2022
Peer-review started: November 28, 2022
First decision: December 19, 2022
Revised: February 6, 2023
Accepted: March 31, 2023
Article in press: March 31, 2023
Published online: May 6, 2023

Jian-Qing Zhang, Yu Duan, Kun Wang, Ke-Hua Jiang, Department of Urology, Guizhou Provincial People's Hospital, Guiyang 550002, Guizhou Province, China

Xiao-Li Zhang, Department of Biomedicine, Guizhou University, Guiyang 550025, Guizhou Province, China

Corresponding author: Ke-Hua Jiang, MD, Professor, Department of Urology, Guizhou Provincial People's Hospital, No. 52 Zhongshan East Road, Nanming District, Guiyang 550002, Guizhou Province, China. tjjkh@sina.com

Abstract

BACKGROUND

Urothelial carcinoma (UC) is a common malignancy of the urinary system that can occur anywhere from the renal pelvis to the proximal urethra. Most UCs are in the bladder and have multifocal growth. Upper urinary tract UC (UTUC), which occurs in the renal pelvis or ureter, accounts for only 5% to 10% of UCs.

CASE SUMMARY

In March 2015, a 70-year-old male who initially presented to a local hospital with a complaint of painless hematuria was diagnosed with UTUC of the right renal pelvis. The doctors administered radical nephroureterectomy and bladder cuff excision. Although the doctors recommended intravesical chemotherapy and regular follow-up, he rejected this advice. In December 2016, the patient presented at our hospital with dysuria. We identified UC in the residual bladder and administered radical cystectomy and left cutaneous ureterostomy. In November 2021, he presented again with urethral bleeding. We detected urethral UC as the cause of urethral orifice bleeding and administered radical urethrectomy. Since then, he has visited regularly for 6-mo follow-ups, and was in stable condition as of December 2022.

CONCLUSION

UTUC is prone to seeding and recurrence. Adjuvant instillation therapy and intense surveillance are crucial for these patients.

Key Words: Upper urinary tract urothelial carcinoma; Bladder urothelial carcinoma; Urethral urothelial carcinoma; Treatment; Case report

Core Tip: Urothelial carcinoma (UC) is a common malignancy in the urinary system, and typically grows from multiple foci. UC is most common in the bladder, and upper urinary tract UC (UTUC) is rare. We describe a male who initially presented at a local hospital in 2015 at the age of 70 years with a complaint of painless hematuria. The doctors diagnosed UTUC of the right renal pelvis. After radical nephroureterectomy and bladder cuff excision, the doctors recommended intravesical chemotherapy and regular follow-up, but he rejected this advice. He presented at our hospital again with dysuria in 2016. We identified UC in the residual bladder and performed radical cystectomy and left cutaneous ureterostomy. Unfortunately, he presented again with urethral orifice bleeding in 2021, and we identified urethral UC as the cause. We thus administered radical urethrectomy. Since this last surgery, he has received regular 6-mo follow-ups and has remained in a stable condition. Treatment for upper UTUC should include adjuvant instillation as immunotherapy and intense surveillance.

Citation: Zhang JQ, Duan Y, Wang K, Zhang XL, Jiang KH. Metachronous urothelial carcinoma in the renal pelvis, bladder, and urethra: A case report. *World J Clin Cases* 2023; 11(13): 3062-3069
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3062.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3062

INTRODUCTION

Urothelial carcinoma (UC) is a common urological malignancy. Bladder tumors account for 90% to 95% of UCs, and upper urinary tract UCs (UTUCs) account for only 5 to 10%[1,2]. Urethral cancer is a rare malignancy of the urinary system (< 1% of all malignancies), and the predominant histological type is UC[3]. Recurrence of UTUC in the bladder occurs in 22% to 47% of these patients, and recurrence in the contralateral upper urinary tract occurs in only 2% to 6%[4,5]. A metachronous UC is a primary UC in which a second primary cancer is diagnosed more than 6 mo after the first primary cancer. There are no previous reports of metachronous UC in the upper urinary tract, bladder, and urethra. Herein, we report such a case to improve recognition and management of this disease.

CASE PRESENTATION

Chief complaints

A 70-year-old male was admitted to our department with a complaint of bloody urethral discharge during the previous month.

History of present illness

The patient reported bloody urethral discharge for one month. He had no flank pain or urethral pain.

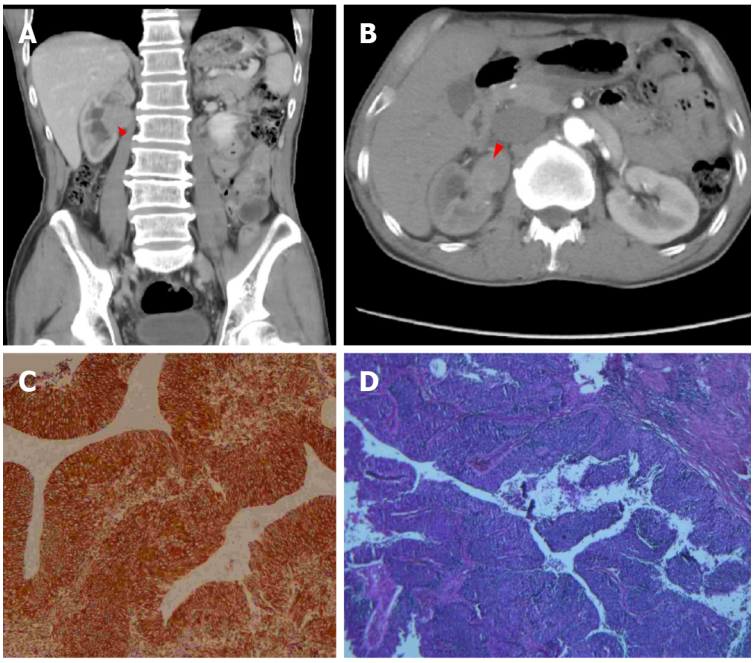
History of past illness

In March 2015, this patient was admitted to a local hospital for painless hematuria. Percussion of the kidneys indicated no enlargement and no renal mass. A cystoscopy indicated hematuria from the right ureteral orifice, but no mass in the bladder or urethra. Computed tomography (CT) of the abdomen showed a tumor with a size of 3.6 cm × 2.9 cm in the right renal pelvis (Figure 1). The urine cytology results were negative.

The doctors performed radical nephroureterectomy and bladder cuff resection. Postoperative pathology showed that the tumor was a high-grade UC that invaded the subepithelial connective tissue (Figure 1). There was no evidence of local or distant metastases. These findings led to a diagnosis of upper UTUC of the right renal pelvis with a clinical stage of T1N0M0. We recommended Bacillus Calmette-Guérin (BCG) intravesical chemotherapy, but he declined and was lost to follow-up.

In December 2016, the patient came to our department because of dysuria for three months. Percussion of the kidneys and inspection of the lymph nodes indicated no enlargement. The red blood cell count was 4.10×10^{12}/L and the hemoglobin concentration was 131.0 g/L. Blood biochemistry showed elevated levels of cancer antigen 19-9: 48.32 U/mL and non-small cell lung cancer antigen: 9.51 U/mL.

Ultrasonography showed multiple masses in the bladder, and a chest X-ray showed a hyperdense nodule with a diameter of 4 mm in the inferior lobe of the right lung (data not shown). Enhanced CT of the urinary tract showed multiple masses in the bladder, the largest of which was about 6.5 cm × 5.0 cm (Figure 2), but there was no evidence of enlarged lymph nodes in the abdominal cavity, the retroperitoneal space, or the pelvic cavity. A cystoscopy confirmed multiple tumors in the bladder, and a biopsy showed no umbrella cells, but evidence of pathological mitotic figures and tissue consisting of low-



DOI: 10.12998/wjcc.v11.i13.3062 **Copyright** ©The Author(s) 2023.

Figure 1 Radiological and histological analysis of the patient at the first hospitalization. A: Computed tomography (CT) identified a mass in the right pelvis in longitudinal section (red arrowhead); B: CT identified a mass in the right pelvis in cross-section (red arrowhead); C: Hematoxylin and eosin staining indicated the tumor was a urothelial carcinoma; D: CK7 staining indicated the tumor was a urothelial carcinoma.

grade UC. We therefore, performed radical cystectomy and left cutaneous ureterostomy. The postoperative pathology results showed the tumor was a low-grade UC that invaded the superficial muscle of bladder wall (Figure 2), but there were no positive margins or involved lymph nodes. Immunohistochemistry showed positive staining for CK7, CK20, CK (L), CK5/6, P40, P53, PHH3, and Ki-67, but no staining for CK (H). There were no local or distant metastases. We therefore diagnosed the patient as having bladder UC with a clinical stage of T2N0M0.

The patient denied any history of injury to the penis, scrotum, or perineum before development of bloody urethral discharge.

Personal and family history

He reported smoking 10 cigarettes daily for over 40 years, and consuming white wine for more than 30 years. He quit smoking and consuming white wine in 2017. There were no similar cases in his family.

Physical examination

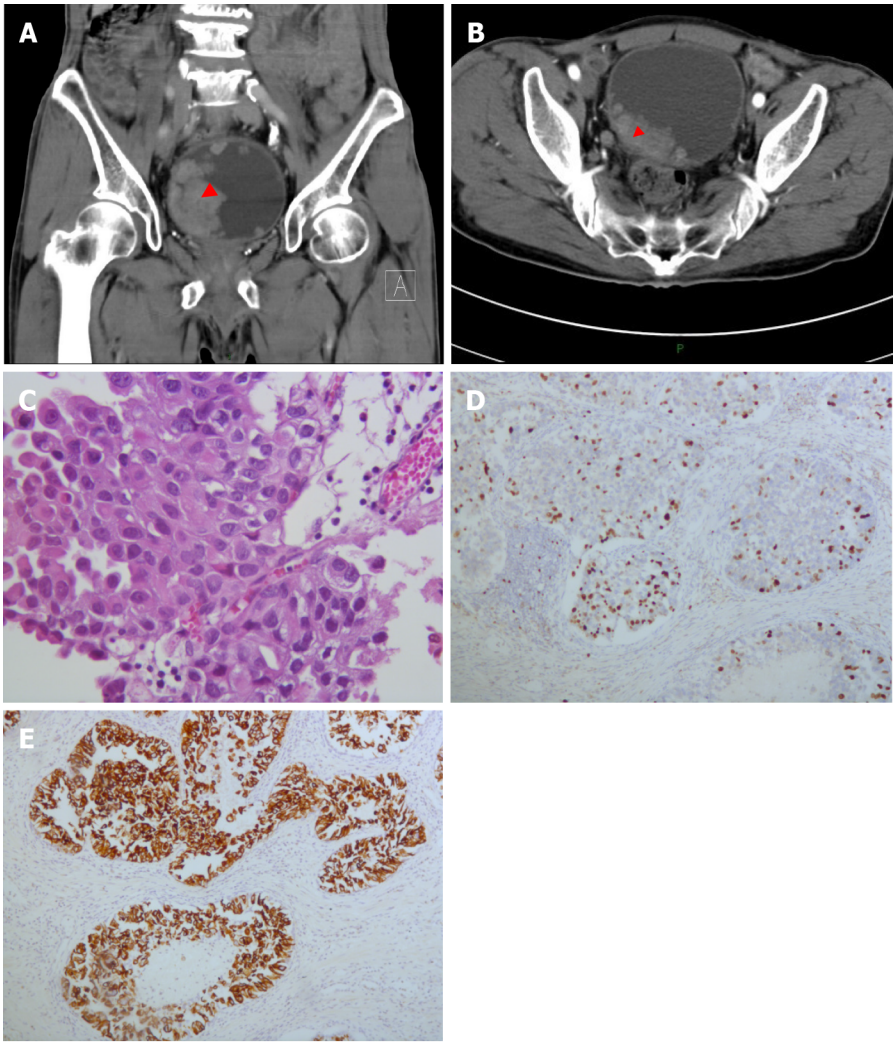
Percussion of the kidneys indicated no enlargement and no renal mass. We observed a 15 cm surgical scar at the right waist, and another 7 cm surgical scar at the lower right abdomen. We also observed that a stoma bag on the left side of the abdomen contained light yellow urine. All the vital signs were stable and there were no other abnormal findings.

Laboratory examinations

Urethroscopy showed a cauliflower-shaped neoplasm with a size of 2.0 cm × 1.5 cm × 0.5 cm in the anterior urethra, and a biopsy revealed the tissue consisted of low-grade UC. The routine blood test showed high levels of white blood cells (12.07×10^9/L) and neutrophils (89.0%), but low levels of red blood cells (4.02×10^{12}/L), hemoglobin (131.0 g/L), and lymphocytes (4.1%). The blood biochemistry showed low levels of estimated glomerular filtration rate (61 mL/min/1.73 m^2) and total protein (61.8 g/L), but a high level of uric acid (438 μmol/L). The coagulation test and the prostate specific antigen test showed no abnormal changes. The results of all other examinations were normal.

Imaging examinations

Except for the absence of the right kidney, there were no abnormal findings in the color Doppler ultrasonography.



DOI: 10.12998/wjcc.v11.i13.3062 **Copyright** ©The Author(s) 2023.

Figure 2 Radiological and histological analysis of the patient at the second hospitalization. A: Computed tomography (CT) showed multiple neoplasms in the bladder in longitudinal section (red arrowhead); B: CT showed multiple neoplasms in the bladder in cross-section (red arrowhead); C-E: Hematoxylin and eosin staining (C) and positive staining for Ki-67 (D) and CK7 (E) confirmed urothelial carcinoma.

FINAL DIAGNOSIS

After admission, the patient was diagnosed with urethral UC.

TREATMENT

We decided radical urethrectomy was the most suitable treatment. Postoperative pathology showed that the urethral tumor consisted of 80% low-grade papillary UC and 20% high-grade papillary UC, and that the tumor invaded the lamina propria. There was no evidence of local or distant metastasis or lymph node involvement. We therefore diagnosed the patient with urethral UC with a clinical stage of T1N0M0[6].

OUTCOME AND FOLLOW-UP

Since this surgery, the patient has visited every 6 mo for follow-up, and was in stable condition as of December 2022. Figure 3 summarizes the treatment timeline.

DOI: 10.12998/wjcc.v11.i13.3062

Figure 3 Treatment timeline of the patient. UC: Urothelial carcinoma.

DISCUSSION

The urinary tract is divided into two parts: The upper region includes the kidneys and ureters and the lower region includes the bladder and urethra. UC is a common malignant tumor of the urinary system. The bladder is the most common site of UC, UTUC is rare[4,5], and urethral UC is even more rare (< 1% of all malignancies)[3]. A metachronous UC, in which a second primary cancer is diagnosed more than 6 mo after the first primary cancer, occurs in a small number of these patients.

The main clinical manifestations of UTUC are hematuria, dysuria, and flank pain. Hematuria is the most common sign, and is painless when it is the sole manifestation. Flank pain is a sign of obstruction and/or hydronephrosis. When a blood clot or tumor clot passes through the tubules, it can trigger renal-colic-like pain. However, when the obstruction is incomplete and hydronephrosis progresses, the resulting flank pain can be dull and chronic. Nevertheless, a patient can also be asymptomatic and diagnosed incidentally from imaging tests. When UC worsens, the patient may develop a flank or abdominal mass, bone pain, anorexia, and weight loss. In these cases, detailed evaluations of metastasis are necessary and a poor prognosis is likely[7,8]. Previous research reported that after surgical treatment, recurrence in the bladder occurred in 22% to 47% of cases, and recurrence in the contralateral upper tract occurred in 2% to 6% of cases[4,5].

Several medical techniques are essential for the diagnosis of UTUC. Ureteroscopy is commonly employed for detection and to determine treatment strategy. A biopsy specimen can be used to determine disease grade. However, the use of diagnostic ureteroscopy is associated with a higher risk of bladder recurrence after radical nephroureterectomy[9,10]. Cystoscopy should be considered because UTUCs are often in the bladder. Cytology can be helpful in diagnosis and determination of treatment, but its sensitivity is low and it has limited ability to detect the origin of tumor cells. CT is commonly utilized because of its high accuracy, ease of use, and wide availability[11,12].

There is a general consensus regarding treatments to be used for UTUC. Radical nephroureterectomy combined with bladder cuff excision is the gold standard treatment for a tumor of the renal pelvis or proximal ureter that is large, high-grade, and suspected of being invasive, provided there is a normal contralateral kidney.

Previous analyses of the pathological characteristics of UTUCs reported that papillary lesions were associated with better outcomes, and sessile lesions with poor outcomes[13,14]. Tumor invasion of muscle is also associated with poor outcome[15]. There is a high rate of ipsilateral recurrence in patients with upper urinary tract tumors, probably because of the multifocality of this tumor and downstream seeding[16-18].

UC of urethra tends to be malignant and to follow bladder cancer. Chen *et al*[19] found that the majority of patients with UC in the urethra (26 of 35 cases, 74%) had high-grade tumors, and more than three-quarters of patients (23 of 30, 77%) had a previous history of either high-grade papillary UC (n = 22) or UC *in situ* (n = 1) of the bladder[19]. It was reported that approximately 2% to 5% of patients with superficial bladder cancer and 40% to 60% of those with muscle-invasive bladder cancer developed urethral cancer[3]. Another study reported that 4% to 8% of male patients developed recurrent UC in the remnant urethra after cystectomy[20]. Erckert *et al*[21] found that the overall incidence of urethral cancer among 2052 events of primary and recurrent bladder tumors was 6.1%. Therefore, prophylactic urethrectomy should be recommended for patients with bladder cancer to prevent subsequent involvement of urethra, although the current guidelines have no relevant recommendations. In regard to urethral UC following bladder cancer, the monoclonality of multifocal cancers in the urinary tract indicate the possible seeding or implantation of bladder cancer cells to the retained urethra after cystectomy[20].

Our patient had metachronous primary UC in the right renal pelvis (March 2015), bladder (December 2016), and urethra (November 2021). The short interval between the first second episodes may be explained by the patient's rejection of the recommended BCG intravesical chemotherapy and the loss to follow-up. Because UTUC is prone to multifocality and downstream seeding, adjuvant immunotherapy

is necessary. Adjuvant intracavitary instillation of BCG is likely to improve the outcome of patients receiving kidney-sparing surgery. Nevertheless, Foerster *et al*[22] found no difference of recurrence rates between patients who received adjuvant instillations of BCG and untreated patients. On the other hand, some evidence showed that adjuvant instillation of mitomycin within 72 h of surgery reduced the recurrence rate within the first year[23]. Also, recent evidence suggests that early single adjuvant intracavitary instillation of mitomycin C in patients with low-grade UTUC might reduce the risk of local recurrence[1,24]. Therefore, the re-appearance of cancer in our patient could be attributable to the lack of adjuvant instillation of BCG and mitomycin.

Follow-up is also important to prevent worsening of the patient's condition. A retrospective study of 275 patients with UTUC reported the prevalence in the bladder was 46% and in the urethra was 2%; the prevalence of contralateral recurrence was 1%, distant metastasis was 7.5%, and local metastasis was 6%. These researchers concluded that UTUC was a unique disease with synchronous and metachronous recurrence that requires long-term surveillance[25].

The interval between our patient's second and third episodes was 5 years, and the third episode involved the urethra, a rare location of UC. Although there are reports of similar cases, these previous patients only had one or two episodes[26,27]. In one rare case, UC spread from the prostatic urethra to the brain[28]. There is a possibility that cutaneous diversion could make it easier to seed the remnant urethra, because if the urethra was used for voiding then viable cancer cells may be shed by urine flow [20].

Analysis of oncogenes can help elucidate the mechanisms of disease recurrence. However, this information was unavailable in our patient.

CONCLUSION

Although UTUC is relatively rare, the possibility of multifocality and downstream seeding indicates the need for intense surveillance and the use of adjuvant instillation of mitomycin to prevent metastasis and recurrence. After radical operation, UC may recur in adjacent downstream tissues, thus emphasizing the significance of long-term patient follow-up.

FOOTNOTES

Author contributions: Zhang JQ, Duan Y and Wang K contributed to this work; Jiang KH designed the study; Zhang JQ and Duan Y drafted the manuscript; Wang K and Zhang XL collected the clinical data; All authors have read and approved the final manuscript.

Supported by National Natural Science Foundation of China, No. 82060462; The Science and Technology Plan Project of Guizhou Province, No. [2019]5405; Foundation of Health and Family Planning Commission of Guizhou Province, No. gzwjkj2019-1-127

Informed consent statement: Written informed consent was obtained from the patient for the publication of this case report.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Jian-Qing Zhang 0000-0001-6112-3782; Yu Duan 0000-0002-5713-4080; Kun Wang 0000-0001-9933-1472; Xiao-Li Zhang 0000-0003-1715-0446; Ke-Hua Jiang 0000-0002-9446-3158.

S-Editor: Liu GL
L-Editor: A
P-Editor: Liu GL

REFERENCES

1 **Babjuk M**, Burger M, Capoun O, Cohen D, Compérat EM, Dominguez Escrig JL, Gontero P, Liedberg F, Masson-Lecomte A, Mostafid AH, Palou J, van Rhijn BWG, Rouprêt M, Shariat SF, Seisen T, Soukup V, Sylvester RJ. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1, and Carcinoma in Situ). *Eur Urol* 2022; **81**: 75-94 [PMID: 34511303 DOI: 10.1016/j.eururo.2021.08.010]

2 **Siegel RL**, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin* 2021; **71**: 7-33 [PMID: 33433946 DOI: 10.3322/caac.21654]

3 **Janisch F**, Abufaraj M, Fajkovic H, Kimura S, Iwata T, Nyirady P, Rink M, Shariat SF. Current Disease Management of Primary Urethral Carcinoma. *Eur Urol Focus* 2019; **5**: 722-734 [PMID: 31307949 DOI: 10.1016/j.euf.2019.07.001]

4 **Xylinas E**, Rink M, Margulis V, Karakiewicz P, Novara G, Shariat SF; Upper Tract Urothelial Carcinoma Collaboration (UTUCC). Multifocal carcinoma in situ of the upper tract is associated with high risk of bladder cancer recurrence. *Eur Urol* 2012; **61**: 1069-1070 [PMID: 22402109 DOI: 10.1016/j.eururo.2012.02.042]

5 **Li WM**, Shen JT, Li CC, Ke HL, Wei YC, Wu WJ, Chou YH, Huang CH. Oncologic outcomes following three different approaches to the distal ureter and bladder cuff in nephroureterectomy for primary upper urinary tract urothelial carcinoma. *Eur Urol* 2010; **57**: 963-969 [PMID: 20079965 DOI: 10.1016/j.eururo.2009.12.032]

6 **Grivas PD**, Davenport M, Montie JE, Kunju LP, Feng F, Weizer AZ. Urethral cancer. *Hematol Oncol Clin North Am* 2012; **26**: 1291-1314 [PMID: 23116581 DOI: 10.1016/j.hoc.2012.08.006]

7 **Raman JD**, Shariat SF, Karakiewicz PI, Lotan Y, Sagalowsky AI, Roscigno M, Montorsi F, Bolenz C, Weizer AZ, Wheat JC, Ng CK, Scherr DS, Remzi M, Waldert M, Wood CG, Margulis V; Upper-Tract Urothelial Carcinoma Collaborative Group. Does preoperative symptom classification impact prognosis in patients with clinically localized upper-tract urothelial carcinoma managed by radical nephroureterectomy? *Urol Oncol* 2011; **29**: 716-723 [PMID: 20056458 DOI: 10.1016/j.urolonc.2009.11.007]

8 **Ito Y**, Kikuchi E, Tanaka N, Miyajima A, Mikami S, Jinzaki M, Oya M. Preoperative hydronephrosis grade independently predicts worse pathological outcomes in patients undergoing nephroureterectomy for upper tract urothelial carcinoma. *J Urol* 2011; **185**: 1621-1626 [PMID: 21419429 DOI: 10.1016/j.juro.2010.12.035]

9 **Marchioni M**, Primiceri G, Cindolo L, Hampton LJ, Grob MB, Guruli G, Schips L, Shariat SF, Autorino R. Impact of diagnostic ureteroscopy on intravesical recurrence in patients undergoing radical nephroureterectomy for upper tract urothelial cancer: a systematic review and meta-analysis. *BJU Int* 2017; **120**: 313-319 [PMID: 28621055 DOI: 10.1111/bju.13935]

10 **Guo RQ**, Hong P, Xiong GY, Zhang L, Fang D, Li XS, Zhang K, Zhou LQ. Impact of ureteroscopy before radical nephroureterectomy for upper tract urothelial carcinomas on oncological outcomes: a meta-analysis. *BJU Int* 2018; **121**: 184-193 [PMID: 29032580 DOI: 10.1111/bju.14053]

11 **Ito A**, Shintaku I, Satoh M, Ioritani N, Aizawa M, Tochigi T, Kawamura S, Aoki H, Numata I, Takeda A, Namiki S, Namima T, Ikeda Y, Kambe K, Kyan A, Ueno S, Orikasa K, Katoh S, Adachi H, Tokuyama S, Ishidoya S, Yamaguchi T, Arai Y. Prospective randomized phase II trial of a single early intravesical instillation of pirarubicin (THP) in the prevention of bladder recurrence after nephroureterectomy for upper urinary tract urothelial carcinoma: the THP Monotherapy Study Group Trial. *J Clin Oncol* 2013; **31**: 1422-1427 [PMID: 23460707 DOI: 10.1200/JCO.2012.45.2128]

12 **Cowan NC**, Turney BW, Taylor NJ, McCarthy CL, Crew JP. Multidetector computed tomography urography for diagnosing upper urinary tract urothelial tumour. *BJU Int* 2007; **99**: 1363-1370 [PMID: 17428251 DOI: 10.1111/j.1464-410X.2007.06766.x]

13 **Fritsche HM**, Novara G, Burger M, Gupta A, Matsumoto K, Kassouf W, Sircar K, Zattoni F, Walton T, Tritschler S, Baba S, Bastian PJ, Martínez-Salamanca JI, Seitz C, Otto W, Wieland WF, Karakiewicz PI, Ficarra V, Hartmann A, Shariat SF. Macroscopic sessile tumor architecture is a pathologic feature of biologically aggressive upper tract urothelial carcinoma. *Urol Oncol* 2012; **30**: 666-672 [PMID: 20933445 DOI: 10.1016/j.urolonc.2010.07.010]

14 **Remzi M**, Haitel A, Margulis V, Karakiewicz P, Montorsi F, Kikuchi E, Zigeuner R, Weizer A, Bolenz C, Bensalah K, Suardi N, Raman JD, Lotan Y, Waldert M, Ng CK, Fernández M, Koppie TM, Ströbel P, Kabbani W, Murai M, Langner C, Roscigno M, Wheat J, Guo CC, Wood CG, Shariat SF. Tumour architecture is an independent predictor of outcomes after nephroureterectomy: a multi-institutional analysis of 1363 patients. *BJU Int* 2009; **103**: 307-311 [PMID: 18990163 DOI: 10.1111/j.1464-410X.2008.08003.x]

15 **Abouassaly R**, Alibhai SM, Shah N, Timilshina N, Fleshner N, Finelli A. Troubling outcomes from population-level analysis of surgery for upper tract urothelial carcinoma. *Urology* 2010; **76**: 895-901 [PMID: 20646743 DOI: 10.1016/j.urology.2010.04.020]

16 **Harris AL**, Neal DE. Bladder cancer--field versus clonal origin. *N Engl J Med* 1992; **326**: 759-761 [PMID: 1738381 DOI: 10.1056/NEJM199203123261108]

17 **Heney NM**, Nocks BN, Daly JJ, Blitzer PH, Parkhurst EC. Prognostic factors in carcinoma of the ureter. *J Urol* 1981; **125**: 632-636 [PMID: 7230332 DOI: 10.1016/s0022-5347(17)55143-5]

18 **Johansson S**, Angervall L, Bengtsson U, Wahlqvist L. A clinicopathologic and prognostic study of epithelial tumors of the renal pelvis. *Cancer* 1976; **37**: 1376-1383 [PMID: 1260657 DOI: 10.1002/1097-0142(197603)37:3<1376::aid-cncr2820370318>3.0.co;2-c]

19 **Chen F**, Joshi S, Carthon BC, Osunkoya AO. A Contemporary Clinicopathologic Analysis of Primary Urothelial Carcinoma of the Urethra Without Concurrent Renal Pelvic, Ureteral, or Bladder Carcinoma. *Int J Surg Pathol* 2022; **30**: 15-22 [PMID: 34255581 DOI: 10.1177/10668969211032481]

20 **Kakizoe T**, Tobisu K. Transitional cell carcinoma of the urethra in men and women associated with bladder cancer. *Jpn J Clin Oncol* 1998; **28**: 357-359 [PMID: 9730148 DOI: 10.1093/jjco/28.6.357]

21 **Erckert M**, Stenzl A, Falk M, Bartsch G. Incidence of urethral tumor involvement in 910 men with bladder cancer. *World J Urol* 1996; **14**: 3-8 [PMID: 8646239 DOI: 10.1007/BF01836337]

22 **Foerster B**, D'Andrea D, Abufaraj M, Broenimann S, Karakiewicz PI, Rouprêt M, Gontero P, Lerner SP, Shariat SF, Soria F. Endocavitary treatment for upper tract urothelial carcinoma: A meta-analysis of the current literature. *Urol Oncol* 2019;

37: 430-436 [PMID: 30846387 DOI: 10.1016/j.urolonc.2019.02.004]

23 **Cassell A 3rd**, Manobah B, Willie S. Diagnostic and Therapeutic Challenges of Rare Urogenital Cancers: Urothelial Carcinoma of the Renal Pelvis, Ureters and Urethra. *World J Oncol* 2021; **12**: 20-27 [PMID: 33738002 DOI: 10.14740/wjon1360]

24 **Gallioli A**, Boissier R, Territo A, Vila Reyes H, Sanguedolce F, Gaya JM, Regis F, Subiela JD, Palou J, Breda A. Adjuvant Single-Dose Upper Urinary Tract Instillation of Mitomycin C After Therapeutic Ureteroscopy for Upper Tract Urothelial Carcinoma: A Single-Centre Prospective Non-Randomized Trial. *J Endourol* 2020; **34**: 573-580 [PMID: 32164441 DOI: 10.1089/end.2019.0750]

25 **Elawdy MM**, Osman Y, Taha DE, El-Halwagy S, El-Hamid MA, Abouelkheir RT. Long-term outcomes of upper tract urothelial carcinoma: A retrospective evaluation of single-center experience in 275 patients. *Turk J Urol* 2019; **45**: 177-182 [PMID: 30817281 DOI: 10.5152/tud.2019.02185]

26 **Kisa E**, Semiz HS, Küçük Ü, İlbey YÖ. Metastatic primary urothelial carcinoma of the prostatic urethra: A case report. *Urologia* 2019; **86**: 161-164 [PMID: 30373476 DOI: 10.1177/0391560318808631]

27 **Moez R**, Boulma R, Hassen K. Primary urothelial carcinoma of the male anterior urethra; A case report. *Ann Med Surg (Lond)* 2022; **76**: 103561 [PMID: 35495412 DOI: 10.1016/j.amsu.2022.103561]

28 **Morita K**, Oda M, Koyanagi M, Saiki M. Metastatic brain tumor from urothelial carcinoma of the prostatic urethra. *Surg Neurol Int* 2016; **7**: S488-S491 [PMID: 27512612 DOI: 10.4103/2152-7806.185784]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3070-3075

DOI: 10.12998/wjcc.v11.i13.3070

ISSN 2307-8960 (online)

CASE REPORT

Unusual phenomenon-"polyp" arising from a diverticulum: A case report

Jacqueline Jin Li Liew, Wei Shyann Lim, Frederick H Koh

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bustamante-Lopez LA, Brazil; Zhang G, China; Zhao S, China

Received: January 31, 2023
Peer-review started: January 31, 2023
First decision: February 17, 2023
Revised: March 1, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 6, 2023

Jacqueline Jin Li Liew, Wei Shyann Lim, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597, Singapore

Frederick H Koh, Colorectal Service, Department of General Surgery, Sengkang General Hospital, Singapore 544886, Singapore

Corresponding author: Frederick H Koh, FRCS (Ed), MBBS, MMed, Assistant Professor, Colorectal Service, Department of General Surgery, Sengkang General Hospital, 110 Sengkang E Way, Singapore 544886, Singapore. frederickkohhx@gmail.com

Abstract

BACKGROUND

Sealed perforation of colonic diverticulum is a common clinical condition and may be differentiated from an underlying malignant perforation using interval endoscopy. We present an uncommon colonoscopy finding of a healed diverticular perforation, mimicking a polyp, 6 wk post-diverticulitis-something that has not been reported in literature. We aim to shed light on the likely process that resulted in the trompe l'œil after diverticulitis. This also introduces the possibility of more targeted colonic resection in the event of a similar recurrence.

CASE SUMMARY

A middle-aged Chinese female presented with a 3-d history of non-colicky left iliac fossa pain. It was associated with fever (T_{max} 37.6 °C), non-bloody diarrhoea and non-bloody, non-bilious vomiting. She had a history of Type 2 diabetes mellitus, well controlled on metformin. Tenderness was noted on the left iliac fossa region with no guarding or mass. Total white cell count (11.45 × 10^9/L) and C-reactive protein levels (213.9 mg/L) were elevated. Computed tomography imaging of the abdomen revealed pericolonic fat stranding and extraluminal air pockets fluid density with peritoneal thickening at the sigmoid colon, likely representing a sealed perforation. Six weeks after the episode, she underwent a follow-up colonoscopy. An exophytic polypoid lesion closely associated with a diverticulum was seen in the sigmoid colon. The lesion was easily "pinched" off without much effort using endoscopic forceps and sent for histology which revealed granulation tissue suggesting a healed diverticular perforation.

CONCLUSION

Granulation tissue associated with healed diverticular perforations resemble polyps. Tattooing around these sites may allow for future targeted colonic resections.

Key Words: Diverticulitis; Colonoscopy; Colonic polyps; Colorectal cancer; Diverticular perforation; Case report

Core Tip: This case report aims to shed light on the possible morphology of a healed diverticular perforation. This is important as patients who have suffered from diverticular perforations are at increased risk of recurrence, with high likelihood of the previously perforated diverticulum being the offending cause. Recognising the appearance of granulation tissue from a possible sealed perforated diverticulum and marking the site with injectable tattoos may allow for targeted resections of the colon if recurrence occurs. This preserves more parenchyma, allows for a potentially faster surgery, and shortens recovery time while achieving an equivalent improvement in quality-of-life.

Citation: Liew JJL, Lim WS, Koh FH. Unusual phenomenon-"polyp" arising from a diverticulum: A case report. *World J Clin Cases* 2023; 11(13): 3070-3075
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3070.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3070

INTRODUCTION

Diverticular disease is a common benign condition defined by the outpouching of all layers of the intestinal mucosa[1]. Diverticular disease of the colon is common in industrialised countries. The prevalence of diverticular disease is similar in men and women. However, the prevalence of diverticular disease increases with age, ranging from 10% in those younger than 40 to 50 years old, to 70% in those above 80 years of age[2-4]. The anatomic distribution of diverticular disease also varies geographically. In the west, diverticuli are commonly limited to the sigmoid colon in 65%, sigmoid plus other colonic diverticuli in 25%, pan colonic diveritculi in 7%, and diverticuli isolated to a segment proximal to the sigmoid colon in 4% of patients[5]. Conversely, in the East, in Asian populations, the anatomic distribution is different and primarily involves the right colon with a prevalence rate of 13% to 25%[6-9].

Perforation of diverticulitis occurs secondary to bowel wall inflammation, subsequent necrosis and the loss of intestinal wall integrity. The principles for the management of diverticular perforations are dependent on the nature of the perforation. Sealed perforations are treated conservatively with antibiotics while frank and free perforations are treated surgically. Surgical management of perforated diverticuli, for instance the Hartmann Procedure, often results in stoma creation, which reduces a patient's quality-of-life[10]. Another complication of surgical management is diarrhoea caused by reduced storage capacity in the colon from extensive colonic resection in view of the inability to identify specific perforation sites. Management for a perforated diverticulitis with peritonitis is highly controversial owing to the lack of high quality data backing management options for personalised surgery [11]. Elective segmental colonic resections are commonly performed, as evidenced by an 8% risk of recurrence in one year, and a 20% risk of recurrence within ten years of patients with resolved acute diverticulitis. Nonetheless, routine follow-up colonoscopies post-acute diverticulitis episodes have a role to play in holistic patient care.

To date, the endoscopic morphology of a healed diverticular perforations has not been documented in literature.

This case report aims to educate clinical endoscopists on how to identify healed diverticular perforations. Our aim is to eventually revolutionise the presently practised elective segmental colonic resection, which is indicated in recurrent or complicated diverticulitis, by encouraging parenchymal-sparing surgeries through the demarcation of past perforation sites.

In this paper, we report about a middle-aged Chinese female who presented for a routine follow-up colonoscopy 6 wk after an episode of acute diverticulitis. Novel colonoscopy findings of the site of perforation is described in this report. These colonoscopy findings were confirmed by histology which showed granulation tissue, indicating an ongoing healing process.

CASE PRESENTATION

Chief complaints

A middle-age Chinese lady initially presented with a 3-d history of constant abdominal pain in the left iliac fossa.

History of present illness

This was associated with a fever of T_{max} 37.6°C, non-bloody diarrhoea, and non-bloody, non-bilious vomiting.

History of past illness

She had a past medical history of Type 2 diabetes mellitus which was well controlled on 850 mg Metformin thrice a day.

Personal and family history

Family history was unremarkable for gastrointestinal malignancy. She was a non-smoker and non-drinker.

Physical examination

Physical examination on initial presentation for acute diverticulitis revealed tenderness on the left flank with no guarding. Otherwise, physical examination was unremarkable. There were no signs of chronic liver disease-no jaundice, caput medusae, scleral icterus, Dupuytren's contractures, clubbing, hepatic asterixis, gynaecomastia, spider naevi, shifting dullness or pedal oedema. There are no signs of anaemia-no conjunctival pallor, no palmar crease pallor. There were no signs pointing to any kidney pathology-no renal bruits and kidneys were non-ballotable. There was no hepatomegaly or splenomegaly. Bowel sounds were active.

Laboratory examinations

Laboratory investigations revealed elevated C-reactive protein levels (213.9 mg/L) and white cell count (11.45×10^9/L).

Imaging examinations

On a computed tomography scan of the abdomen, a confined pericolic abscess was seen (Figure 1).

FINAL DIAGNOSIS

This confirmed the presence of a Modified Hinchey Ib diverticulitis.

TREATMENT

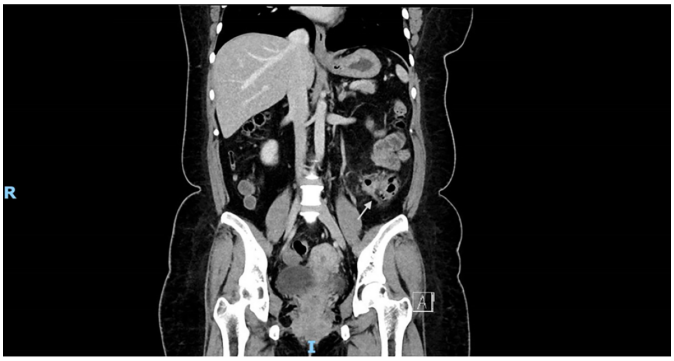
It was managed conservatively with the following course of antibiotics for 5 d–IV ceftriaxone 2 g once a day, and IV metronidazole 500 mg thrice a day. Subsequently, the patient was started on oral co-amoxiclav for a total of 4 wk.

OUTCOME AND FOLLOW-UP

Interval follow-up colonoscopy 6 wk after the acute event revealed polyps in the sigmoid colon. One of the lesions, which was in close proximity to a diverticulum (Figure 2), was easily "pinched" off using endoscopic forceps and sent for histology, revealing an abundance of fibroblasts, keratinocytes, and endothelial cells, characteristic of granulation tissue and consistent with healing (Figure 3)[12]. Neither tubular, nor villous growth patterns were noted, ruling out a diagnosis of adenomatous polyps. Therefore, the "polyp" likely represented the previous site of diverticular perforation.

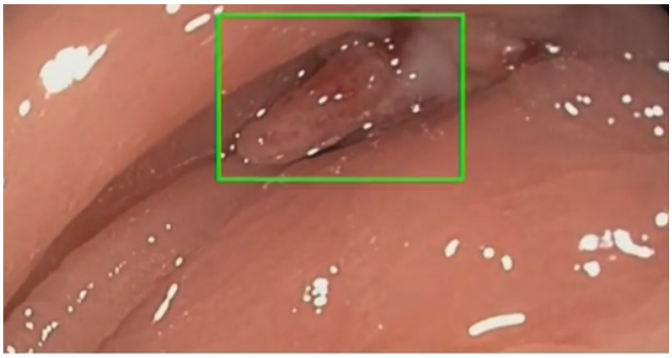
DISCUSSION

Currently there is limited literature on the appearance and possible morphologies of healed diverticular perforations. Therefore, with this case report we hope to provide an insight into how healed diverticular perforations may appear. Current literature focuses primarily on the pathophysiology, risk factors, along with the possible acute management methods of a diverticular perforation, and not its endoscopic morphology. Furthermore, reports on the endoscopic appearance of diverticular disease largely play the role of clinching the diagnosis of diverticular disease[13] as opposed to studying the possible different morphologies of diverticular disease, particularly after an episode of perforated diverticulitis. Of those that have described the endoscopic appearance of diverticular disease, some have elaborated on the possible histopathologic resemblance between the non-diverticular mucosa in such patients and other



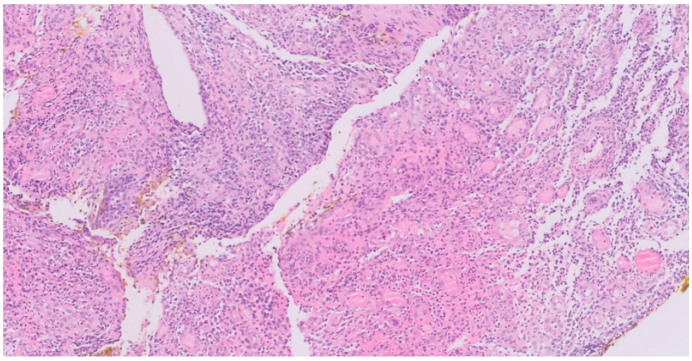
DOI: 10.12998/wjcc.v11.i13.3070 **Copyright** ©The Author(s) 2023.

Figure 1 Computed tomography of abdomen pelvis coronal cut, showing signs of pericolonic fat stranding and extraluminal air pockets fluid density with peritoneal thickening at the sigmoid colon, likely representing a sealed perforation.



DOI: 10.12998/wjcc.v11.i13.3070 **Copyright** ©The Author(s) 2023.

Figure 2 Endoscopic image of exophytic polypoid lesion closely associated with a diverticulum seen in the sigmoid colon.



DOI: 10.12998/wjcc.v11.i13.3070 **Copyright** ©The Author(s) 2023.

Figure 3 Hematoxylin-eosin stain at 200 × magnification revealing an abundance of fibroblasts, keratinocytes, and endothelial cells, characteristic of granulation tissue and consistent with healing.

mucosal diseases like Crohn's disease or ulcerative colitis[14,15]. Therefore, to the best of our knowledge, the presented case is the first in literature to report the development of polyp-resembling granulation tissue at the site of a previous diverticular perforation. This can potentially offer an alternative angle of management of such sealed perforations.

The rate of recurrence of diverticulitis remains relatively modest, Broderick-Villa *et al*[16] reported on 2366 of 3165 patients (75%) hospitalized with acute diverticulitis and treated nonoperatively in the Kaiser Permanente system. Eighty-six percent of those patients required no further inpatient care for diverticulitis over the 8.9 years of follow-up. Recurrence occurred in only 13.3% of patients and only 3.9% had a second recurrence[17]. Moreover, recurrence of diverticulitis is greater after an episode of complicated diverticulitis at 24%, as opposed to after an episode of uncomplicated diverticulitis at 23.4% [18]. Ultimately, the authors concluded that recurrence overall is rare and there is therefore a decreasing need for elective colectomies following episodes of diverticulitis[19]. However, if a recurrence were to

happen often enough, according to the American Society of Gastrointestinal Endoscopy, surgical resection of the offending site of recurrent diverticulitis is recommended[20]. As the actual offending diverticulum is often not identified, anatomical resection of segments of the colon is performed, which leads to significant amount of colonic length loss which may have implications on quality of life for these patients.

The utility of colonic mucosal tattoo placements lies in marking lesions for subsequent surgical resection, for later endoscopic resection, or to mark an endoscopic resection site for easy endoscopic follow-up of the resection site[21]. We propose the utility of such a mucosal tattoo to mark the potential site of a healed diverticular perforation, if successfully identified. This can potentially help guide surgical resection when the need arises with a more targeted resection. In this way, colonic length can potentially be spared to maintain quality-of-life for the affected patients. A proposal of this nature, when supported by further prospective data and larger series, can potentially modify the way we treat recurrent complicated diverticulitis.

CONCLUSION

This case report displays the morphology of granulation tissue associated with healed diverticular perforations on colonoscopy. This serves to guide endoscopists during colonoscopy to help identify sites of recent perforations. Nonetheless, biopsies of lesions resembling our findings should still be taken, to rule out other pathologies. Tattoo placements may guide clinical treatment by allowing for more targeted colonic resections in the event of recurrence of complicated diverticulitis at the same location. From our preliminary glimpse into the description of the morphology of healed perforated diverticulum, further studies may be conducted to broaden our understanding of the topic.

FOOTNOTES

Author contributions: Koh FH is responsible for research design; Liew JJL, Lim WS are responsible for research and data curation; Koh FH, Liew JJL and Lim WS analysed data; Liew JJL and Lim WS are responsible for the original draft preparation; Koh FH is responsible for reviews and editing; Liew JJL and Lim WS wrote the paper; Koh FH contributed to supervision.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Singapore

ORCID number: Jacqueline Jin Li Liew 0000-0002-7579-5114; Wei Shyann Lim 0000-0003-2964-1971; Frederick H Koh 0000-0002-3717-4480.

S-Editor: Hu YR
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Linzay CD**, Pandit S. Acute Diverticulitis. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459316/
2 **Jacobs DO**. Clinical practice. Diverticulitis. *N Engl J Med* 2007; **357**: 2057-2066 [PMID: 18003962 DOI: 10.1056/NEJMcp073228]
3 **Ferzoco LB**, Raptopoulos V, Silen W. Acute diverticulitis. *N Engl J Med* 1998; **338**: 1521-1526 [PMID: 9593792 DOI: 10.1056/NEJM199805213382107]

4 **Tursi A**. Acute diverticulitis of the colon--current medical therapeutic management. *Expert Opin Pharmacother* 2004; **5**: 55-59 [PMID: 14680435 DOI: 10.1517/14656566.5.1.55]

5 **Parks TG**. Natural history of diverticular disease of the colon. *Clin Gastroenterol* 1975; **4**: 53-69 [PMID: 1109820]

6 **Ngoi SS**, Chia J, Goh MY, Sim E, Rauff A. Surgical management of right colon diverticulitis. *Dis Colon Rectum* 1992; **35**: 799-802 [PMID: 1644006 DOI: 10.1007/BF02050332]

7 **Wang FW**, Chuang HY, Tu MS, King TM, Wang JH, Hsu CW, Hsu PI, Chen WC. Prevalence and risk factors of asymptomatic colorectal diverticulosis in Taiwan. *BMC Gastroenterol* 2015; **15**: 40 [PMID: 25888375 DOI: 10.1186/s12876-015-0267-5]

8 **Markham NI**, Li AK. Diverticulitis of the right colon--experience from Hong Kong. *Gut* 1992; **33**: 547-549 [PMID: 1582600 DOI: 10.1136/gut.33.4.547]

9 **Chan CC**, Lo KK, Chung EC, Lo SS, Hon TY. Colonic diverticulosis in Hong Kong: distribution pattern and clinical significance. *Clin Radiol* 1998; **53**: 842-844 [PMID: 9833789 DOI: 10.1016/s0009-9260(98)80197-9]

10 **Moro-Valdezate D**, Royo-Aznar A, Martín-Arévalo J, Pla-Martí V, García-Botello S, León-Espinoza C, Fernández-Moreno MC, Espín-Basany E, Espí-Macías A. Outcomes of Hartmann's procedure and subsequent intestinal restoration. Which patients are most likely to undergo reversal? *Am J Surg* 2019; **218**: 918-927 [PMID: 30853093 DOI: 10.1016/j.amjsurg.2019.02.025]

11 **Nascimbeni R**, Amato A, Cirocchi R, Serventi A, Laghi A, Bellini M, Tellan G, Zago M, Scarpignato C, Binda GA. Management of perforated diverticulitis with generalized peritonitis. A multidisciplinary review and position paper. *Tech Coloproctol* 2021; **25**: 153-165 [PMID: 33155148 DOI: 10.1007/s10151-020-02346-y]

12 **Reinke JM**, Sorg H. Wound repair and regeneration. *Eur Surg Res* 2012; **49**: 35-43 [PMID: 22797712 DOI: 10.1159/000339613]

13 **Kim YS**. [Diagnosis and Treatment of Colonic Diverticular Disease]. *Korean J Gastroenterol* 2022; **79**: 233-243 [PMID: 35746837 DOI: 10.4166/kjg.2022.072]

14 **West AB**, Losada M. The pathology of diverticulosis coli. *J Clin Gastroenterol* 2004; **38**: S11-S16 [PMID: 15115923 DOI: 10.1097/01.mcg.0000124005.07433.69]

15 **Weizman AV**, Nguyen GC. Diverticular disease: epidemiology and management. *Can J Gastroenterol* 2011; **25**: 385-389 [PMID: 21876861 DOI: 10.1155/2011/795241]

16 **Broderick-Villa G**, Burchette RJ, Collins JC, Abbas MA, Haigh PI. Hospitalization for acute diverticulitis does not mandate routine elective colectomy. *Arch Surg* 2005; **140**: 576-81; discussion 581 [PMID: 15967905 DOI: 10.1001/archsurg.140.6.576]

17 **Rai V**, Mishra N. Surgical Management of Recurrent Uncomplicated Diverticulitis. *Clin Colon Rectal Surg* 2021; **34**: 91-95 [PMID: 33642948 DOI: 10.1055/s-0040-1716700]

18 **Eglinton T**, Nguyen T, Raniga S, Dixon L, Dobbs B, Frizelle FA. Patterns of recurrence in patients with acute diverticulitis. *Br J Surg* 2010; **97**: 952-957 [PMID: 20474006 DOI: 10.1002/bjs.7035]

19 **Morris AM**, Regenbogen SE, Hardiman KM, Hendren S. Sigmoid diverticulitis: a systematic review. *JAMA* 2014; **311**: 287-297 [PMID: 24430321 DOI: 10.1001/jama.2013.282025]

20 **Qaseem A**, Etxeandia-Ikobaltzeta I, Lin JS, Fitterman N, Shamliyan T, Wilt TJ; Clinical Guidelines Committee of the American College of Physicians*, Crandall CJ, Cooney TG, Cross JT Jr, Hicks LA, Maroto M, Mustafa RA, Obley AJ, Owens DK, Tice J, Williams JW Jr; Clinical Guidelines Committee of the American College of Physicians. Colonoscopy for Diagnostic Evaluation and Interventions to Prevent Recurrence After Acute Left-Sided Colonic Diverticulitis: A Clinical Guideline From the American College of Physicians. *Ann Intern Med* 2022; **175**: 416-431 [PMID: 35038270 DOI: 10.7326/M21-2711]

21 **Rex DK**. The Appropriate Use and Techniques of Tattooing in the Colon. *Gastroenterol Hepatol (N Y)* 2018; **14**: 314-317 [PMID: 29991940]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3076-3085

DOI: 10.12998/wjcc.v11.i13.3076

ISSN 2307-8960 (online)

CASE REPORT

Idiopathic steno-occlusive disease with bilateral internal carotid artery occlusion: A Case Report

Sherifa Ahmed Hamed, Hosam Abozaid Yousef

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mzhavanadze ND, Russia; Tang W, China

Received: December 19, 2022
Peer-review started: December 19, 2022
First decision: February 17, 2023
Revised: February 23, 2023
Accepted: March 27, 2023
Article in press: March 27, 2023
Published online: May 6, 2023

Sherifa Ahmed Hamed, Department of Neurology and Psychiatry, Assiut University, Faculty of Medicine, Assiut 71516, Assiut, Egypt

Hosam Abozaid Yousef, Department of Radiology, Assiut University, Faculty of Medicine, Assiut 71516, Assiut, Egypt

Corresponding author: Sherifa Ahmed Hamed, MD, Professor, Department of Neurology and Psychiatry, Assiut University, Faculty of Medicine, Assiut University Hospital Street, No. 1, Assiut 71516, Assiut, Egypt. hamedsherifa@aun.edu.eg

Abstract

BACKGROUND

Moyamoya disease (MMD) is a rare cause of acute stroke and transient ischemic attacks in children. We described clinical, diagnostic features and follow-ups of a young child with acute stroke.

CASE SUMMARY

We report a 4-year-old girl with left hemiparesis after an acute ischemic stroke. Her history was also significant for repeated left or right focal motor seizures, generalized tonic-clonic convulsions and transient ischemic attacks. Her magnetic resonance imaging and computed tomography (CT) of the brain and magnetic resonance angiography, CT angiography and venography on the cerebral vessels revealed evidence of bilateral fronto-parietal ischemic infarctions, occlusion of the right and left internal carotid arteries started at its bifurcation and non-visualization of right and left anterior and middle cerebral arteries. There was evidence of progression in angiography manifested as development of collaterals from the basal perforating vessels, increase in the extent of large intracranial arterial stenosis/occlusion and extensive collateral circulation with predominance from the posterior circulation. Physical and neurological evaluation and comprehensive laboratory investigations excluded an obvious comorbid disease or risk factor for the child's condition. The diagnosis of MMD was highly suggested as a cause of the child's steno-occlusive condition. She was treated symptomatically with levetiracetam, an antiepileptic medication. Aspirin was prescribed for secondary prevention. Her clinical manifestations were improved during the three years of follow-up. Revascularization surgery was postponed.

CONCLUSION

Up to our knowledge, this is the first report for MMD in a child in our country. The clinical improvement and the stabilization of the child's condition over the 3

years of follow-up could be attributed to the rapid and extensive recruitment of collaterals and absence of risk factors or comorbidities. Revascularization surgery is highly recommended.

Key Words: Steno-occlusive disease; Moyamoya disease; Internal carotid artery; Collateral circulation; Neovascularization; Case report

Core Tip: Stroke in children is a significant cause of long-lasting morbidity. The advances in neuroimaging and laboratory investigations serve an important role in proper evaluation of stroke in children and identification of its potential etiologies, risk factors and outcomes. Moyamoya disease (MMD) is a rare progressive non-inflammatory steno-occlusive arteriopathy of the large cerebral blood vessels. It is a rare cause of ischemic stroke and recurrent transient attacks in children. The disease is very under-recognized in different areas of the world except East Asia, predominantly Japan. MMD can be sporadic or familial. The Japanese term "moyamoya" refers to the puff of smoke morphology of the dilated basal collateral vessels within the brain tissue seen on cerebral angiography. Compared to other arteriopathies, MMD is unique as its treatment solely relies on surgical revascularization. Therefore, increasing reporting and evaluation of cases with MMD from different ethnicities may help in better understanding of its causes and proper management.

Citation: Hamed SA, Yousef HA. Idiopathic steno-occlusive disease with bilateral internal carotid artery occlusion: A Case Report. *World J Clin Cases* 2023; 11(13): 3076-3085
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3076.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3076

INTRODUCTION

Moyamoya disease (MMD) is an idiopathic progressive steno-occlusive arteriopathy of the large cerebral blood vessels. It is a rare and under-estimated cause of acute ischemic stroke and transient ischemic attacks (TIAs) in children and cerebral and subarachenoid hemorrhages in adults[1]. MMD usually presents between the ages of 3 to 10 years old or even earlier and in the 3rd and 4th decades of life [1,2]. Some studies from Asia and Europe reported that MMD is the cause of cerebrovascular stroke in 6% to 22% of children[3]. Familial MMD has been reported in 7% to 12% from Japan and approximately 6% from United States[4,5]. The ring finger protein 213 or the p.4810K variant in the *RNF213* gene has been identified by both genome- wide association studies and whole exome sequencing in 95.0% for familial and 75.0% for sporadic cases with MMD. *RNF213* gene has been suggested to be the most frequent susceptibility gene in MMD. However, there are other genes, allelic heterogeneity and ethnic specific variants that also has been thought to contribute rarely to the susceptibility, clinical characteristics and outcomes of MMD. Also some studies emphasized the effect of genetic variants on risk stratification and clinical presentation, follow-up of patients and surgical outcomes of MMD[4-6].

MMD is typically characterized by endothelial hyperplasia and fibrocellular thickening of the intima, and duplication of the internal elastic lamina of the large intracranial vessels with parallel evolution of contiguous collateral anastomotic changes[7]. The anterior circulation is involved more commonly than the posterior circulation with particular involvement of the distal terminal segments of the internal carotid arteries (ICAs), M1 segment of the middle cerebral arteries (MCAs), A1 segment of the anterior cerebral arteries (ACAs) and the proximal portion of the posterior cerebral arteries (PCAs) or the basilar artery (BA)[8]. Manifestations of MMD include TIAs, ischemic strokes, intracranial hemorrhages, seizures, headaches, choreiform movements, cognitive deficits and visual deficits[1]. There are common childhood behaviors which induce cerebrovascular insults in a child with MMD, which include crying, coughing, or blowing (*i.e.* hyperventilation) and other activities which result in hypocapnia-induced cerebral vasoconstriction of the already maximally dilated cerebral blood vessels[9]. The definite diagnosis of MMD depends on specific angiographic criteria[8] which are: (1) Bilateral stenosis/occlusion of the distal terminal part of ICAs and/or the proximal parts of ACAs and/or MCAs; and (2) visualization of the moyamoya vessels, an abnormal arterial vascular network from deep perforating dilated arteries, in proximity to the stenosed/occluded vessels[10]. These vessels also appear as concurrent large flow voids in the basal ganglia and thalamus in magnetic resonance imaging (MRI) of the brain[11]. Suzuki *et al*[12] provided stages for MMD based on the angiographic finding. These stages explain the pathological changes seen over a period of time in each patient with MMD, but they do not correlate with the disease severity. The initial stages (stages 1-3) involve the occlusion of the distal parts of the ICAs with the development of moyamoya vessels, the late stages (stages 4-5) involve the ICAs-

ECAs (the external carotid arteries) anastomosis followed by fading of moyamoya vessels and the last stage (stage 6) involves complete occlusion of ICAs.

The long-term outcome of MMD is poor in up to 66% of patients with the development of symptomatic neurological and cognitive deteriorations (*i.e.* progression) within the next five years following its diagnosis. The surgical revascularization is recommended at young age to prevent recurrence of ischemic insults[13-15]. Management of acute ischemic stroke due to MMD is symptomatic[8]. Conservative treatment can be used for secondary prevention using anti-platelet drugs and calcium channel blockers. Anti-platelet drugs (as aspirin in a dose of 1 to 5 mg/kg/d or clopidogrel in a dose of 1 mg/kg/d) are recommended for at least 3 to 5 years after the acute ischemic stroke to prevent thrombosis and thromboembolism at the sites of arterial stenosis[14] It has been reported that calcium channel blockers (as nicardipine) can be used for secondary prevention from ischemic insults. Nicardipine (in a dose of 0.25-0.5 mg/kg/d every 12 h by oral route) may improve the hemodynamics in patients with MMD by optimizing the collateral circulation[16].

CASE PRESENTATION

Chief complaints

A 4-year-old female (DOB: 2015) with left sided hemiparesis.

History of present illness

She presented in June 2019 with left sided hemiparesis and recurrent focal motor seizures.

History of past illness

Her history was significant since October 2017 for repeated attacks of loss of consciousness (LOC), sudden falls without LOC, convulsions or body discoloration. There were also attacks of dysarthria or speech arrest or deviation of the angle of the mouth to the left side which lasted for 20-30 min. The mother noticed that excessive crying could provoke sudden falls and hot water bath could result in drowsiness for few minutes. Her neurological examination and computed tomography (CT) of the brain were unremarkable. She was diagnosed as having epilepsy and treated with sodium valproate (VPA), an anticonvulsant drug but she discontinued treatment after few months.

In September 2018, she developed recurrent motor seizures starting in the right perioral area followed by the right upper and lower limbs. She was re-treated with VPA. In October 2018, she developed motor seizures on the left side of the body. There was no impaired awareness during the attacks and her neurological examination and repeated CT scan of the brain were normal. The treating physician prescribed VPA in a dose of 200 mg every 12 h and levetiracetam (LEV), another anticonvulsant drug, in a dose of 100 mg every 12 h. The seizures subsided with medications. In January 2019, she developed two attacks of generalized tonic-clonic convulsions (GTC) without regaining consciousness in between the attacks. She was admitted to the hospital. On admission, her oral temperature was 38.0 °C. There were no signs of meningeal irritation. Her electroencephalography showed diffuse delta slowing. Her routine laboratory investigations and chemistry analysis of the cerebrospinal fluid (CSF) were unremarkable.

MRI (Siemens machine, 1.5 Tesla) of the brain was performed. It showed bilateral abnormal signal intensities involving both frontal lobes (with gyral pattern) being hypointense in T1-weighted imaging (T1WI) and hyperintense in T2-weighted imaging (T2WI), fluid attenuation inversion recovery (FLAIR) views and diffusion weighted imaging (DWI) (*i.e.* restricted diffusion). There was no mass effect or perilesional edema (Figure 1). Treatment was started with ceftriaxone, an antibiotic, and acyclovir, an antiviral drug, for concern of being an attack of encephalitis/meningoencephalitis. Intravenous LEV was also prescribed. The patient regained consciousness within days but found to have left sided hemiplegia. She was discharged after few days on oral LEV (200 mg every 12 h).

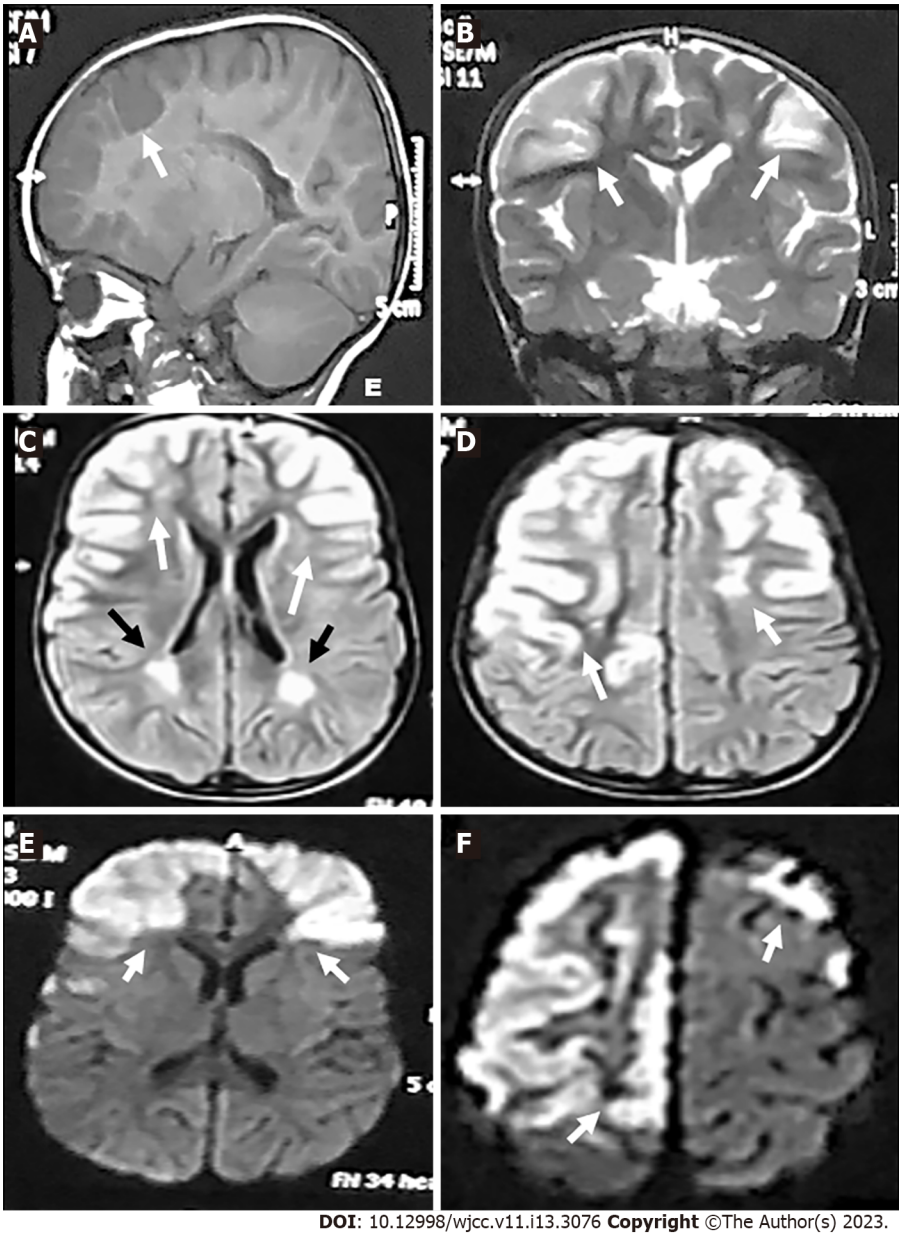
There was no history of traumatic head or neck injuries. There was no comorbid medical or surgical condition. There was no history of risk factors in temporal relation with disease onset (*e.g.* infection/inflammation, vaccination, *etc.*).

Personal and family history

Her body weight was 18 kg. She was a product of normal pregnancy and delivery and had normal development, speech and intelligence. She was an active girl. Her detailed history, comprehensive investigations (hematological and metabolic laboratory testing) and medical and cardiac evaluations excluded an underlying diseases or predisposing factors as a cause of stroke. There was no family history of similar condition.

Physical examination

Neurological examination at presentation (June 2019) revealed left spastic hemiparesis (muscle power was 3/5), left upper motor neuron facial paralysis, exaggerated left deep tendon jerks and left Babinski



DOI: 10.12998/wjcc.v11.i13.3076

Figure 1 Magnetic resonance imaging-brain views (Date: July 2019). A: Sagittal T1-weighted imaging revealed hypointense lesions in the fronto-parietal regions (white arrow); B: Coronal T2-weighted imaging; C and D: Axial fluid attenuation inversion recovery; E and F: Diffusion weighted imaging. Revealed hyperintense lesions in the right and left fronto-parietal areas (gyral pattern) (white arrows) and in the white matter adjacent to the lateral ventricle (C and D) (black arrows).

sign. Her fundus examination was normal.

Laboratory examinations

They included complete blood cell count, prothrombin time, partial thromboplastin time, erythrocyte sedimentation rate, antinuclear, anticardiolipin and antiphospholipid antibodies, protein C and S, serum lactate and pyruvate, sickle cell preparation, serum amino acids, triglycerides, cholesterol. electrocardiogram and echocardiogram. No genetic testing was done.

Further diagnostic work-up

This will include genetic testing with special emphasis to *RNF213* gene variants.

Imaging examinations

In October 2019, she did follow-up MRI of the brain and magnetic resonance angiography (MRA) of the cerebral vessels. MRA was performed using three-dimension (3D) technique and maximum intensity projection images (MIP) were obtained. MRI showed bilateral abnormal high signal intensities in the frontal and parietal gray and white matters in T2WI, FLAIR and diffusion/perfusion weighted imaging views which did not contrast enhanced. There were ex vacuo dilatation of the frontal horns and bodies

of lateral ventricles with relative prominence of the overlying sulci. There were variable sized hypointense foci with near CSF intensity within the right frontal white matter indicating frontal gliotic changes and cystic encephalomalacia in brain areas supplied by ICAs/MCAs (Figure 2). MRA showed complete occlusion of the supraclinoid portion of both ICAs. The ACAs and MCAs were not visualized. The basilar artery (BA) and PCAs had normal sizes and calibers. Collaterals were predominantly from the posterior circulation (Figure 3).

In January 2021, follow up pre- and post-contrast multi-slice CT of the brain and CT angiography (CTA) and CT venography (CTV) on the cerebral vessels were done. CT of the brain showed bilateral frontal subcortical and slightly cortical hypodense lesions with CSF density. There were dilated ventricular systems, and prominent cortical sulci and basal cisterns (Figure 4). CTA showed non-visualization of right and left ACAs and MCAs, the left ICA ended blindly before the siphon, non-visualization of the left posterior communicating artery (PCoA) and attenuation of the distal parts of the right vertebral artery (VA) (compared to its proximal part) and BA. There was dominance of the posterior circulation with extensive bilateral collaterals (compared to early MRA findings) and prominence of the dilated basal perforating vessels (moyamoya vessels) (Figure 5). CTV showed normal opacification of the dural venous sinuses with no filling defects. The superficial and deep cerebral veins were normal.

FINAL DIAGNOSIS

MMD.

TREATMENT

Her treatment regimen included LEV (200 mg every 12 h) and aspirin (75 mg/d). The child was also seizure-free on LEV in a maintenance dose of 200 mg every 12 h. Recommendations included continuation of aspirin in a maintenance dose of 75 mg/d. The decision for revascularization surgery was postponed.

OUTCOME AND FOLLOW-UP

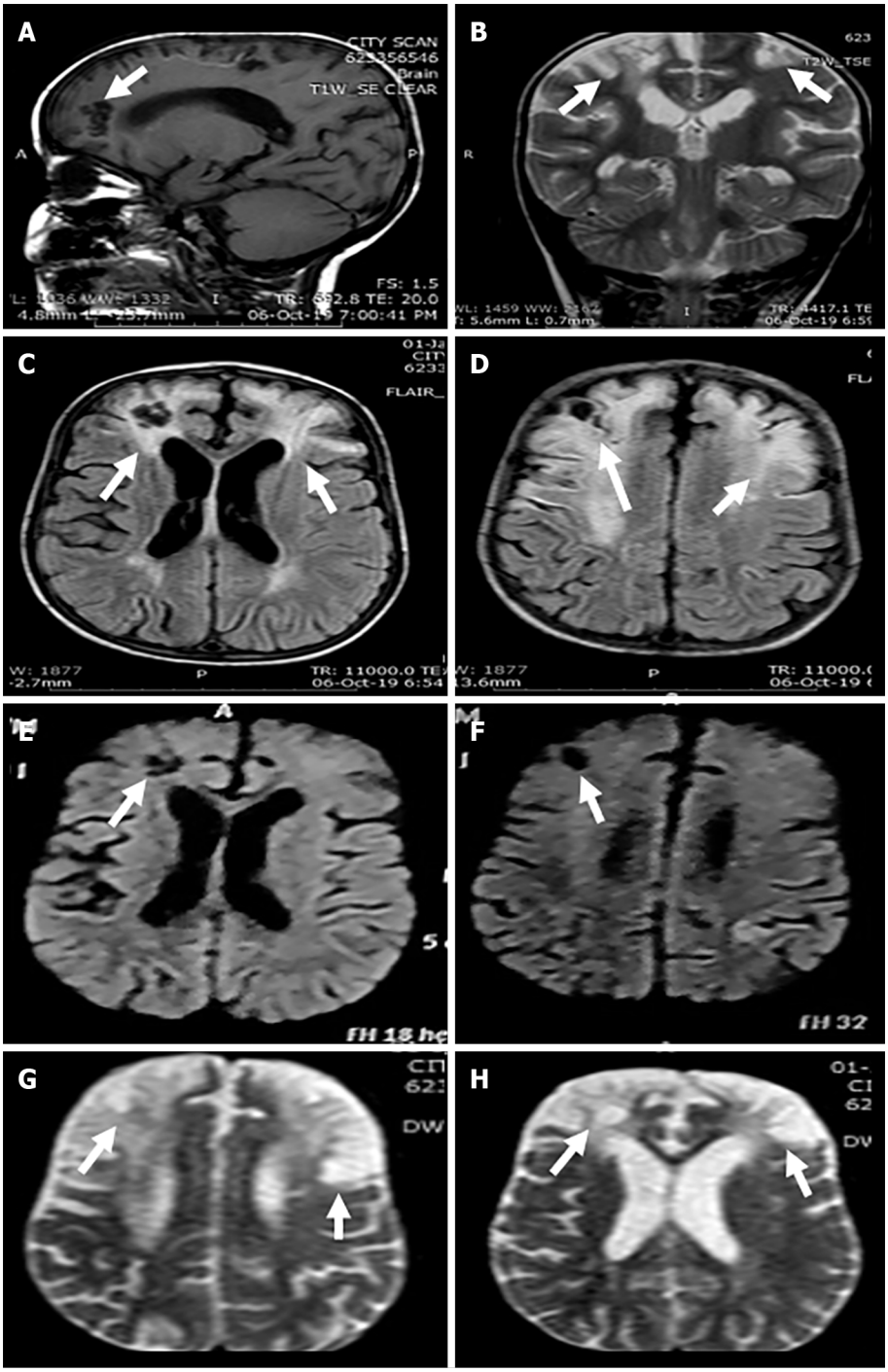
Clinical follow-up over at least 3 years showed no new ischemic insults or exacerbation of the existing deficits.

DISCUSSION

We present a younger female child with epilepsy right and left focal seizures and GTC and TIAs. She developed left sided hemiparesis after an attack of ischemic cerebrovascular stroke. A common child behavior which triggered the TIA was crying (*i.e.* hyperventilation or hyperpnea excitement). She had no family history of similar condition. There were no risk factors (*e.g.* infection, vaccination, *etc.*) in temporal relation to the disease onset. There were no comorbid other neurological or extra-neurological manifestations. Her comprehensive laboratory investigations did not reveal an identifiable cause for the ischemic attacks. Her MRI, MRA and CTA findings are highly supportive for the diagnosis of MMD.

For the presented child, the diagnosis of MMD was provided based on the followings: (1) The bilateral involvement (stenosis/occlusion) of the distal terminal parts of ICAs. The brain infarcts involved the fronto-parietal areas (areas supplied by the ICAs/MCAs) and appeared with "gyral pattern" which was atypical from infarcts of conventional ischemic strokes due to other steno-occlusive diseases which typically have territorial, border zone, deep lacunar or multiple-dots patterns[17-19]. The occlusion of the ICA started at its bifurcation, *i.e.* in the supraclinoid part distal to the ophthalmic and anterior choroidal arteries. The right and left ophthalmic arteries and PCoAs were visualized on MRA but the ACAs and MCAs were not visualized. There were no infarcts in basal ganglia, diencephalon, midbrain and temporal lobes, *i.e.* brain areas supplied by the anterior choroidal artery; and (2) There were imaging evidences for disease progressive overtime regardless to the apparent symptomatic improvement. They included: (1) The robustness of bilateral collaterals which was seen overtime; and (2) the visualization of the basal moyamoya vessels or "puff of smoke".

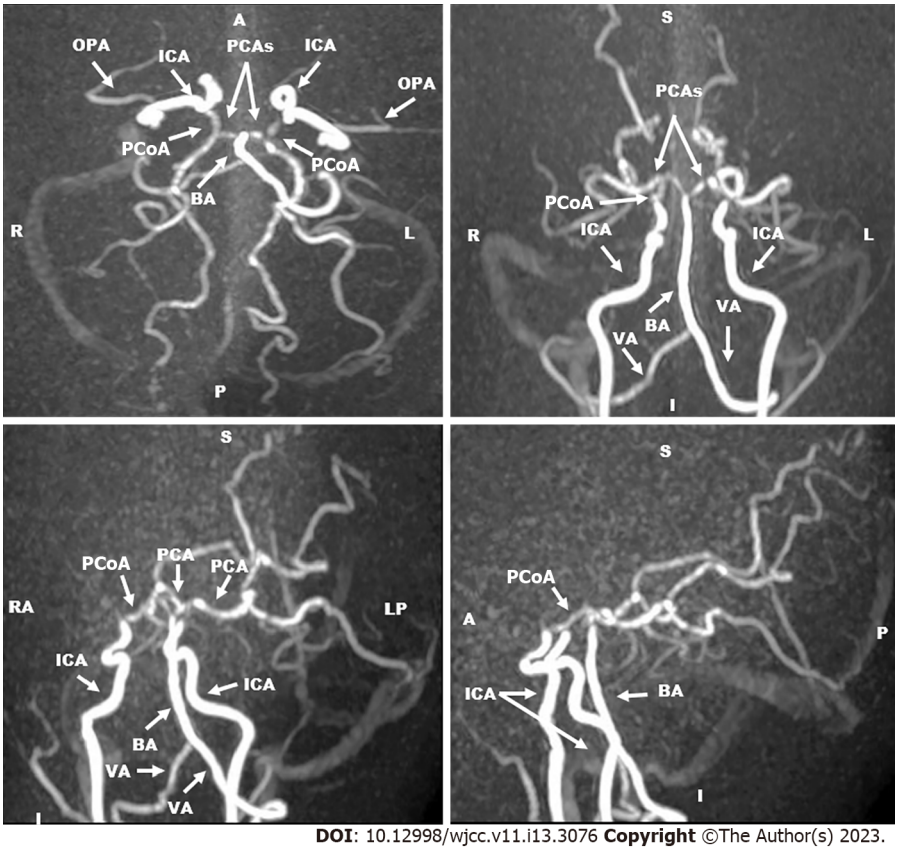
Studies of large cohort of children found that the development of collaterals occurred before any significant hemodynamic impairment or development of ischemic stroke due to arterial occlusion, indicating that the neo-vascularization in MMD is a dynamic process triggered by progressive stenosis and not a passive compensation for the ischemic stroke or arterial occlusion[10]. Authors also found a development of new arterioles from pre-existing vascular structures (*i.e.* arteriogenesis), which



DOI: 10.12998/wjcc.v11.i13.3076

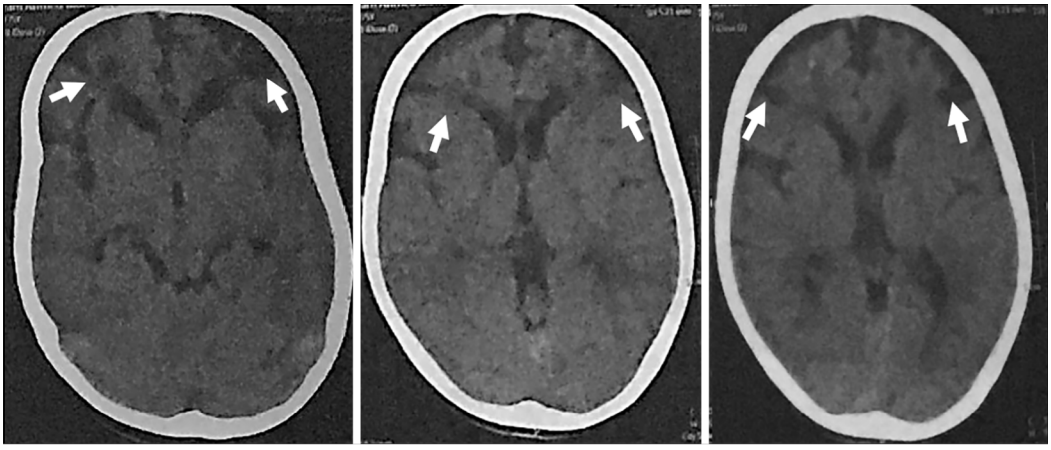
Figure 2 Magnetic resonance imaging-brain views (Date: October 2019). A: Sagittal T1-weighted imaging; B: Coronal; C and D: Axial fluid attenuation inversion recovery; E and F: Diffusion weighted imaging; G and H: Diffusion/perfusion weighted. A, E and F revealed hypointense lesions in the fronto-parietal regions and areas of encephalomalacia (cerebrospinal fluid density) (white arrows). B-D, G, and H views revealed hyperintense lesions in the right and left fronto-parietal areas and areas of encephalomalacia (white arrows).

developed within days after arterial occlusion in children with MMD (but not in other steno-occlusive diseases) and the reformation of small sized collaterals into large sized vessels overtime[20,21]; (2) the non-visualization of left PCoA; (3) the attenuation of the distal terminal part of the VA and the distal part of the BA (*i.e.* stenosis); and (4) the stenosis/occlusion of the left ICA before the siphon. The absence of visual impairment and the normal fundus examination at the time of CTA (done 15 mo after the acute stroke) confirmed that the progressive stenosis/occlusion of the left ICA was distal to the left ophthalmic artery. It also seems that the progressive left ICA pathology might also be distal to the left anterior choroidal artery, because there were no clinical or CT evidences for the presence of infarctions in brain areas supplied by the anterior choroidal artery. However, CT is less sensitive than MRI for visualization of deep brain infarcts[12]. Previous studies indicated that CTA is non-invasive technique.



DOI: 10.12998/wjcc.v11.i13.3076 **Copyright** ©The Author(s) 2023.

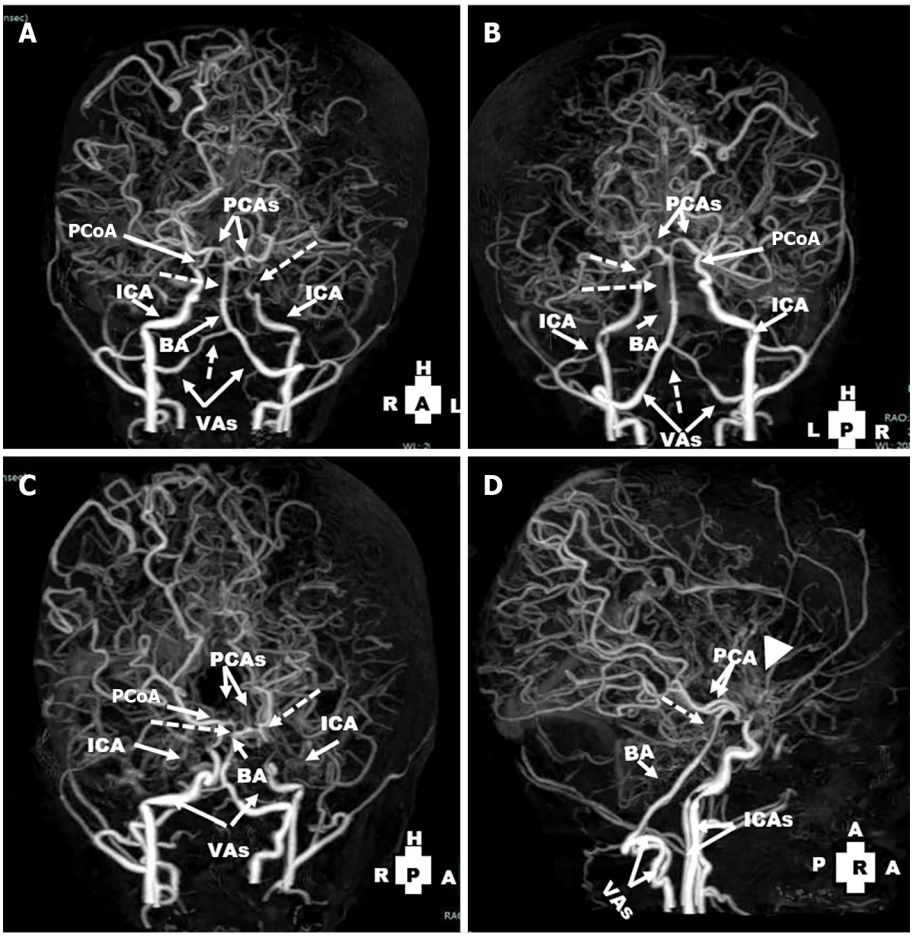
Figure 3 Magnetic resonance angiography of cerebral vessels three-dimension technique and maximum intensity projection images (Date: October 2019). They revealed occlusion of the supraclinoid portion of internal carotid arteries. The right and left anterior cerebral arteries and middle cerebral arteries were not visualized. The basilar artery and the right and left posterior cerebral arteries had normal sizes and calibers. Collaterals were predominantly from the posterior circulation. OPA: The ophthalmic artery; ICA: The internal carotid artery; PCAs: The posterior cerebral arteries; PCoA: The posterior communicating artery; BA: The basilar artery; VA: The vertebral artery.



DOI: 10.12998/wjcc.v11.i13.3076 **Copyright** ©The Author(s) 2023.

Figure 4 Axial computed tomography-brain views (Date: January 2021). They revealed bilateral frontal subcortical and slightly cortical hypodense lesions (the cerebrospinal fluid density) (white arrows).

It captures snapshots in different contrast bolus phases and provides more relevant data regarding secondary collateral flow, which significantly correlates with the neurological outcome. They also indicated that combined MRI, MRA and MRV, non-invasive imaging tests, are enough for the diagnosis of suspected MMD in a child with sensitivity of 92% and a specificity of 100%[8]. It has been found that MRA is beneficial for diagnosis of large basal intracranial vessels and Willisian, leptomeningeal, and transdural collaterals[17,18], whereas conventional angiography is better for diagnosis of smaller moyamoya collaterals and extracranial distal collateral networks[8]. MRI and MRA also differentiate MMD from the mimicking conditions including vascular dissection, inflammatory vasculitis and cystic



DOI: 10.12998/wjcc.v11.i13.3076

Figure 5 Computed tomography angiography views of the cerebral vessels (Date: January 2021): They revealed non-visualization of right and left anterior cerebral arteries and middle cerebral arteries. A-C: The left internal carotid artery ended blindly before the siphon (dotted arrow), non-visualization of the left posterior communicating artery) and attenuation of the distal part of the right vertebral arteries and basilar artery (dotted arrows); D: There were extensive bilateral collaterals and prominence of moyamoya vessels (arrow head). PCoA: The posterior communicating artery; PCAs: The posterior cerebral arteries; ICA: The internal carotid artery; BA: The basilar artery; VAs: The vertebral arteries.

medial necrosis[8]. The patient did not perform conventional angiography. In practice, cerebral conventional angiography must be reserved for children with MMD in the following circumstances due to its invasiveness: (1) If diagnosis was uncertain; and (2) inconsistency between the clinical progression and the finding of MRA or CTA during follow-up, during pre-operative planning, and sometimes during follow-up evaluation after surgical re-vascularization[12].

The long-term outcome of this patient has to be followed overtime. The clinical improvement (marked reduction of TIAs and seizures) and stabilization of her clinical condition during the 3 years period of follow-up could be attributed to the rapid and extensive recruitment of collaterals and absence of risk factors or comorbidities. However, there are factors indicative for poor prognosis which included: (1) The early age at onset of symptoms[9]; (2) the large extent of infarctions seen on MRI at the time of initial presentation; (3) the presence of encephalomalacia and atrophy of the cerebral hemispheres (*i.e.* evidence of severe stroke); and (4) CTA evidence of progressive arteriopathy. We suggest that the marked difference in the extent of collaterals between MRA, which was done 3 mo after the cerebrovascular stroke, and the follow-up CTA, which was done 15 mo after the stroke, indicates the rapid and progressive degree of carotid stenosis/occlusion. Therefore, surgical revascularization is indicated for this child to reduce the recurrence of stroke[15]. However, experience of this type of surgery is not locally available.

Management of the patient was symptomatic treatment for epilepsy. Aspirin was prescribed in a dose of 75 mg/d for secondary prevention[8,14]. It has been indicated that the main line of treatment of MMD is surgical revascularization[15]. However, conservative treatment using the anti-platelet drugs (as aspirin or clopidogrel)[13] and the calcium channel blockers (as nicardipine)[16] may play a supportive role especially when surgical treatment is not available locally. Furthermore, because patients with MMD have deficit in cerebral hemodynamics and cerebral vascular reserve, thus advices for prevention of rapid deterioration included: Avoidance of situations which induce hyperventilation, dehydrations and hypotension. In MMD, hyperventilation causes decrease in arterial carbon dioxide

tension which causes vasoconstriction, induces cerebral hypoxia and may result in steal response in brain areas which already have chronic hemodynamic stress[22].

CONCLUSION

To the best of our knowledge, this is the first case report of a child with MMD disease from our locality. Clinical and imaging follow-ups for the child was done over a period of at least 3 years after the acute ischemic stroke. Her clinical manifestations were improved and no further ischemic insults were happened which could be attributed to the massive development of bilateral collaterals. Revascularization surgery is highly recommended for optimal treatment of the patient.

ACKNOWLEDGEMENTS

I would like to thank the patient's parents for their cooperation and approval to publish the clinical, laboratory and imaging results of their daughter.

FOOTNOTES

Author contributions: Hamed SA performed the clinical follow-ups of the patient, wrote the manuscript and had the final responsibility to submit the manuscript for publication; Yousef HA performed the neuroimaging, verified the underlying data and interpretation of the results and final approval of the manuscript.

Informed consent statement: The consent form to treat the child and to publish the child's clinical, laboratory and imaging date and treatment has been signed by the child's father.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read CARE Checklist (2016), and the manuscript was prepared and revised according to CARE Checklist (2016).

Country/Territory of origin: Egypt

ORCID number: Sherifa Ahmed Hamed 0000-0002-1441-3530.

S-Editor: Li L
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Lee S**, Rivkin MJ, Kirton A, deVeber G, Elbers J; International Pediatric Stroke Study. Moyamoya Disease in Children: Results From the International Pediatric Stroke Study. *J Child Neurol* 2017; **32**: 924-929 [PMID: 28715924 DOI: 10.1177/0883073817718730]
2 **Suzuki J**, Kodama N. Moyamoya disease--a review. *Stroke* 1983; **14**: 104-109 [PMID: 6823678 DOI: 10.1161/01.str.14.1.104]
3 **Amlie-Lefond C**, Bernard TJ, Sébire G, Friedman NR, Heyer GL, Lerner NB, DeVeber G, Fullerton HJ; International Pediatric Stroke Study Group. Predictors of cerebral arteriopathy in children with arterial ischemic stroke: results of the International Pediatric Stroke Study. *Circulation* 2009; **119**: 1417-1423 [PMID: 19255344 DOI: 10.1161/CIRCULATIONAHA.108.806307]
4 **Søgaard I**, Jørgensen J. Familial occurrence of bilateral intracranial occlusion of the internal carotid arteries (Moya Moya). *Acta Neurochir (Wien)* 1975; **31**: 245-252 [PMID: 1181815 DOI: 10.1007/BF01406296]
5 **Kitahara T**, Okumura K, Semba A, Yamaura A, Makino H. Genetic and immunologic analysis on moya-moya. *J Neurol Neurosurg Psychiatry* 1982; **45**: 1048-1052 [PMID: 6983566 DOI: 10.1136/jnnp.45.11.1048]
6 **Shlobin NA**, Hoffman SC, Clark JR, Du RY, Lam S. Clinical Usefulness of Genetic Testing For Patients with Moyamoya Disease: A Systematic Review. *World Neurosurg* 2021; **152**: 198-205.e1 [PMID: 34098142 DOI:

10.1016/j.wneu.2021.05.130]

7 **Takagi Y**, Kikuta K, Nozaki K, Hashimoto N. Histological features of middle cerebral arteries from patients treated for Moyamoya disease. *Neurol Med Chir (Tokyo)* 2007; **47**: 1-4 [PMID: 17245006 DOI: 10.2176/nmc.47.1]

8 **Fukui M**. Guidelines for the diagnosis and treatment of spontaneous occlusion of the circle of Willis ('moyamoya' disease). Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease) of the Ministry of Health and Welfare, Japan. *Clin Neurol Neurosurg* 1997; **99** Suppl 2: S238-S240 [PMID: 9409446]

9 **Tagawa T**, Naritomi H, Mimaki T, Yabuuchi H, Sawada T. Regional cerebral blood flow, clinical manifestations, and age in children with moyamoya disease. *Stroke* 1987; **18**: 906-910 [PMID: 3629650 DOI: 10.1161/01.str.18.5.906]

10 **Takahashi M**. Magnification angiography in moyamoya disease: new observations on collateral vessels. *Radiology* 1980; **136**: 379-386 [PMID: 7403514 DOI: 10.1148/radiology.136.2.7403514]

11 **Yamada I**, Suzuki S, Matsushima Y. Moyamoya disease: comparison of assessment with MR angiography and MR imaging *vs* conventional angiography. *Radiology* 1995; **196**: 211-218 [PMID: 7784569 DOI: 10.1148/radiology.196.1.7784569]

12 **Suzuki J**, Takaku A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. *Arch Neurol* 1969; **20**: 288-299 [PMID: 5775283 DOI: 10.1001/archneur.1969.00480090076012]

13 **Scott RM**, Smith JL, Robertson RL, Madsen JR, Soriano SG, Rockoff MA. Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. *J Neurosurg* 2004; **100**: 142-149 [PMID: 14758941 DOI: 10.3171/ped.2004.100.2.0142]

14 **Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis**; Health Labour Sciences Research Grant for Research on Measures for Infractable Diseases. Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis). *Neurol Med Chir (Tokyo)* 2012; **52**: 245-266 [PMID: 22870528 DOI: 10.2176/nmc.52.245]

15 **Wouters A**, Smets I, Van den Noortgate W, Steinberg GK, Lemmens R. Cerebrovascular events after surgery *vs* conservative therapy for moyamoya disease: a meta-analysis. *Acta Neurol Belg* 2019; **119**: 305-313 [PMID: 31215004 DOI: 10.1007/s13760-019-01165-9]

16 **Hosain SA**, Hughes JT, Forem SL, Wisoff J, Fish I. Use of a calcium channel blocker (nicardipine HCl) in the treatment of childhood moyamoya disease. *J Child Neurol* 1994; **9**: 378-380 [PMID: 7822727 DOI: 10.1177/088307389400900407]

17 **Patrick JT**, Fritz JV, Adamo JM, Dandonna P. Phase-contrast magnetic resonance angiography for the determination of cerebrovascular reserve. *J Neuroimaging* 1996; **6**: 137-143 [PMID: 8704287 DOI: 10.1111/jon199663137]

18 **Grond M**, Rudolf J, Schneweis S, Terstegge K, Sobesky J, Kracht L, Neveling M, Heiss WD. Feasibility of source images of computed tomographic angiography to detect the extent of ischemia in hyperacute stroke. *Cerebrovasc Dis* 2002; **13**: 251-256 [PMID: 12011549 DOI: 10.1007/BF00270916]

19 **Cho HJ**, Jung YH, Kim YD, Nam HS, Kim DS, Heo JH. The different infarct patterns between adulthood-onset and childhood-onset moyamoya disease. *J Neurol Neurosurg Psychiatry* 2011; **82**: 38-40 [PMID: 20587492 DOI: 10.1136/jnnp.2009.181487]

20 **Kim SJ**, Son TO, Kim KH, Jeon P, Hyun SH, Lee KH, Yeon JY, Kim JS, Hong SC, Shin HJ, Bang OY. Neovascularization precedes occlusion in moyamoya disease: angiographic findings in 172 pediatric patients. *Eur Neurol* 2014; **72**: 299-305 [PMID: 25323466 DOI: 10.1159/000365286]

21 **van Royen N**, Piek JJ, Buschmann I, Hoefer I, Voskuil M, Schaper W. Stimulation of arteriogenesis; a new concept for the treatment of arterial occlusive disease. *Cardiovasc Res* 2001; **49**: 543-553 [PMID: 11166267 DOI: 10.1016/s0008-6363(00)00206-6]

22 **Nariai T**, Senda M, Ishii K, Wakabayashi S, Yokota T, Toyama H, Matsushima Y, Hirakawa K. Posthyperventilatory steal response in chronic cerebral hemodynamic stress: a positron emission tomography study. *Stroke* 1998; **29**: 1281-1292 [PMID: 9660374 DOI: 10.1161/01.str.29.7.1281]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3086-3091

DOI: 10.12998/wjcc.v11.i13.3086

ISSN 2307-8960 (online)

CASE REPORT

Solitary acral persistent papular mucinosis nodule: A case report and summary of eight Korean cases

Yu Jeong Park, Hui Young Shin, Woo Kyoung Choi, Ai-Young Lee, Seung Ho Lee, Jong Soo Hong

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Fan L, China

Received: December 29, 2022
Peer-review started: December 29, 2022
First decision: March 10, 2023
Revised: March 22, 2023
Accepted: March 31, 2023
Article in press: March 31, 2023
Published online: May 6, 2023

Yu Jeong Park, Hui Young Shin, Woo Kyoung Choi, Ai-Young Lee, Seung Ho Lee, Jong Soo Hong, Department of Dermatology, Dongguk University Ilsan Hospital, College of Medicine, Dongguk University, Goyang-si, Gyeonggi-do, Korea 10326, South Korea

Corresponding author: Jong Soo Hong, MD, PhD, Professor, Department of Dermatology, Dongguk University Ilsan Hospital, College of Medicine, Dongguk University, Dongguk University Ilsan Medical Center, 27, Dongguk-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do, Korea 10326, South Korea. jsttjstt@hanmail.net

Abstract

BACKGROUND

Acral persistent papular mucinosis (APPM) is a rare idiopathic subtype of localized lichen myxedematosus. To date, there have been 40 APPM cases reported worldwide; however, only 7 cases have been reported in the Korean literature.

CASE SUMMARY

A 70-year-old man was referred to our hospital with a solitary pinkish nodule on the dorsum of his right hand. Despite the absence of symptoms, the patient wanted to know the exact diagnosis; thus, a biopsy was performed. Histopathological examination of a biopsy specimen obtained from the nodule on the dorsum of his hand revealed orthokeratotic hyperkeratosis with patchy parakeratosis, prominent hypergranulosis, and diffuse dissecting mucinous deposition between collagen bundles, along with some bland-looking spindle cells throughout the dermis. The nodule was histologically diagnosed as an APPM, and an intralesional triamcinolone injection (2.5 mg/mL) was started every 2 wk. After three sessions of treatment, the patient showed marked improvements.

CONCLUSION

To the best of our knowledge, this is the first case of a Korean APPM presenting as a solitary nodule that showed a marked response to triamcinolone intralesional injection. Since it is a rare disease, we report this case to contribute to future research on the pathogenesis and treatment of APPM.

Key Words: Acral persistent papular mucinosis; Localized lichen myxedematosus; Cutaneous mucinosis; Mucin; Case report

Core Tip: Acral persistent papular mucinosis (APPM) is a rare idiopathic subtype of localized lichen myxedematosus. To date, 40 cases have been reported worldwide; however, only seven cases have been reported in the Korean literature. This article reports on a rare case of solitary APPM, which was histologically diagnosed in a 70-year-old Korean man with a pinkish nodule on the dorsum of his hand. The patient showed marked improvement after three sessions of intralesional triamcinolone injection. This is the first reported case of a Korean APPM presenting as a solitary nodule and emphasizes the importance of continued research into the pathogenesis and treatment of this rare disease.

Citation: Park YJ, Shin HY, Choi WK, Lee AY, Lee SH, Hong JS. Solitary acral persistent papular mucinosis nodule: A case report and summary of eight Korean cases. *World J Clin Cases* 2023; 11(13): 3086-3091
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3086.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3086

INTRODUCTION

Acral persistent papular mucinosis (APPM) is a rare idiopathic subtype of localized lichen myxedematosus (LM)[1]. It is characterized by white or skin-colored, 2–5 mm papules on the hands, wrists, and extensor aspects of the forearms[1]. The number of papules varies from a few to hundreds and is usually asymptomatic; however, some patients complain of pruritus[1].

Most cases have a favorable prognosis and require no treatment; however, in some cases, tacrolimus ointments or triamcinolone intralesional injections have been administered.

To date, there have been 40 APPM cases reported worldwide[1,2], however, only 7 cases have been reported in the Korean literature. Herein, we present a new case of an older Korean adult with solitary APPM as an atypical manifestation. In addition, we summarized 8 cases of APPM, including ours.

CASE PRESENTATION

Chief complaints

A 70-year-old man was referred to our hospital with a solitary pinkish nodule on the dorsum of his right hand (Figure 1A).

History of present illness

The patient was asymptomatic and did not complain of pruritus or pain.

History of past illness

His medical history showed that he had psoriasis for decades, which was managed using topical agents.

Personal and family history

He denied any other familial history of dermatologic or endocrinologic diseases.

Physical examination

Despite the absence of symptoms, the patient wanted to know the exact diagnosis; thus, biopsy and blood tests were performed.

Laboratory examinations

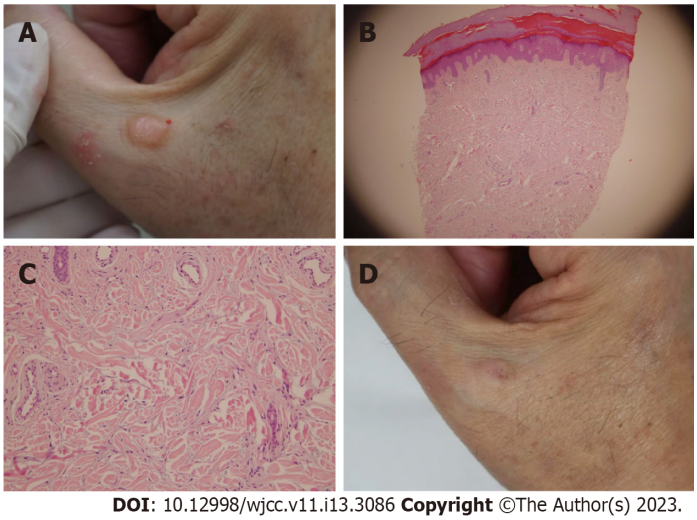
Blood tests showed no endocrine abnormalities including thyroid function.

Imaging examinations

Histopathological examination of a biopsy specimen obtained from the nodule on the dorsum of his hand revealed orthokeratotic hyperkeratosis with patchy parakeratosis, prominent hypergranulosis, and diffuse dissecting mucinous deposition between collagen bundles, along with some bland-looking spindle cells throughout the dermis (Figure 1B and C).

FINAL DIAGNOSIS

The nodule was histologically diagnosed as an APPM.



DOI: 10.12998/wjcc.v11.i13.3086

Figure 1 A pinkish, solitary nodule measuring 1 cm was found on the right dorsum of the hand. A: A clinical image taken before treatment showed the appearance of the nodule; B: Biopsy results showed orthokeratotic hyperkeratosis with patchy parakeratosis, prominent hypergranulosis; C: Diffuse dissecting mucinous deposition between collagen bundles, along with some bland-looking spindle cells throughout the dermis (H&E; B: ×40, C: ×200); and D: Following three sessions of intralesional triamcinolone injection every 2 wk, a marked improvement was observed.

TREATMENT

To reduce the size, intralesional triamcinolone injection (2.5 mg/mL) was administered once every 2 wk.

OUTCOME AND FOLLOW-UP

After three sessions of treatment, the patient showed marked improvements (Figure 1D).

DISCUSSION

Cutaneous mucinosis is a medical term used for a diverse group of skin disorders that involve a localized or widespread accumulation of mucin in the skin or within the hair follicle[3,4]. Mucin is composed of mucopolysaccharides acid or hyaluronic acid and is generally present as part of the connective tissue of the dermis[3,4]. Its main function is to maintain the balance of salt and water in the dermis. The excessive deposition of mucin manifests as a clinically specific lesion or a mucinous rash[3,4]. Cutaneous mucinosis can be divided into two main groups: Generalized form (scleromyxedema), which classically presents with systemic abnormalities, such as monoclonal gammopathy or thyroid disease; and localized form (LM), which is a rare form and classically presents with a lack of systemic disease[3,4].

APPM was first described by Rongioletti *et al*[1] in 1986. It is one of the five subtypes of LM, namely, a discrete form, APPM, self-healing papular mucinosis, papular mucinosis of infancy, and a pure nodular form[3]. APPM is a chronic idiopathic cutaneous mucinosis characterized by lichenoid papules or nodules with mucin deposition and the absence of associated thyroid disease, paraproteinemia, and other systemic abnormalities[3-5]. Patients with this diagnosis are typically women and present with a bilaterally symmetrical distribution on their hands and wrists but not on the trunk and face[6].

The etiology of APPM is still unknown; however, family cases have shown that genetic and environmental factors play an important role[7]. Interleukin-1, interferon gamma, tumor necrosis factor-alpha (TNF-α), and transforming growth factor beta may stimulate glycosaminoglycan synthesis, but the true triggers are unknown, and there is a report of cutaneous mucinosis developing after using a biological agent, such as a TNF-α inhibitor, in patients with psoriasis[8]. Our patient had psoriasis for a long time; however, the direct link between cutaneous mucinosis and psoriasis is not well-known, with no reported literature. Human immunodeficiency virus (HIV) infection can also be linked to primary cutaneous mucinoses, and 18 cases of primary cutaneous mucinoses in HIV-infected patients have been reported, 2 of which are APPM. It has been speculated that direct stimulation of fibroblasts by HIV infection or fibroblast stimulation by activated serum cytokines owing to overactive B-cell function may be associated with mucin deposition, but no definitive mechanism has been elucidated[9].

Table 1 Summary of the Korean cases of acral persistent popular mucinosis

Case	Ref.	Age/Sex	Onset	Past medical history	Clinical manifestation	Treatment	Outcome
1	Kim *et al*[11], 1993	F/56	1 mo ago	s/p Rt. Nephrectomy d/t renal cancer	Multiple, flesh-colored papules on both forearms, wrists and hands without symptoms	None	-
2	Lee *et al*[12], 2000	M/43	6-7 years ago	None	Multiple discrete white to flesh-colored papules are present on the extensor surface of hand without symptoms	None	-
3	Lee *et al*[12], 2000	M/50	7 years ago	None	Multiple whitish papules on dorsum of the hand without symptoms	None	-
4	Song *et al*[6], 2002	F/50	3 years ago	None	Pruritic numerous papular eruption on the dorsa of the hands, and the extensor surface of the forearms	Intralesional triamcinolone injection	No improvement
5	Ryu *et al*[13], 2003	M/64	15 years ago	s/p Subtotal gastrectomy d/t gastric ulcer	Asymptomatic flesh-colored or translucent papules on wrists, back of the hands, and distal forearms	None	-
6	Choi *et al*[9], 2007	M/31	2 mo ago	AIDS	Multiple tiny flesh-colored papules on the extensor surface of the wrist and the distal part of forearm	After 5 wk of starting highly active antiretroviral therapy for AIDS, the skin lesions were also resolved	Resolved
7	Jun *et al*[10], 2016	F/53	7-8 years ago	None	Asymptomatic 1-3 mm flesh-colored papules symmetrically located on both dorsum of hands and wrists, and on anterior chest	Tacrolimus ointment 0.1% once a day	After 15 wk, responded partially

AIDS: Acquired immunodeficiency syndrome.

Since APPM has rarely been reported in Korea, we have summarized the characteristics of APPM cases that have occurred in Korea[6,9-13] (Table 1). To the best of our knowledge, there are eight cases, including the present one, of which five were reported in males and three in females. Their ages ranged from 31 to 70 years, and most were middle-aged. Most had no underlying disease and only two patients had reported underlying medical conditions; one, who was a patient in our case, had psoriasis, while the other had HIV. Only one patient complained of itching, while the rest were asymptomatic. Notably, except for our case, all cases presented symmetrical, multiple papules. To the best of our knowledge, this is the first case of a large solitary nodule. As it is a rare form that has not been previously reported, the possibility of APPM should be considered even with a single nodule. Among the 40 cases reported worldwide, it is interesting that 8 were Korean and 24 were Japanese[1,2], suggesting a racial influence; however, further studies are necessary to confirm this because of the small number of samples.

No effective treatment has been established for APPM. Treatment options range from topical steroids or tacrolimus and intralesional corticosteroids to oral tranilast, which inhibits the release of histamine and prostaglandins from mast cells[2]. However, the effects of these treatments are variable. In the Korean cases, four patients were not treated, and the exact outcome could not be identified owing to loss of follow-up. One patient showed some improvement after 15 wk of topical application of tacrolimus. In another case, an intralesional steroid injection was administered but no improvement was noted, and the exact number and interval of treatment were not known. In one case with acquired immunodeficiency syndrome (AIDS) as an underlying disease, APPM improved with antiviral treatment for AIDS without any specific treatment for APPM[6,9-13]. In our case, intralesional triamcinolone injection was effective; therefore, it can be estimated that intralesional corticosteroids are effective in APPM alone, but additional research is needed. Recently, since the main component of mucin is hyaluronic acid, there have been several case reports in which scleromyxedema and popular dermal mucinosis were treated with hyaluronidase[14,15]. Another therapeutic option is electrocoagulation or erbium-YAG laser[16,17].

CONCLUSION

To the best of our knowledge, this is the first case of a Korean APPM presenting as a solitary nodule that showed a marked response to triamcinolone intralesional injection. Since it is a rare disease, we report this case to contribute to future research on the pathogenesis and treatment of APPM.

ACKNOWLEDGEMENTS

The authors declare that they have no proprietary, commercial, or financial interests that could be construed to have inappropriately influenced this study.

FOOTNOTES

Author contributions: Park YJ and Hong JS wrote the first draft of the manuscript, and all authors reviewed and edited the manuscript and approved the final version of the manuscript.

Informed consent statement: The primary version of the consent that has been signed by the patient in the study is attached as a separate file.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: South Korea

ORCID number: Yu Jeong Park 0000-0003-2462-5278; Hui Young Shin 0000-0003-2523-9504; Woo Kyoung Choi 0000-0003-1675-3720; Ai-Young Lee 0000-0001-7720-7833; Seung Ho Lee 0000-0001-5057-1379; Jong Soo Hong 0000-0003-3813-3055.

S-Editor: Liu XF
L-Editor: A
P-Editor: Zhang XD

REFERENCES

1 **Rongioletti F**, Ferreli C, Atzori L. Acral persistent papular mucinosis. *Clin Dermatol* 2021; **39**: 211-214 [PMID: 34272012 DOI: 10.1016/j.clindermatol.2020.10.001]
2 **Mori A**, Shinkuma S, Mitsui Y, Ogawa K, Miyagawa F, Asada H. Acral persistent papular mucinosis: A case report and summary of 24 Japanese cases. *J Dermatol* 2021; **48**: 1574-1578 [PMID: 34169556 DOI: 10.1111/1346-8138.16043]
3 **Rongioletti F**, Rebora A. Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. *J Am Acad Dermatol* 2001; **44**: 273-281 [PMID: 11174386 DOI: 10.1067/mjd.2001.111630]
4 **Cárdenas-Gonzalez RE**, Ruelas MEH, Candiani JO. Lichen myxedematosus: a rare group of cutaneous mucinosis. *An Bras Dermatol* 2019; **94**: 462-469 [PMID: 31644623 DOI: 10.1590/abd1806-4841.20198478]
5 **Harris JE**, Purcell SM, Griffin TD. Acral persistent papular mucinosis. *J Am Acad Dermatol* 2004; **51**: 982-988 [PMID: 15583597 DOI: 10.1016/j.jaad.2004.07.002]
6 **Song JY**, Lee SW, Kim CW, Kim HO. A case of acral persistent popular mucinosis. *Ann Dermatol***14**: 178-180 [DOI: 10.5021/ad.2002.14.3.178]
7 **Menni S**, Cavicchini S, Brezzi A, Gianotti R, Caputo R. Acral persistent papular mucinosis in two sisters. *Clin Exp Dermatol* 1995; **20**: 431-433 [PMID: 8593726 DOI: 10.1111/j.1365-2230.1995.tb01366.x]
8 **Zhou X**, Mubanga D, Chen Z, Bi X. Secondary Generalized Cutaneous Mucinosis Developed During Etanercept Treatment in a Patient with Psoriasis. *Clin Cosmet Investig Dermatol* 2022; **15**: 987-992 [PMID: 35669090 DOI: 10.2147/CCID.S368390]
9 **Choi JE**, Kim JW, Cho HM, Ahn HH, Kye YC, Kim SN. A case of acral persistent popular mucinosis in patient with HIV infection. *Korean J Dermatol* 2007; **45**: 951-955
10 **Jun JY**, Oh SH, Shim JH, Kim JH, Park JH, Lee DY. Acral Persistent Papular Mucinosis with Partial Response to Tacrolimus Ointment. *Ann Dermatol* 2016; **28**: 517-519 [PMID: 27489445 DOI: 10.5021/ad.2016.28.4.517]
11 **Kim YH**, Yoon JS, Lee JS, Lee JH, Park JK. A case of acral persistent popular mucinosis. *Kor J Dermatol* 1993; **31**: 232-235
12 **Lee MW**, Choi JH, Sung KJ, Moon KC, Koh JK. Acral persistent popular mucinosis. *Kor J Dermatol* 2000; **38**: 236-239
13 **Ryu HJ**, Son SW, Kim Aeree, Kim IH. A case of acral persistent popular mucinosis. *Ann Dermatol* 2003; **15**: 8-11 [DOI: 10.5021/ad.2003.15.1.8]
14 **Akaslan TÇ**, Yıldız P, Onsun N. Clinical and histopathological improvement of scleromyxedema-induced microstomia after hyaluronidase injection. *J Cosmet Dermatol* 2022; **21**: 4319-4322 [PMID: 35441782 DOI: 10.1111/jocd.15007]
15 **Ramamurthi A**, Bicknell L, McCarty M. Hyaluronidase in the treatment of papular dermal mucinosis: first case reported

in North America. *J Surg Dermatol* 2016; **4**: 9-13 [DOI: 10.18282/jsd.v1.i2.43]

16 **André Jorge F**, Mimura Cortez T, Guadalini Mendes F, Esther Alencar Marques M, Amante Miot H. Treatment of acral persistent papular mucinosis with electrocoagulation. *J Cutan Med Surg* 2011; **15**: 227-229 [PMID: 21781629 DOI: 10.2310/7750.2011.10030]

17 **Graves MS**, Lloyd AA, Ross EV. Treatment of acral persistent papular mucinosis using an Erbium-YAG laser. *Lasers Surg Med* 2015; **47**: 467-468 [PMID: 25952726 DOI: 10.1002/Lsm.22368]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3092-3098

DOI: 10.12998/wjcc.v11.i13.3092

ISSN 2307-8960 (online)

CASE REPORT

Eosinophilic fasciitis difficult to differentiate from scleroderma: A case report

Tian-Yi Lan, Zi-Han Wang, Wei-Ping Kong, Jin-Ping Wang, Nan Zhang, Di-Er Jin, Jing Luo, Qing-Wen Tao, Ze-Ran Yan

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bugaj AM, Poland; Hakim GD, Turkey

Received: January 8, 2023
Peer-review started: January 8, 2023
First decision: February 20, 2023
Revised: March 2, 2023
Accepted: March 27, 2023
Article in press: March 27, 2023
Published online: May 6, 2023

Tian-Yi Lan, Zi-Han Wang, Graduate College, Beijing University of Chinese Medicine, Beijing 100029, China

Wei-Ping Kong, Jin-Ping Wang, Nan Zhang, Di-Er Jin, Jing Luo, Qing-Wen Tao, Ze-Ran Yan, Traditional Chinese Medicine Department of Rheumatism, China-Japan Friendship Hospital, Beijing 100029, China

Corresponding author: Ze-Ran Yan, PhD, Doctor, Traditional Chinese Medicine Department of Rheumatism, China-Japan Friendship Hospital, No. 2 Yinghua Street East, Beijing 100029, China. yanzeran@126.com

Abstract

BACKGROUND

Eosinophilic fasciitis (EF) is a rare connective tissue disease that can cause swelling and sclerosis of the extremities, and special attention is needed to differentiate EF from systemic sclerosis. Misdiagnosis or omission markedly delays treatment of EF, and severe skin sclerosis in advanced stages can cause joint contracture and tendon retraction, worsening the patient's prognosis and quality of life.

CASE SUMMARY

We report a case of EF in a young woman diagnosed by tissue biopsy, confirming the difficulty of differential diagnosis with scleroderma.

CONCLUSION

Focusing on skin manifestations, completing tissue biopsy and radiography can help diagnose EF effectively. Clinicians should enhance their understanding of the differences between EF and scleroderma, and early diagnosis and standardized treatment can improve the prognosis of patients with EF.

Key Words: Eosinophilic fasciitis; Scleroderma; Biopsy; Diagnose; Prognosis; Case report

Core Tip: Eosinophilic fasciitis (EF) is a rare connective tissue disease and special attention should be paid to differentiating it from scleroderma. Misdiagnosis or omission markedly delays the appropriate treatment of EF, worsening the prognosis and reducing the quality of life of the patient. We report a case of EF in a young woman diagnosed by tissue biopsy, confirming the difficulty of differential diagnosis with scleroderma. Clinicians should be more aware of EF, and early diagnosis and standardized treatment may improve the prognosis of patients.

Citation: Lan TY, Wang ZH, Kong WP, Wang JP, Zhang N, Jin DE, Luo J, Tao QW, Yan ZR. Eosinophilic fasciitis difficult to differentiate from scleroderma: A case report. *World J Clin Cases* 2023; 11(13): 3092-3098
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3092.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3092

INTRODUCTION

Eosinophilic fasciitis (EF) is a rare connective tissue disease involving the deep fascia of the limbs, with symmetrical skin swelling and sclerosis as the typical manifestation[1,2]. The onset of EF is sudden in 50% of patients, while other patients have a slow onset, and EF usually occurs between the ages of 30 and 60, with a higher incidence in men. The etiology and pathogenesis of EF are unclear. Previous studies suggest that the development of EF may be related to exertion, trauma, immunity, infection, and other factors[3,4], and that EF may be an autoimmune disease in which genetic and environmental factors participate in the development, with less systemic involvement. EF can be misdiagnosed as scleroderma because both conditions can cause sclerosis of the skin of the limbs; however, there are major differences in clinical manifestations and treatment between these two conditions. Unlike scleroderma, EF usually involves the skin and fascia and can extend to the muscles[5], but does not typically affect the hands or face, and there is no Raynaud's phenomenon, capillary dilatation, or vascular changes in the nail folds[6]. EF is more sensitive to hormones in treatment compared with scleroderma, while immunosuppressants are mostly used in the treatment of scleroderma. Consequently, careful examination of the skin and perfect histopathological biopsy are necessary to differentiate between the two conditions and select the appropriate treatment.

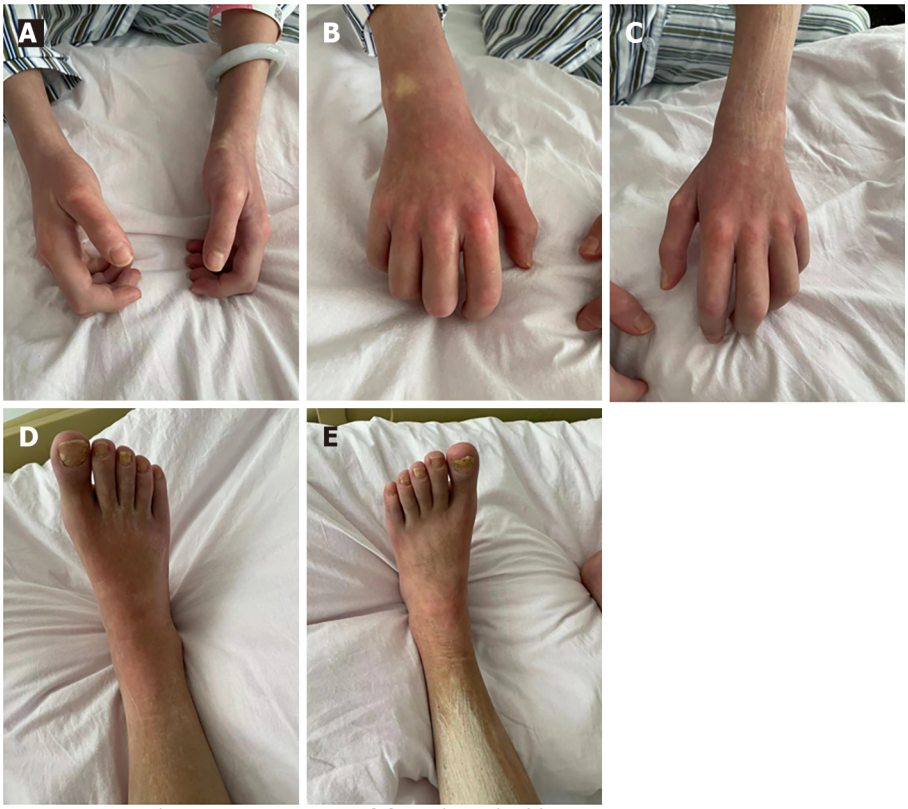
CASE PRESENTATION

Chief complaints

A 28-year-old woman presented at the China-Japan Friendship Hospital complaining of redness and swelling of the extremities for 16 mo and stiffness of the skin of the extremities for more than 11 mo. Upon examination, the patient had stiff skin on both lower limbs; swollen and stiff skin on both arms; restricted movement of wrist joints, metacarpophalangeal joints, and interphalangeal joints of both hands; restricted fist clenching and wrist flexion and extension of both hands; and no swelling or sclerosis of fingers (Figure 1). When the skin of the patient's fingers on both hands was pressed, slow blood filling and localized whitening was observed, followed by slow recovery, and no signs of reddening and purpling. The patient denied Raynaud's phenomenon and had never experienced pale, red, and then purple hands after cold or emotional excitement, cold water test was negative, and no abnormalities in perinail nailfold capillaries.

History of present illness

Sixteen months ago, the patient developed edema of both lower limbs (calves) without any obvious cause, which was aggravated by prolonged standing and slightly relieved by lying down. Subsequently, the redness and swelling increased, spreading from calves to knees and feet with skin stiffness. The patient was diagnosed with "lymphangitis of both lower extremities" in a local hospital, and was given anti-inflammatory and magnesium sulfate topical treatment, but the treatment did not have an obvious effect. The patient then gradually developed redness and swelling of both upper extremities, which later worsened with skin stiffness. Ten months ago, she consulted the local hospital for redness and swelling of the extremities and skin stiffness without significant improvement, and was considered to have "scleroderma", and skin pathology biopsy resulted in a diagnosis of "suspected eosinophilic cellulitis". Six months ago, the patient was seen again at the above hospital, where she was diagnosed with EF after a supplemental antinuclear antibody (ANA) profile test showed ANA 1:1280 speckled. Prednisone acetate 60 mg once a day orally was prescribed for anti-inflammation, and intravenous cyclophosphamide 200 mg was given to control her condition; symptoms then improved. After discharge from the hospital, the prednisone acetate dose was reduced by 5 mg every three weeks, and oral cyclophos-



DOI: 10.12998/wjcc.v11.i13.3092

Figure 1 Photographs of the patient's limbs while in hospital. All images are front views. A: Both arms; B: Right arm; C: Left arm; D: Right leg; E: Left leg.

phamide 4 tablets once a week were started after one month. Two months ago, due to the aggravation of the condition, the patient was given prednisone acetate 40 mg, cyclophosphamide intravenously to control the disease, and leflunomide 10 mg once a day, and her symptoms were relieved more than before.

History of past illness

Diabetes mellitus (DM) for more than one month.

Personal and family history

Unmarried and infertile. Menstruation started at age 15 years, with a cycle of about 28 d, 3-4 d per period, low volume, dark red, clots, no dysmenorrhea. The patient's grandmother was diagnosed with rheumatoid arthritis.

Physical examination

Body temperature was normal, bilateral tonsils were not enlarged, respiratory sounds of both lungs were clear, no dry and wet rales were heard, local over-clear sounds on percussion, no obvious abnormalities on cardiac and abdominal examination. The skin of both upper and lower extremities was dark purple or pink, with lead tube-like changes, and was tight and hard, and could not be lifted. Restricted flexion and extension of both wrists, inability to make fists with both hands, and restricted movement of both ankles.

Laboratory examinations

Blood tests indicated white blood cells of 6.51 × 10^9/L (reference range: 3.5–9.5 × 10^9/L), lymphocyte of 0.9 × 10^9/L (reference range: 1.1–3.2 × 10^9/L), neutrophil percentage of 78.5% (reference range: 40%–75%), triglycerides of 3.16 mmol/L (reference range: < 1.7 mmol/L), creatine kinase of 19 IU/L (reference range: 26–200 IU/L), lactate of 3.92 mmol/L (reference range: 0.5–2.96 mmol/L), hypersensitive C-reactive protein of 5.02 mg/L (reference range: < 3.0), ANA of 1:320 nuclear granule type, C-reactive protein of 0.645 mg/dL (reference range: < 0.8 mg/L), erythrocyte sedimentation rate of 5 mm/h (reference range: 0–20 mm/h), immunoglobulin G (IgG) of 663 mg/dL (reference range: 694–1620 mg/dL), serum IgG2 of 92.8 mg/dL (reference range: 169–786 mg/dL), CD3+ T-cell count of 684.2 cells/μL (reference range: 835–2217 cells/μL), CD3+CD4+ T-cell count of 267 cells/μL (reference range: 395–1264 cells/μL), natural killer (NK) cell count of 46 cells/μL (reference range: 136–880 cells/μL), CD19+ B-cell count of 65.58 cells/μL (reference range: 92–498 cells/μL), glycosylated hemoglobin

of 7.1% (reference range: 4%–6%), normal rheumatoid factors, and no significant abnormalities seen in coagulation function. Cytokine-related assays, such as interleukin (IL)-2, IL-3, and IL-6, were not significantly abnormal, and angiotensin-converting enzyme was not abnormal.

Imaging examinations

Imaging examinations were not conducted.

Dermatopathological examinations

Reticular basket-like hyperkeratosis with roughly normal epidermal thickness and numerous eosinophilic granulocytes, a few lymphocytes, and histiocytes infiltrating the deep dermis and collagen in the subcutaneous fat layer.

FINAL DIAGNOSIS

(1) EF; and (2) DM.

TREATMENT

Combined with the symptoms and signs and ancillary tests, the diagnosis was considered EF with suspected scleroderma. The selected treatment regimen included oral prednisone acetate 25 mg once daily, leflunomide 10 mg once daily, and immediate intravenous cyclophosphamide 0.4 g. The patient was a young woman and we intended to adjust the treatment regimen to methotrexate 10 mg once a week and mycophenolate mofetil 0.5 g three times a day to ensure reproductive function; however, the patient refused this option due to financial factors. Therefore, the final regimen was prednisone acetate 25 mg once daily (reduce the dosage by 5 mg every three weeks) cyclophosphamide 100 mg orally every other day and leflunomide 10 mg orally once a day. The patient was asked to calculate the cumulative amount of cyclophosphamide and adjust the regimen when it reached 12.0 g or when menstrual disorders appeared.

The patient's glycosylated hemoglobin was 7.1%, higher than the normal range, suggesting poor glycemic control in the past three months. We considered that this might be caused by the continued application of prednisone acetate or the slow reduction of dosage. Consequently, we administered a combination of human insulin injection (6 IU subcutaneous injection before lunch and 6 IU subcutaneous injection before dinner) and metformin hydrochloride tablets (0.5 g orally twice a day) to control blood glucose.

As the patient had been taking hormone for a long time, we used calcium carbonate tablets (0.75 g orally three times a day) and osteoporotic triol gel (0.50 μg orally once a day) to prevent the development of osteoporosis.

The patient's CD3+ T-cell count, CD3+CD4+ T-cell count, and NK-cell count were low, suggesting low immunity, and the patient still needed long-term immunosuppression. Thus, to prevent infection, one tablet of compound sulfamethoxazole every other day was administered.

OUTCOME AND FOLLOW-UP

The patient was treated at the hospital, and the skin stiffness of the extremities and the degree of swelling of both arms were well controlled and did not progress further. After being discharged from the hospital and continuing to take prednisone acetate, leflunomide and cyclophosphamide for 2 mo, the swelling of both arms subsided, the degree of skin stiffness of the extremities was well controlled, and the patient expressed satisfaction with the treatment effect. The administration of cyclophosphamide requires close monitoring of the cumulative amount; therefore, we informed the patient that she needs regular follow up to adjust the medication.

DISCUSSION

EF is a connective tissue disease with scleroderma-like symptoms involving the deep fascia of the limb skin, with symmetrical skin swelling and sclerosis as its main clinical manifestations. In the early stage, some patients may experience systemic symptoms such as fever and fatigue, and painful redness and swelling are common in the distal extremities and may also affect the proximal extremities, but rarely involve the hands, face, and multiple systems. The onset of the disease may be induced by a history of strenuous exercise or by exposure to certain drugs (such as statins, ramipril, heparin, pembrolizumab,

immune checkpoint inhibitors, and anti-tumor necrosis factor drugs)[7,8], while in many patients no clear cause has been found, as in the present case. The patient denied a history of muscle strain and trauma prior to the onset of the disease, as well as the application of medications that could have contributed disease onset. During the treatment of this patient, in addition to the conventional drugs for EF (prednisone acetate, cyclophosphamide, and leflunomide), hypoglycemic drugs such as metformin and human insulin, and calcium carbonate tablets, osteoporosis triol gel, and compound sulfamethoxazole were used to treat EF complications, *i.e.*, diabetes, osteoporosis, and prevention of infection. However, there is no previous evidence that these drugs may have contributed to the development and exacerbation of EF. The patient had no suspicious medication history prior to onset, so the possibility that the drugs caused EF was ruled out.

Approximately 20%–30% of patients can have a combination of limited scleroderma, in addition, some cases of EF are misdiagnosed as scleroderma[9]. However, the treatment options for EF and scleroderma are different, so it is crucial to clarify whether a diagnosis of EF can be made in the clinical setting. Currently, the EF diagnostic criteria proposed by Pinal-Fernandez I *et al*[2] in 2014 (Table 1) are commonly applied, where EF is diagnosed by meeting two major criteria, or one major criterion plus two minor criteria, after excluding systemic sclerosis. The patient in this report met two major diagnostic criteria and was diagnosed with EF. Diffuse fascial thickening, fibrosis, and sclerosis with "groove" or "orange peel" changes are often seen in the late stage of EF, but the "groove" sign was not observed in the extremities of this patient, which may be related to the disease duration and individual differences. Some patients with EF may present with positive antinuclear antibodies, rheumatoid factor, immune complexes, etc.; the patient in this case had a positive ANA profile[10,11]. The previous test examination in the patient did not find obvious signs of current systemic involvement, and combined with the patient's skin manifestations and other clinical symptoms, a diagnosis of scleroderma cannot be determined at present. In the follow-up, attention should be paid to whether there is systemic involvement—for diagnosis of combined scleroderma—after disease progression and standard treatment, and there should be timely adjustment of the treatment plan accordingly.

EF tissue biopsy usually shows fascial thickening with massive infiltration of inflammatory cells, such as plasma cells and neutrophils, and visible eosinophil infiltration, but this predominantly occurs in the early stages of the disease[12]. Scleroderma biopsy lesions mostly occur in the dermis and can be seen as fibrosis in the dermis, which can also involve fascia and muscle as the disease progresses. There are many cases of EF in which eosinophil exudation is not observed though, which makes the differential diagnosis with scleroderma difficult[13]. However, patients with EF mostly have bilateral symmetrical limb lesions, mainly manifesting as diffuse tissue sclerosis, while scleroderma presents predominantly as unilateral limb involvement with well-defined lesions, and this can be considered as an auxiliary diagnosis when tissue biopsy cannot clearly differentiate. In this case, a tissue biopsy revealed a large number of eosinophils, a few lymphocytes, and histiocytes infiltrating the deep dermis and collagen in the subcutaneous fat layer. Combined with the patient's bilateral limb symmetrical sclerosis, the exudation of eosinophils in the tissue biopsy pathology further clarified the diagnosis of EF, and this pathological finding was not a characteristic manifestation of scleroderma. In addition to tissue biopsy, an increasing number of scholars have reported that magnetic resonance imaging can facilitate the diagnosis of EF, and high-signal fascia on T2-weighted images was included as a secondary diagnostic criterion for EF in the 2014 criteria[2].

In terms of treatment, systemic hormone therapy is the preferred regimen for this disease[13,14], with a recommended starting dose of 20–30 mg/d, and this treatment can be effective in 90% of patients, especially those with a predominantly early inflammatory response. If clinical manifestations such as skin hardness, limb range of motion, and other examinations show favorable outcomes during the course of treatment, hormones can be gradually discontinued in 1–2 years under the standardized guidance of physicians. For a small number of patients with a very poor response to hormones, immunosuppressants such as cyclosporine, cyclophosphamide, methotrexate, etc. may be used depending on the individual response[15]. Early treatment of the disease with immunosuppressive agents in combination with glucocorticoids has been suggested to improve the remission rate and aid in hormone reduction in patients with EF[16]. The patient in this case achieved relief of the pain and hardness of the limb to a good extent after the early application of hormones, but the hormone reduction may have been slow, resulting in elevated blood glucose. Therefore, the patient was treated symptomatically with additional hypoglycemic drugs combined with cyclophosphamide therapy, which strengthened the effect of immune regulation and may also have played a positive role in the hormone reduction. The regimen was later proposed to be adjusted to methotrexate and mycophenolate mofetil, but cyclophosphamide was continued because of the patient's personal factors. In addition to pharmacological treatment, physical therapy is also advocated to maintain limb mobility in patients with joint involvement. Approximately 50%–56% of patients with EF experience joint spasm owing to involvement of the fascia over the joint, and the patient in this case was instructed to increase activity exercise appropriately, if possible.

Table 1 Diagnostic criteria for eosinophilic fasciitis proposed in 2014

Criteria	Items
Major criteria	(1) Swelling, induration, and thickening of the skin and subcutaneous tissue that is symmetrical or non-symmetrical, diffuse (extremities, trunk, and abdomen) or localized (extremities); and (2) Fascial thickening with accumulation of lymphocytes and macrophages with or without eosinophilic infiltration (determined by full-thickness wedge biopsy of clinically affected skin)
Minor criteria	(1) Eosinophilia N 0.5 × 10^9/L; (2) Hypergammaglobulinemia N 1.5 g/L; (3) Muscle weakness and/or elevated aldolase levels; (4) Groove sign and/or peau d'orange; and (5) Hyperintense fascia on magnetic resonance imaging T2-weighted images
Exclusion criteria	Diagnosis of systemic sclerosis
Establishes the diagnosis	Presence of both major criteria, or one major criterion plus 2 minor criteria

CONCLUSION

In this case, the diagnosis and treatment of EF was reviewed, while emphasizing the differential diagnosis with scleroderma. Clinically, increased awareness of EF and scleroderma is needed to reduce the progression of disease—such as irreversible skin sclerosis and joint spasm—due to misdiagnosis and underdiagnosis. Early diagnosis and standardized treatment can significantly reduce skin sclerosis and fibrosis at a later stage, which can improve the prognosis and quality of life of patients to a certain extent.

ACKNOWLEDGEMENTS

This report was supported by doctors working in the Traditional Chinese Medicine Department of Rheumatism, China-Japan Friendship Hospital in acquisition, analysis, and interpretation of data.

FOOTNOTES

Author contributions: Yan ZR conceived and designed the study; Lan TY collected the data and wrote the manuscript; Wang ZH performed the patient follow-up; all authors read and approved the final manuscript.

Supported by National Natural Science Foundation of China, No. 81704050; and National High Level Hospital Clinical Research Funding, No. 2022-NHLHCRF-LX-02-0103 and No. 2022-NHLHCRF-LX-02-0104.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Tian-Yi Lan 0000-0001-6820-4569; Zi-Han Wang 0000-0003-4588-480X; Wei-Ping Kong 0000-0001-9481-7684; Jin-Ping Wang 0000-0002-9751-0327; Nan Zhang 0009-0004-8360-2310; Di-Er Jin 0009-0007-0047-7131; Jing Luo 0000-0002-2454-2168; Qing-Wen Tao 0000-0002-9163-8426; Ze-Ran Yan 0000-0003-4105-0314.

S-Editor: Hu YR
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Marzano AV**, Genovese G. Eosinophilic Dermatoses: Recognition and Management. *Am J Clin Dermatol* 2020; **21**: 525-539 [PMID: 32394361 DOI: 10.1007/s40257-020-00520-4]

2 **Pinal-Fernandez I**, Selva-O'Callaghan A, Grau JM. Diagnosis and classification of eosinophilic fasciitis. *Autoimmun Rev* 2014; **13**: 379-382 [PMID: 24424187 DOI: 10.1016/j.autrev.2014.01.019]

3 **Lakhanpal S**, Ginsburg WW, Michet CJ, Doyle JA, Moore SB. Eosinophilic fasciitis: clinical spectrum and therapeutic response in 52 cases. *Semin Arthritis Rheum* 1988; **17**: 221-231 [PMID: 3232080 DOI: 10.1016/0049-0172(88)90008-x]

4 **Wright NA**, Mazori DR, Patel M, Merola JF, Femia AN, Vleugels RA. Epidemiology and Treatment of Eosinophilic Fasciitis: An Analysis of 63 Patients From 3 Tertiary Care Centers. *JAMA Dermatol* 2016; **152**: 97-99 [PMID: 26559760 DOI: 10.1001/jamadermatol.2015.3648]

5 **Lebeaux D**, Francès C, Barete S, Wechsler B, Dubourg O, Renoux J, Maisonobe T, Benveniste O, Gatfossé M, Bourgeois P, Amoura Z, Cacoub P, Piette JC, Sène D. Eosinophilic fasciitis (Shulman disease): new insights into the therapeutic management from a series of 34 patients. *Rheumatology (Oxford)* 2012; **51**: 557-561 [PMID: 22120602 DOI: 10.1093/rheumatology/ker366]

6 **Jinnin M**, Yamamoto T, Asano Y, Ishikawa O, Sato S, Takehara K, Hasegawa M, Fujimoto M, Ihn H. Diagnostic criteria, severity classification and guidelines of eosinophilic fasciitis. *J Dermatol* 2018; **45**: 881-890 [PMID: 29235676 DOI: 10.1111/1346-8138.14160]

7 **Mazilu D**, Boltașiu Tătaru LA, Mardale DA, Bijă MS, Ismail S, Zanfir V, Negoi F, Balanescu AR. Eosinophilic Fasciitis: Current and Remaining Challenges. *Int J Mol Sci* 2023; **24** [PMID: 36768300 DOI: 10.3390/ijms24031982]

8 **Teboul A**, Chouchana L, Durrieu G, Eftekhari P, Treluyer JM, Mouthon L, Chaigne B. Drug-induced eosinophilic fasciitis: A dual pharmacovigilance analysis. *J Am Acad Dermatol* 2022; **86**: 1372-1375 [PMID: 34052335 DOI: 10.1016/j.jaad.2021.05.030]

9 **Matsuura T**, Yamade M, Matsushita N, Kawasaki S, Terai T, Uotani T, Takayanagi Y, Yamada T, Kodaira C, Sugimoto M, Furuta T, Sugimoto K, Osawa S, Ikuma M. [A case of eosinophilic gastroenteritis accompanied with fasciitis of the extremities]. *Nihon Shokakibyo Gakkai Zasshi* 2011; **108**: 444-450 [PMID: 21389666]

10 **Kent LT**, Cramer SF, Moskowitz RW. Eosinophilic fasciitis: clinical, laboratory, and microscopic considerations. *Arthritis Rheum* 1981; **24**: 677-683 [PMID: 6972219 DOI: 10.1002/art.1780240508]

11 **Seibold JR**, Rodnan GP, Medsger TA Jr, Winkelstein A. Circulating immune complexes in eosinophilic fasciitis. *Arthritis Rheum* 1982; **25**: 1180-1185 [PMID: 6982714 DOI: 10.1002/art.1780251006]

12 **Chaigne B**, Tieu A, Beeker N, Zuelgaray E, Bouaziz JD, Sène D, Dupin N, Mouthon L. Cluster analysis reveals eosinophilia and fibrosis as poor prognostic markers in 128 patients with eosinophilic fasciitis. *J Am Acad Dermatol* 2022; **87**: 997-1005 [PMID: 35995088 DOI: 10.1016/j.jaad.2022.08.026]

13 **Ihn H**. Eosinophilic fasciitis: From pathophysiology to treatment. *Allergol Int* 2019; **68**: 437-439 [PMID: 30910631 DOI: 10.1016/j.alit.2019.03.001]

14 **Fermon C**, Lessard LER, Fenouil T, Meyer A, Faruch-Bilfeld M, Robert M, Landel V, Hot A, Authier FJ, Streichenberger N, Gallay L. Revisiting idiopathic eosinophilic myositis: toward a clinical-pathological continuum from the muscle to the fascia and skin. *Rheumatology (Oxford)* 2022 [PMID: 36200845 DOI: 10.1093/rheumatology/keac556]

15 **Fleming CJ**, Clarke P, Kemmett D. Eosinophilic fasciitis with myelodysplasia responsive to treatment with cyclosporin. *Br J Dermatol* 1997; **136**: 297-298 [PMID: 9068764 DOI: 10.1111/j.1365-2133.1997.tb14929.x]

16 **Berianu F**, Cohen MD, Abril A, Ginsburg WW. Eosinophilic fasciitis: clinical characteristics and response to methotrexate. *Int J Rheum Dis* 2015; **18**: 91-98 [PMID: 25530187 DOI: 10.1111/1756-185X.12499]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3099-3104

DOI: 10.12998/wjcc.v11.i13.3099

ISSN 2307-8960 (online)

CASE REPORT

Misdiagnosis of scalp angiosarcoma: A case report

Zhao-Hong Yan, Zhen-Lan li, Xiao-Wei Chen, Ya-Wen Lian, Li-Xin Liu, Hao-Yang Duan

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Alkhatib AJ, Jordan; Covantsev S, Russia; Guo HR, Taiwan

Received: January 27, 2023
Peer-review started: January 27, 2023
First decision: March 10, 2023
Revised: March 20, 2023
Accepted: March 31, 2023
Article in press: March 31, 2023
Published online: May 6, 2023

Zhao-Hong Yan, Zhen-Lan li, Xiao-Wei Chen, Ya-Wen Lian, Hao-Yang Duan, Department of Rehabilitation Medicine, The First Hospital of Jilin University, Changchun 130021, Jilin Province, China

Li-Xin Liu, Department of Plastic and Aesthetic Surgery, The First Hospital of Jilin University, Changchun 130021, Jilin Province, China

Corresponding author: Hao-Yang Duan, PhD, Attending Doctor, Doctor, Department of Rehabilitation Medicine, The First Hospital of Jilin University, No. 1 Xinmin Street, Changchun 130021, Jilin Province, China. duanhy101129@163.com

Abstract

BACKGROUND

Angiosarcoma is a rare malignant tumor. Owing to the lack of specific clinical manifestations of this disease, it is difficult to achieve early diagnosis and start early treatment.

CASE SUMMARY

A 78-year-old male patient was admitted to the hospital because of a bump on his head that did not heal for 4 mo. The patient was diagnosed with a refractory head wound. The patient underwent neoplasm resection and skin grafting surgery in the Plastic Surgery. The neoplasm was sent for pathological examination during the operation. The final pathological results were confirmed scalp angiosarcoma.

CONCLUSION

Our research suggests that pathological examination should be performed for refractory ulcers of the scalp, and physical factor therapy should be used with caution before the diagnosis is clear.

Key Words: Scalp angiosarcoma; Refractory head wound; Pathological examination; Case report

Core Tip: Angiosarcoma is a rare malignant tumor. Owing to the lack of specific clinical manifestations of this disease, it is difficult to achieve early diagnosis and start early treatment. Our research suggests that pathological examination should be performed for refractory ulcers of the scalp, and physical factor therapy should be used with caution before the diagnosis is clear.

Citation: Yan ZH, li ZL, Chen XW, Lian YW, Liu LX, Duan HY. Misdiagnosis of scalp angiosarcoma: A case report. *World J Clin Cases* 2023; 11(13): 3099-3104
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3099.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3099

INTRODUCTION

Angiosarcoma is a rare malignant tumor that originates from the endothelial cells of blood vessels or lymphatic vessels and accounts for approximately 1% to 2% of soft tissue sarcomas, of which more than 50% occur in the head and neck, accounting for 0.1% of head and neck malignancies[1]. Because the incidence of scalp angiosarcoma is extremely low, it attracts little clinical attention. Owing to the lack of specific clinical manifestations of this disease, it is difficult to achieve early diagnosis and start early treatment. Some patients suffer from head trauma, and the wound is repeatedly ruptured and is difficult to heal. Angiosarcoma is difficult to diagnose at an early stage, and treatment of the condition is often delayed by mistakenly attributing it to trauma-related abrasions and abscesses. Imaging examinations such as computed tomography (CT) or magnetic resonance imaging have a certain value for understanding the location, extent of invasion and whether there is distant metastasis. Thus, timely local tissue biopsy is the main method of diagnosis. The diagnosis is finally confirmed by pathological examination. Recently, the department of rehabilitation of the first hospital of jilin university used physical methods to treat a patient with refractory scalp wounds. The treatment was ineffective. Finally, the pathological examination was used to diagnose scalp angiosarcoma. The report is as follows.

CASE PRESENTATION

Chief complaints

A 78-year-old male patient was admitted to the hospital because of a bump on his head that did not heal for 4 mo.

History of present illness

The patient accidentally bumped his head on a cabinet approximately 4 mo ago, which caused the skin of the top of the skull to rupture. After the injury, the patient was conscious, with headache, no nausea or vomiting, and no ulceration of the lips. There were no abnormal secretions in the nose, mouth and external auditory canal, no incontinence, and no convulsions. Motor movements were normal. The patient had been treated at a local hospital for head wounds, but the wounds did not heal. The patient was sent to our hospital for further diagnosis and treatment. The outpatient was admitted to the neurosurgery department of our hospital for head and neck refractory wounds, based on the symptoms, signs and examination (October 20, 2017).

History of past illness

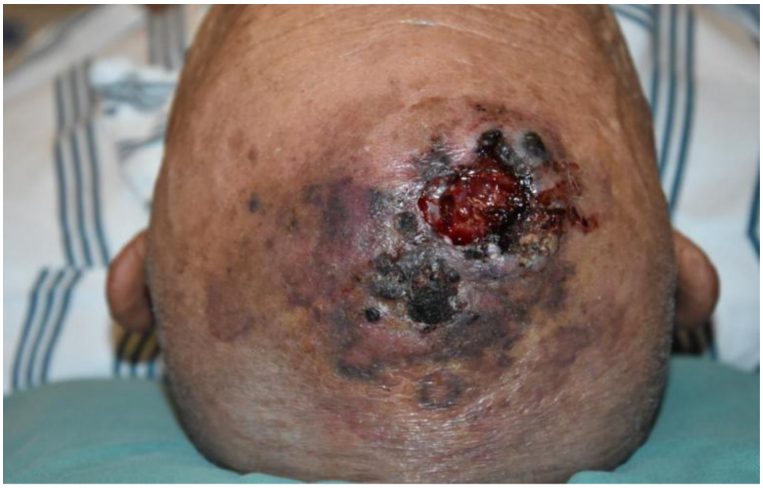
There is no obvious history of past illness related to this disease.

Personal and family history

There is no obvious personal or family history related to this disease.

Physical examination

On admission to the hospital, he was conscious; his vital signs were stable, and no enlarged lymph nodes were discovered in the neck or behind the ears. Both muscle strength and muscle tension of the extremities were normal, and voluntary activities were normal. The bilateral Babinski sign and neck stiffness were negative. The ulcerated wound was visible on the top of the skull; the wound was 3 cm × 4 cm, and some bloody scabs and granulation tissue could be observed on the top of the wound, with a small amount of secretions and no peculiar smell (Figure 1).



DOI: 10.12998/wjcc.v11.i13.3099

Figure 1 The rupture on the skull.

Laboratory examinations

Routine blood test (October 20, 2017) results were as follows: White blood cell count, 7.30 × 10^9/L (reference value: 3.50-9.50 × 10^9/L); neutrophil percentage: 78% (reference value: 20%-75%). The patient was diagnosed with a refractory head wound.

Imaging examinations

Brain CT showed no obvious abnormalities in the skull and brain tissue.

MULTIDISCIPLINARY EXPERT CONSULTATION

After admission, the patient received routine disinfection treatment. After the wound was fully disinfected, it was covered with sterile gauze, which was fixed with a mesh cap, once every 2 d. After the wound had no secretions, surgical treatment was planned. After 14 d of treatment, the wound showed no signs of healing, with a small amount of secretions still remaining. The patient began feeling pain and was then transferred to the department of rehabilitation. Considering that the patient had a history of trauma and a high white blood cell count, semiconductor laser treatment, ultra violet treatment and ultrashort-wave treatment were administered once a day. After 14 d of treatment, the wound did not heal, and the pain was not relieved. The patient underwent neoplasm resection and skin grafting surgery in the plastic surgery department on November 16, 2017 (Figure 2). The neoplasm was sent for pathological examination during the operation (Figure 3). The rapid pathological results showed angiosarcoma.

FINAL DIAGNOSIS

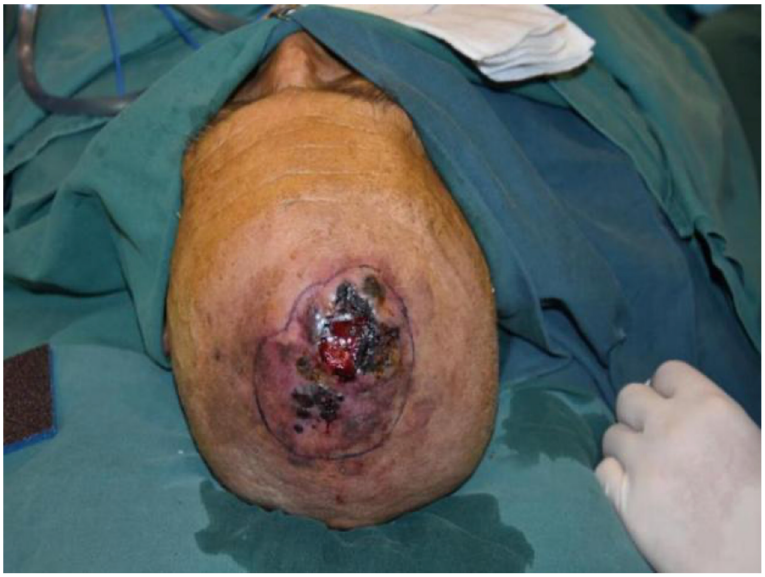
The final pathological results were reported on November 21, 2017 and confirmed scalp angiosarcoma (Figure 4).

TREATMENT

No tumor was observed on the front, back, left, and right margins, but the tumor was close to the undercut margin. The patient was advised to undergo radiotherapy, but he discontinued the treatment and was discharged.

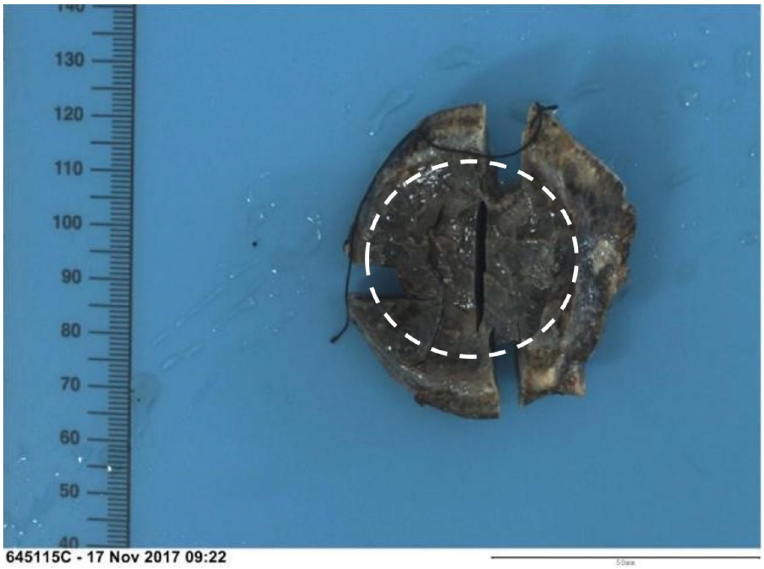
OUTCOME AND FOLLOW-UP

A follow-up was continued after the discharge. In March 2018, the wound on the top of the head ruptured again, and disinfection was conducted at home. In August 2018, the patient passed away, the cause of death is the recurrence of tumor.



DOI: 10.12998/wjcc.v11.i13.3099 **Copyright** ©The Author(s) 2023.

Figure 2 The patient was treated with mass resection and skin grafting.

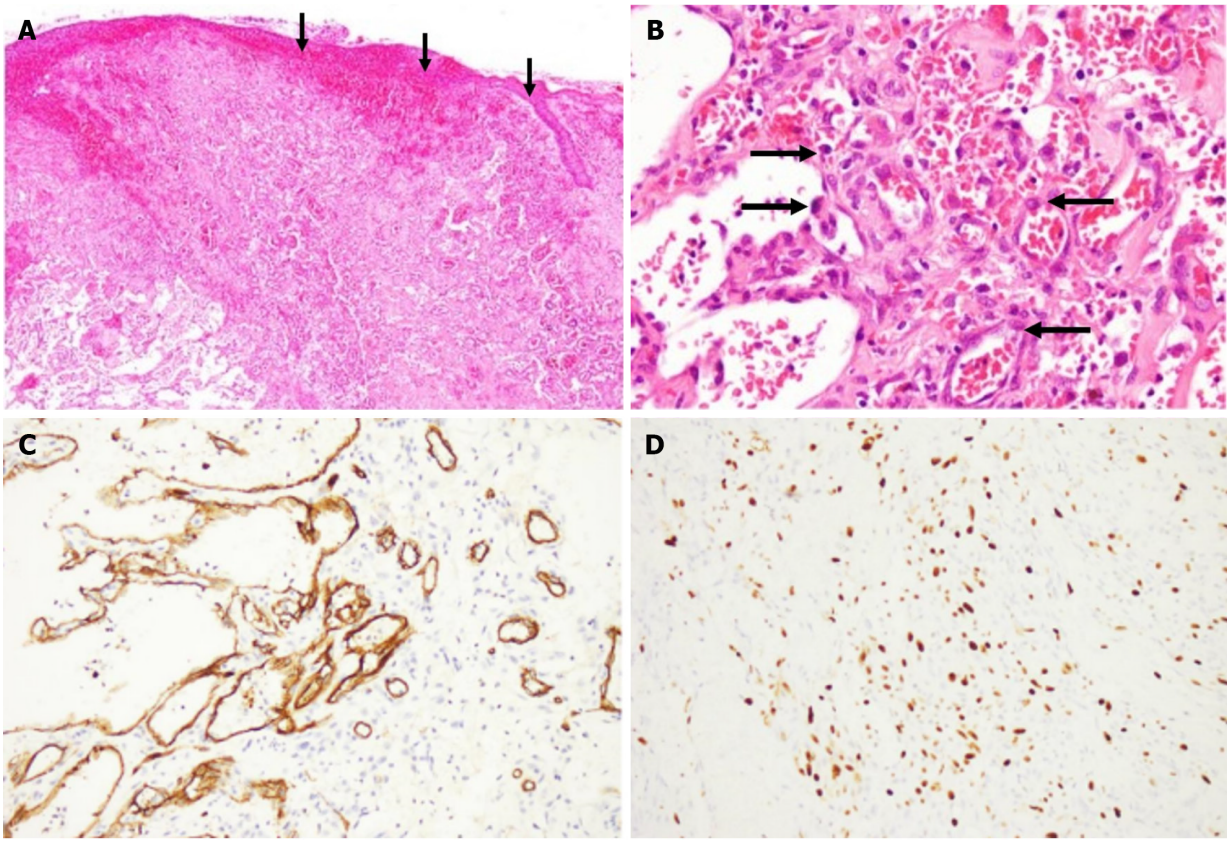


DOI: 10.12998/wjcc.v11.i13.3099 **Copyright** ©The Author(s) 2023.

Figure 3 Pathological examination during surgery.

DISCUSSION

Angiosarcoma, also known as malignant hemangioendothelioma, is a malignant tumor of blood vessels, originating from endothelial cells. Angiosarcoma can occur in various parts of the body[2,3], such as the head, neck, breasts, limbs and trunk, and most of the tumor is mainly located in the skin. Because of different clinical manifestations and biological behaviors of these malignant vascular proliferations, Enzinger and Weiss in 1983 divided these tumors into 4 groups according to their location: (1) Cutaneous angiosarcoma not related to lymphedema; (2) Angiosarcoma of the skin related to lymphedema, namely, lymphangiosarcoma; (3) Deep soft tissue angiosarcoma; and (4) Breast angiosarcoma. Angiosarcoma of the scalp is the most common form, which mainly affects the skin of the head[4]. This disease occurs more often in the elderly. The skin lesions are characterized by infiltration and expansion to the surrounding or subcutaneous tissues, which involve the scalp, before metastasis. Owing to these extensive infiltrations, the edges of the damage are often unclear. The disease progresses rapidly and can be spread to nearby lymph nodes or to the lungs, liver, bones, *etc.*, through blood circulation. Owing to its highly aggressive and multifocal nature, the prognosis of angiosarcoma is poor, with a 5-year survival rate of less than 35%. Moreover, 75% of patients have local recurrence within 24 mo of local treatment[5].



DOI: 10.12998/wjcc.v11.i13.3099

Figure 4 Morphological features of the angiosarcoma. A: Under low magnification: The tumor cells diffusely infiltrated the dermis, involving the skin appendages and ulceration; B: Under high magnification: Proliferated vessels with fissures were composed of vascular endothelial cells with heteromorphic hyperplasia and nucleoli, and red blood cells were extravasated; C: Under high magnification: The intense positivity for an antiCD34 antibody shows that angiosarcomatous cells formed irregular vessels; D: Under high magnification: A high mitotic index was confirmed by immunohistochemical study for Ki67.

There is currently no radical cure for angiosarcoma, and the prognosis is poor. The importance of early diagnosis and early treatment is emphasized. Scalp angiosarcoma is the first choice for extensive surgical resection. As far as possible, extensive surgical resection of skin lesions should be performed; otherwise, angiosarcoma is prone to recurrence. For those with multiple or extensive skin lesions, which are difficult to operate, radiotherapy can be used before or after surgery. For patients with distant metastases, chemotherapy-based treatment is the main option, but there is currently no standard chemotherapy regimen[6], and the remission period is short. Cyclophosphamide, epirubicin, vincristine and dacarbazine are often used clinically. Ye *et al*[7] believed that scalp angiosarcoma recurred and metastasized after surgery. After failure of a first-line chemotherapy, docetaxel, cisplatin, gemcitabine, and radiotherapy can be administered to patients to prolong their overall survival time. For patients with a poor physical status or an old age, monotherapy with taxanes is recommended[8]. For general refractory wounds, using appropriate physical methods can promote wound healing. The patient in this case was older, had high neutrophils in the blood routine at the first visit, exuded fluid on the scalp ulcer wound, had a risk of infection, and could not be treated directly by surgery. Therefore, local physical factor treatment was adopted to reduce the wound exudate and prevent wound infection, but the treatment effect was not ideal, and wound healing was not promoted. The pathological results allowed us to confirm the patient's diagnosis as scalp angiosarcoma. Physical factor therapy is ineffective for scalp angiosarcoma, and it should be noted that some physical factor therapy is contraindicated for the treatment of local tumors. In future clinical work, pathological examination should be performed for refractory ulcers in any part of the skin, and physical factors should be used with caution before the diagnosis is clear, because this may delay the correct treatment plan.

CONCLUSION

Our research suggests that pathological examination should be performed for refractory ulcers of the scalp, and physical factor therapy should be used with caution before the diagnosis is clear.

FOOTNOTES

Author contributions: Yan ZH and Duan HY contributed equally to this work; Yan ZH, Li ZL and Duan HY designed the research study; Yan ZH, Duan HY and Lian YW performed the research; Chen XW and Liu LX analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

Informed consent statement: The study participant's legal guardian provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Hao-Yang Duan 0000-0002-9107-0762.

S-Editor: Liu XF
L-Editor: A
P-Editor: Zhang XD

REFERENCES

1 **Guadagnolo BA**, Zagars GK, Araujo D, Ravi V, Shellenberger TD, Sturgis EM. Outcomes after definitive treatment for cutaneous angiosarcoma of the face and scalp. *Head Neck* 2011; **33**: 661-667 [PMID: 20960566 DOI: 10.1002/hed.21513]
2 **Qitao Huang**, Haiming Wei, Lili Li. Angiosarcoma: A case report. *Journal of Clinical Dermatology* 2015; **44**: 810-811
3 **Hillenbrand T**, Menge F, Hohenberger P, Kasper B. Primary and secondary angiosarcomas: a comparative single-center analysis. *Clin Sarcoma Res* 2015; **5**: 14 [PMID: 26413264 DOI: 10.1186/s13569-015-0028-9]
4 **Cuda J**, Mirzamani N, Kantipudi R, Robbins J, Welsch MJ, Sundram UN. Diagnostic utility of Fli-1 and D2-40 in distinguishing atypical fibroxanthoma from angiosarcoma. *Am J Dermatopathol* 2013; **35**: 316-318 [PMID: 23518636 DOI: 10.1097/DAD.0b013e318266b197]
5 **Yu Liang**, Jianzhong Cao, Hong Li. Rh-endostatin combined with radiotherapy in treatment of scalp angiosarcoma: Report of one case and review of literatur. *Cancer Res* 2017; **29**: 273-275 [DOI: 10.21275/6011702]
6 **Fujisawa Y**, Yoshino K, Kadono T, Miyagawa T, Nakamura Y, Fujimoto M. Chemoradiotherapy with taxane is superior to conventional surgery and radiotherapy in the management of cutaneous angiosarcoma: a multicentre, retrospective study. *Br J Dermatol* 2014; **171**: 1493-1500 [PMID: 24814962 DOI: 10.1111/bjd.13110]
7 **Ye J**, Li XF, Wang YD, Yuan Y. Long-term survival of a patient with scalp angiosarcoma and multiple metastases treated using combination therapy: A case report. *Oncol Lett* 2015; **9**: 1725-1728 [PMID: 25789030 DOI: 10.3892/ol.2015.2919]
8 **Karube R**, Sasaki H, Shinozuka K, Fujisawa Y, Yanagawa T, Yamagata K, Onizawa K, Otsuka F, Bukawa H. Angiosarcoma of the scalp diagnosed by the presence of neck inflammation: a case report. *Int J Oral Sci* 2012; **4**: 166-169 [PMID: 22699262 DOI: 10.1038/ijos.2012.36]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 May 6; 11(13): 3105-3113

DOI: 10.12998/wjcc.v11.i13.3105

ISSN 2307-8960 (online)

CASE REPORT

Discrepancy among microsatellite instability detection methodologies in non-colorectal cancer: Report of 3 cases

Elif Şenocak Taşçı, İbrahim Yıldız, Sibel Erdamar, Leyla Özer

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Leal RF, Brazil; Wang Z, China

Received: February 7, 2023
Peer-review started: February 7, 2023
First decision: February 28, 2023
Revised: March 16, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 6, 2023

Elif Şenocak Taşçı, İbrahim Yıldız, Leyla Özer, Department of Medical Oncology, Acıbadem MAA University, Istanbul 12345, Turkey

Sibel Erdamar, Department of Pathology, Acıbadem MAA University, Istanbul 12345, Turkey

Corresponding author: Leyla Özer, Doctor, MD, Associate Professor, Department of Medical Oncology, Acıbadem MAA University, Acibadem Mehmet Ali Aydinlar University Atakent Hospital, Turgut Ozal Bulvarı, No. 16, Halkalı, Istanbul 12345, Turkey.
leyla.ozer@acibadem.com

Abstract

BACKGROUND

Microsatellite instability (MSI) is a predictive biomarker for cancer immunotherapy. The tumor-agnostic nature of MSI makes it a denominator for immunotherapy in several solid tumors. It can be assessed using next-generation sequencing (NGS), fluorescent multiplex PCR, and immunohistochemistry (IHC).

CASE SUMMARY

Here, we report 3 cases with discordant MSI results detected using different methods. A cholangiocellular carcinoma case revealed proficient mismatch repair (MMR) by IHC but high MSI (MSI-H) by liquid NGS. A cervical cancer case revealed deficient MMR by IHC, microsatellite stable by PCR, and MSI-H by NGS. Lastly, an endometrial cancer case revealed proficient MMR by IHC but MSI-H by NGS.

CONCLUSION

IHC for MMR status is the first choice due to several advantages. However, in cases of indeterminate IHC results, molecular testing by MSI-PCR is preferred. Recently, NGS-based MSI assays are being widely used to detect MSI-H tumors. All three methods have high accuracy; however, the inconsistencies between them may lead to misdiagnosis.

Key Words: Discordance; Immunohistochemistry; Microsatellite instability; Next-generation sequencing; Case report

Core Tip: Microsatellite instability (MSI), a predictive biomarker for cancer immunotherapy can be assessed using next-generation sequencing, fluorescent multiplex PCR, and immunohistochemistry (IHC). Even though IHC for mismatch repair status is the first choice, in cases of indeterminate IHC results, molecular testing by MSI-PCR is preferred. Recently, next-generation sequencing-based MSI assays are also being widely used. Although all methods have high accuracy, they may have inconsistent results leading to misdiagnosis.

Citation: Şenocak Taşçı E, Yıldız İ, Erdamar S, Özer L. Discrepancy among microsatellite instability detection methodologies in non-colorectal cancer: Report of 3 cases. *World J Clin Cases* 2023; 11(13): 3105-3113
URL: https://www.wjgnet.com/2307-8960/full/v11/i13/3105.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i13.3105

INTRODUCTION

In the era of immunotherapy, microsatellite instability (MSI) is a key biomarker of genetic alteration. It is indicated by a high number of mutations within microsatellites, which are repeat sequences of 1-9 nucleotides[1]. While the DNA mismatch repair (MMR) system can correct DNA replication errors in normal tissues, the loss of function or lack of *MMR* genes in tumor cells causes MSI[2]. Thus, MSI is an important factor in tumor development, and its incidence correlates positively to survival[3].

MSI can be distinguished into three types: high (MSI-H); low; and stable (MSS)[4]. Lately, MSI has been identified in several cancer types[5]. The recent American Society of Clinical Oncology provisional guidelines on somatic mutations in metastatic and locally advanced cancer recommends the evaluation of MMR deficiency status, as MSI is accepted as a tumor-agnostic factor in all patients who are potential candidates for immunotherapy[6].

The most widely used methods for MSI assessment are next-generation sequencing (NGS), fluorescent multiplex PCR, and immunohistochemistry (IHC)[1]. IHC is the gold standard method due to its easy access, high sensitivity, and practical nature. It detects the expression of MMR proteins (MLH1, PMS2, MSH2, and MSH6) in tumor tissues[7]. NGS-based multiplex gene assay, approved for use in all solid tumors, can indirectly measure MMR status using DNA extracted from formalin-fixed paraffin-embedded tissue specimens, where deficient MMR tumors usually have a hypermutated phenotype[8]. Finally, PCR is a molecular approach that can be carried out on tumor DNA, measuring the MMR protein apparatus functionality[9]. Cases of indeterminate MSI status with IHC can occur if loss of only one heterodimer unit is present. Two reference panels of PCR, Bethesda and pentaplex, were designed for colorectal cancer (CRC) and have shown poor performance in other cancer types[10]. Despite the high accuracy of these methods (94.6%, 99.9%, and 89.0%-95.0% for PCR, NGS, and IHC, respectively), the inconsistency between them may result in misdiagnosis[11-13]. The specific guidance regarding preferred methodology is still lacking.

Here, we report a cholangiocellular carcinoma case revealing proficient MMR by IHC but MSI-H by liquid NGS. A cervical cancer case revealed deficient MMR by IHC, MSS by PCR but MSI-H by NGS. An endometrial cancer case revealed proficient MMR by IHC but MSI-H by NGS.

CASE PRESENTATION

Chief complaints

Case 1: A 43-year-old female patient with a history of Klatskin tumor was referred to our clinic with progressive disease.

Case 2: A 29-year-old female patient with a history of locally advanced cervical cancer was referred to our clinic for a second opinion.

Case 3: A 62-year-old female patient with a history of endometrial cancer presented with acute, intermittent mid-back pain for the 3 mo prior to admission.

History of present illness

Case 1: Progression of the present illness was found during treatment response evaluation 2 wk prior.

Case 2: Progression of cervical cancer was found during a screening a week prior.

Case 3: Pain had worsened for the prior 2-3 wk.

History of past illness

Case 1: She had presented with jaundice, epigastric pain, itching, and weakness to her doctor in 2018, and her abdominal ultrasonography revealed a mass near the liver. Magnetic resonance imaging (MRI) of the abdomen confirmed obstruction due to tumor confluence of the bile ducts. Secondary to the mechanical obstruction, there was external drainage of the bile ducts from the right anterior and posterior sections of the liver. She underwent a left hemi hepatectomy with total caudal lobectomy, cholecystectomy, and extended lymphadenectomy. The pathology revealed moderately differentiated adenocarcinoma, $CK7^{+}/CK20^{-}/CK17^{+}$, consistent with cholangiocarcinoma, thus stage IIA disease. IHC revealed PD-L1 combined positive score of 0 and MSS disease. She received six cycles of adjuvant gemcitabine-cisplatin treatment. During follow-up in 2020, computed tomography (CT) demonstrated recurrence of the underlying disease with predominance of peritoneal carcinomatosis, after which she was again initiated on gemcitabine and cisplatin. After five treatment cycles, cisplatin intolerance developed and treatment was continued with capecitabine and gemcitabine. The response evaluation CT revealed progression of the underlying disease with an increase in the size of the known lesions, ascites, and pleural effusion.

Case 2: She was first diagnosed in 2019 and had received radical chemoradiotherapy. Local recurrence occurred in 2020. She received four cycles of carboplatin-paclitaxel and underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. Topotecan and bevacizumab were administered in June 2021 due to disease progression; however, a ureterovaginal fistula developed, for which she underwent surgery.

Case 3: She had undergone a surgery in 2010 for endometrioid adenocarcinoma with squamous differentiation. The pathology results revealed pT1bN0 with 60% estrogen receptor, 90% progesterone receptor, and 50% Ki-67 expression and was classified as stage I disease. She did not receive any adjuvant treatment.

Personal and family history

Significant family or personal history was not detected for any of the cases.

Physical examination

Case 1: Vital signs were in the normal ranges. No abnormalities were found during systemic examination.

Case 2: Vital signs were as follows: body temperature, 36.0 °C; blood pressure, 100/60 mmHg; and heart rate, 90/min. She had colostomy. No other abnormalities were found during systemic examination.

Case 3: On physical examination, the vital signs were as follows: body temperature, 36.5 °C; blood pressure, 110/68 mmHg; and heart rate, 80/min. Systemic examination did not reveal any pathology.

Laboratory examinations

Case 1: Carbohydrate antigen 19-9 level was elevated (1200 U/mL). Other analyses were in the normal ranges.

Case 2: Carbohydrate antigen 19-9 level was elevated (264000 U/mL). Other analyses were in the normal ranges.

Case 3: Levels of serum tumor markers were elevated (carbohydrate antigen 125, 51 U/mL; carbohydrate antigen 19-9, 175 U/mL).

Imaging examinations

Case 1: Positron emission tomography (PET/CT) was carried out for re-staging, and it revealed development of new hypermetabolic lesions in the left supraclavicular region, L2 corpus, and peritoneum.

Case 2: PET/CT was carried out for optimal staging in August 2021, which revealed increased uptake in the pelvis, more prominent in the left supra/peri vesical, left paracolic, and cutaneous regions. She was referred to our clinic with the results. We performed an MRI of the abdomen, which confirmed a recurrent mass, 60 mm × 81 mm in size, near the sigmoid colon.

Case 3: MRI of the lumbar spine performed due to back pain showed a 5 cm soft tissue mass near the left renal vein. Staging PET/CT confirmed the mass lesion without distant metastases.

FURTHER DIAGNOSTIC WORK-UP

Case 1: NGS (FoundationOne CDx, 2021) was recommended for detailed molecular analysis instead of IHC and PCR. The molecular results from the surgical specimen revealed *STK11* and *ARID1A* mutations and MSI-H disease (Figure 1).

Case 2: A biopsy was performed for molecular analysis and concluded as metastasis of cervical cancer. IHC for MMR proteins showed loss of MLH-1 and PMS-2 expression, leading to a conclusion of MSI-H disease (Figure 2A). NGS (FoundationOneCDx, 2021) results from the pelvic mass revealed *AKT1, ATR, CREBBP,* and *MLH1* mutations, as well as a tumor mutation burden (TMB) of 6 Mb (Figure 2B). Her MSI status could not be determined. PCR was performed to confirm the MSI status, and MSS disease was noted (Figure 2C).

Case 3: Renal mass and lymph node biopsy confirmed an adenocarcinoma, $PAX8^{+}/CK7^{+}$, consistent with primary endometrial cancer (stage IV endometrial cancer). IHC revealed no staining for human epidermal growth factor receptor 2 and did not show any losses for MMR proteins. NGS was recommended for detailed molecular analysis. However, NGS results from the metastases revealed MSI-H disease with a TMB of 54 mutations/Mb (Figure 3).

FINAL DIAGNOSIS

Case 1: The final diagnosis was stage IV Klatskin tumor.

Case 2: The patient was diagnosed with metastatic cervical cancer.

Case 3: The patient was diagnosed with recurrent endometrial carcinoma.

TREATMENT

Case 1: FOLFIRINOX chemotherapy was initiated with palliative radiotherapy.

Case 2: Pembrolizumab treatment was initiated with gemcitabine-carboplatin and showed 50% metabolic regression after four treatment cycles. Secondary to the bladder and rectum invasion, pelvic sepsis developed, and pelvic exenteration was performed. The pathology revealed moderately differentiated squamous cell carcinoma infiltrating the bladder and rectum (pT3bN0). IHC findings of the surgical specimen again showed loss of MLH-1 and PMS-2 expression.

Case 3: Due to the recurrence of endometrial carcinoma, she underwent surgery for tumor removal, and the pathology results are pending.

OUTCOME AND FOLLOW-UP

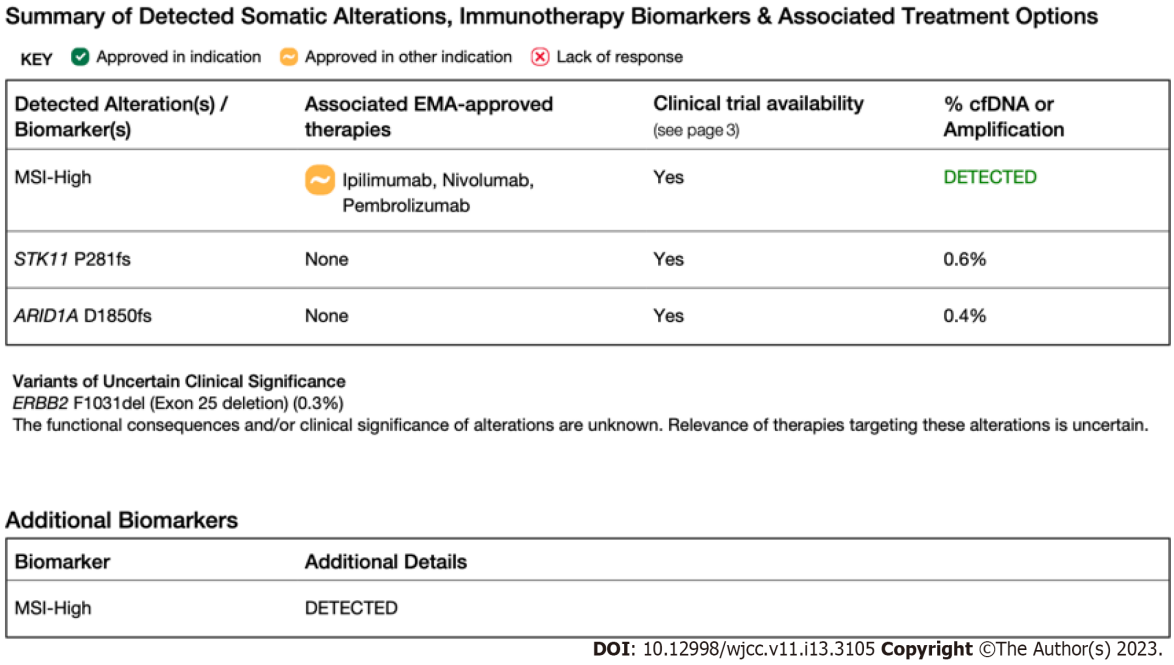
Case 1: She was lost to follow-up months after admission to our hospital.

Case 2: Since the patient was tumor-free, pembrolizumab monotherapy was planned. After 3 mo of immunotherapy, a restaging PET/CT demonstrated marked disease progression with multiple abdominopelvic hypermetabolic lesions. She was initiated on XELOX chemotherapy but could not tolerate the treatment. Her situation deteriorated, and she died after 3 mo of palliative treatment.

Case 3: She was lost to follow-up.

DISCUSSION

The incidence of MSI differs across solid tumors. Most of the studies in this field focus on CRC, which is closely related to MSI. Our case series included three different solid tumors with discordant MSI results, which to our knowledge is the first in the literature. According to recent reports, the frequency of MSI is 0%-2.1%, 12.0%, and 25.0% for cholangiocarcinoma, cervical, and endometrial cancers, respectively[14, 15]. The optimal method for detection of MSI remains unclear. In addition to sensitivity, easily accessible and cost-effective methods are required in daily practice; therefore, IHC is most frequently used. There are limited data on the concordance analysis of MSI status between IHC and NGS for CRC and gynecological cancers and a lack of data for other solid tumors.



Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

KEY ✓ Approved in indication ~ Approved in other indication ✗ Lack of response

Detected Alteration(s) / Biomarker(s)	Associated EMA-approved therapies	Clinical trial availability (see page 3)	% cfDNA or Amplification
MSI-High	~ Ipilimumab, Nivolumab, Pembrolizumab	Yes	DETECTED
STK11 P281fs	None	Yes	0.6%
ARID1A D1850fs	None	Yes	0.4%

Variants of Uncertain Clinical Significance
ERBB2 F1031del (Exon 25 deletion) (0.3%)
The functional consequences and/or clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Additional Biomarkers

Biomarker	Additional Details
MSI-High	DETECTED

DOI: 10.12998/wjcc.v11.i13.3105

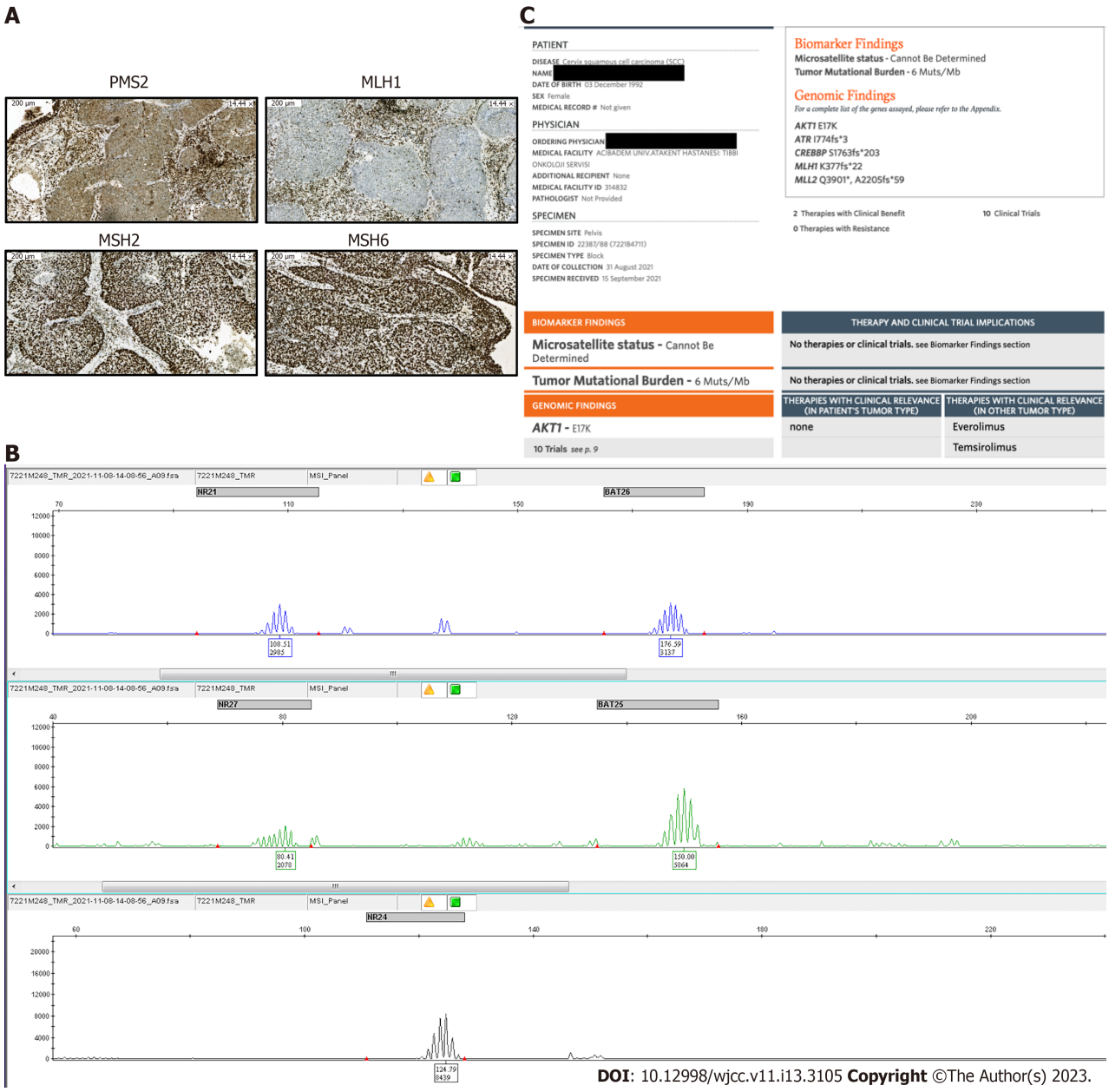
Figure 1 Next-generation sequencing result of the cholangiocarcinoma case. EMA: European Medicines Agency; cfDNA: Cell-free DNA; MSI: Microsatellite instability.

The decision to screen for DNA MMR gene mutations using IHC and/or PCR and/or NGS for MSI involves several considerations. IHC, as a gold standard, has several advantages such as its high specificity (96.1%), accuracy (99.2%), and sensitivity[16]. In addition, it is inexpensive and easy to use. Moreover, it can be performed on small biopsy samples and can clearly suggest the affected gene (*MLH1, MSH2, MSH6, or PMS2*). However, there are some limitations, such as quality of tissue preparation interfering with results, an experienced pathologist needed, and non-immunoreactivity due to missing missense or frameshift/truncation mutations[17]. Studies comparing different methodologies in MSI analysis concluded that some MSI-H cases may be missed if IHC is used alone, with the incidence ranging between 11.8%-32.9%[18-20]. In addition, IHC results were prone to change after neoadjuvant and radiation therapy, which may have changed the preferred screening in some cases[21].

An alternative method, PCR, mostly covers the inadequacies of IHC, especially since it is not limited to protein expression. However, it has its disadvantages, such as the need for a specialized genetic facility, longer turnaround time, normal tissue requirement, and the fact that pre-analytic issues such as fixation, may interfere with the PCR reaction[22]. The most important limitation is the *MSH6* mutation, which may cause a non-diagnostic MSI test by PCR, secondary to functional redundancy, leading to misdiagnosis as MSS.

Although both methods are close to 100% sensitivity/accuracy, neither of the methods help identify all tumors with defective *MMR* genes. The likelihood of misdiagnosis can be overcome using both methods; however, there may be discordant results. Berardinelli *et al*[16] evaluated MSI with IHC and PCR and reported eight discordant results in a total of 996 patients with CRC. Thus, for these cases, they proposed the addition of a new marker as complementary analysis and suggested the use of PCR over IHC. Several other studies including CRC found discordances between IHC and molecular analysis ranging from 1%-10%[10]. The cause of the discordance was mostly related to factors like low tumor cell proportion, pre-analytical difficulties, non-expert physician, neoadjuvant treatment, tumor heterogeneity, and discordance of tumor biopsy[10]. It was also mentioned that molecular panels used during PCR analysis were principally recommended for CRC. However, they were used in all types of solid tumors and may show poor performance in other types of cancer[9].

False positive results are important to overcome since recent reports suggest that primary resistance to immune checkpoint inhibitors may be related to the misinterpretation of MMR tests[10]. The development of NGS led to the emergence of a new technique to improve MSI detection. NGS can simultaneously detect MSI and screen for MMR mutations. Although it has 100% sensitivity and specificity, the high cost limits its use[23]. In addition, the panels used in NGS show better performance in non-CRC[9]. A study evaluating the concordance analysis of MSI between PCR and NGS for solid tumors reported a concordance of 98.8%[24]. Another study investigating discrepant MMR IHC and MSI PCR test results in gynecologic cancers reported 6 out of 328 discordant results using NGS and demonstrated that NGS could help resolve discrepant MMR and MSI results[25]. The usefulness of NGS in the determination of MSI, with a sensitivity of 95.8%, specificity of 99.4%, positive predictive value of 94.5%, and negative predictive value of 99.2% in 26 cancer types, was supported by several other studies



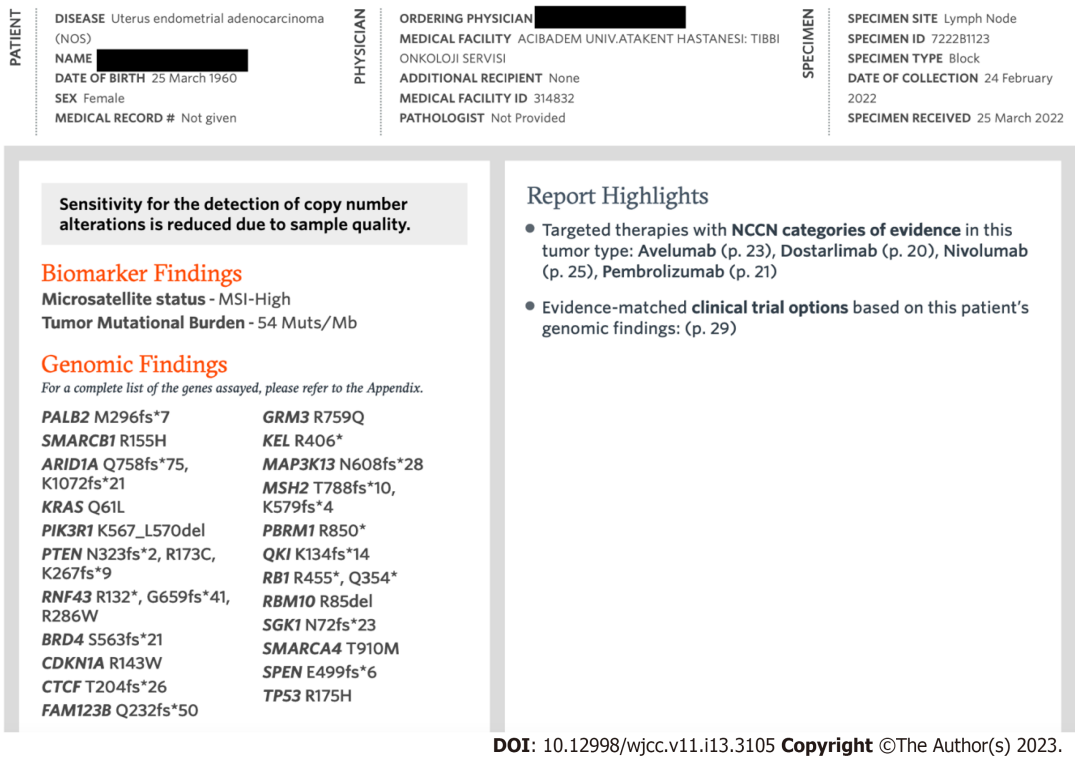
DOI: 10.12998/wjcc.v11.i13.3105 **Copyright** ©The Author(s) 2023.

Figure 2 Immunohistochemistry, next-generation sequencing, and PCR results of the cervical cancer case. A: MLH1, MSH2, MSH6 and PMS2 immunohistochemistry (× 14.44, 200 μm). Absence of MLH1 and PMS2 staining in tumor epithelium yet positive internal control staining of lymphocytes in the stroma; B: Next-generation sequencing result; and C: Suspicious instability seen in NR27 after PCR analysis.

with a concordance of 99.4% compared with PCR-based testing[26].

At our clinic, we prefer screening MSI using IHC due to its fast turnaround time and using NGS as an additional method to investigate a large variety of gene alterations at once. The discordant results were interpreted as MSI-H. MSI-H status is supported by high TMB results, a finding apparent in our third case. This finding has also been conclusively reported by other studies[27]. However, the reliability of the IHC results remains uncertain when NGS shows an MSS tumor. Our second case with cervical cancer showed rapid progression after the surgery. Although, seeding during the exenteration procedure may explain the recurrence, another reason may be the loss of tumor antigenicity after the surgery, restricting the trigger in the host cell immune response since the patient was tumor-free. These facts may also explain resistance to immunotherapy rather than the discordance. More trials comparing the IHC and NGS results are needed for better assessment.

There may be two limitations to our study. The first is different pathologists performing the histological analysis. Although international guidelines exist in terms of evaluation, the experience of the pathologist may interfere with the results. Second, as seen in other studies, different samples may cause discrepancy between the results. However, it is not always easy to access the surgical/biopsy specimens when the time interval between the diagnosis and metastases is long.



DOI: 10.12998/wjcc.v11.i13.3105

Figure 3 Next-generation sequencing result of the case with endometrial carcinoma. MSI: Microsatellite instability; NCCN: National Comprehensive Cancer Network.

CONCLUSION

The rare non-colorectal MSI cases in the literature and the lack of investigation into IHC-NGS discordance highlights the uniqueness of our cases. Today, the gold standard of MSI analysis is IHC. However, considering the defined 100% and 98.7% positive and negative predictive values, respectively [24], with reduced costs and turnaround time, NGS may be the preferred first-line option for MSI analysis to reduce the incidence of misdiagnoses in the future.

FOOTNOTES

Author contributions: Yıldız İ and Özer L designed research; Şenocak Taşçı E performed research; Erdamar S analyzed data; and Şenocak Taşçı E and Yıldız İ wrote the paper.

Informed consent statement: Informed written consent was obtained from the patients for publication of this report.

Conflict-of-interest statement: All authors report having no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Turkey

ORCID number: Elif Şenocak Taşçı 0000-0002-1686-1628; İbrahim Yıldız 0000-0001-9094-7289; Leyla Özer 0000-0003-4092-5051.

S-Editor: Liu XF
L-Editor: Filipodia
P-Editor: Zhao S

REFERENCES

1 **Baudrin LG**, Deleuze JF, How-Kit A. Molecular and Computational Methods for the Detection of Microsatellite Instability in Cancer. *Front Oncol* 2018; **8**: 621 [PMID: 30631754 DOI: 10.3389/fonc.2018.00621]

2 **Lower SS**, McGurk MP, Clark AG, Barbash DA. Satellite DNA evolution: old ideas, new approaches. *Curr Opin Genet Dev* 2018; **49**: 70-78 [PMID: 29579574 DOI: 10.1016/j.gde.2018.03.003]

3 **Le DT**, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357**: 409-413 [PMID: 28596308 DOI: 10.1126/science.aan6733]

4 **Bonneville R**, Krook MA, Chen HZ, Smith A, Samorodnitsky E, Wing MR, Reeser JW, Roychowdhury S. Detection of Microsatellite Instability Biomarkers *via* Next-Generation Sequencing. *Methods Mol Biol* 2020; **2055**: 119-132 [PMID: 31502149 DOI: 10.1007/978-1-4939-9773-2_5]

5 **Maraka S**, Singh Ospina NM, Mastorakos G, O'Keeffe DT. Subclinical Hypothyroidism in Women Planning Conception and During Pregnancy: Who Should Be Treated and How? *J Endocr Soc* 2018; **2**: 533-546 [PMID: 29850652 DOI: 10.1210/js.2018-00090]

6 **Chakravarty D**, Johnson A, Sklar J, Lindeman NI, Moore K, Ganesan S, Lovly CM, Perlmutter J, Gray SW, Hwang J, Lieu C, André F, Azad N, Borad M, Tafe L, Messersmith H, Robson M, Meric-Bernstam F. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. *J Clin Oncol* 2022; **40**: 1231-1258 [PMID: 35175857 DOI: 10.1200/JCO.21.02767]

7 **Li K**, Luo H, Huang L, Zhu X. Microsatellite instability: a review of what the oncologist should know. *Cancer Cell Int* 2020; **20**: 16 [PMID: 31956294 DOI: 10.1186/s12935-019-1091-8]

8 First Comprehensive Companion Diagnostic OK'd. *Cancer Discov* 2018; **8**: OF4 [PMID: 29339360 DOI: 10.1158/2159-8290.CD-NB2017-182]

9 **Waalkes A**, Smith N, Penewit K, Hempelmann J, Konnick EQ, Hause RJ, Pritchard CC, Salipante SJ. Accurate Pan-Cancer Molecular Diagnosis of Microsatellite Instability by Single-Molecule Molecular Inversion Probe Capture and High-Throughput Sequencing. *Clin Chem* 2018; **64**: 950-958 [PMID: 29632127 DOI: 10.1373/clinchem.2017.285981]

10 **Evrard C**, Tachon G, Randrian V, Karayan-Tapon L, Tougeron D. Microsatellite Instability: Diagnosis, Heterogeneity, Discordance, and Clinical Impact in Colorectal Cancer. *Cancers (Basel)* 2019; **11** [PMID: 31618962 DOI: 10.3390/cancers11101567]

11 **Cheah PL**, Li J, Looi LM, Koh CC, Lau TP, Chang SW, Teoh KH, Mun KS, Nazarina AR. Screening for microsatellite instability in colorectal carcinoma: Practical utility of immunohistochemistry and PCR with fragment analysis in a diagnostic histopathology setting. *Malays J Pathol* 2019; **41**: 91-100 [PMID: 31427545 DOI: 10.1186/1746-1596-6-56]

12 **Arulananda S**, Thapa B, Walkiewicz M, Zapparoli GV, Williams DS, Dobrovic A, John T. Mismatch Repair Protein Defects and Microsatellite Instability in Malignant Pleural Mesothelioma. *J Thorac Oncol* 2018; **13**: 1588-1594 [PMID: 30056163 DOI: 10.1016/j.jtho.2018.07.015]

13 **Hempelmann JA**, Lockwood CM, Konnick EQ, Schweizer MT, Antonarakis ES, Lotan TL, Montgomery B, Nelson PS, Klemfuss N, Salipante SJ, Pritchard CC. Microsatellite instability in prostate cancer by PCR or next-generation sequencing. *J Immunother Cancer* 2018; **6**: 29 [PMID: 29665853 DOI: 10.1186/s40425-018-0341-y]

14 **Naganuma A**, Sakuda T, Murakami T, Aihara K, Watanuki Y, Suzuki Y, Shibasaki E, Masuda T, Uehara S, Yasuoka H, Hoshino T, Kudo T, Ishihara H, Ogawa T, Kitamoto Y, Ogawa A. Microsatellite Instability-high Intrahepatic Cholangiocarcinoma with Portal Vein Tumor Thrombosis Successfully Treated with Pembrolizumab. *Intern Med* 2020; **59**: 2261-2267 [PMID: 32536644 DOI: 10.2169/internalmedicine.4588-20]

15 **Lorenzi M**, Amonkar M, Zhang J, Mehta S, Liaw KL. Epidemiology of microsatellite instability high (MSI-H) and deficient mismatch repair (dMMR) in solid tumors: A structured literature review. *J Oncol* 2020; **2020**: 1-17 [DOI: 10.1155/2020/1807929]

16 **Berardinelli GN**, Scapulatempo-Neto C, Durães R, Antônio de Oliveira M, Guimarães D, Reis RM. Advantage of HSP110 (T17) marker inclusion for microsatellite instability (MSI) detection in colorectal cancer patients. *Oncotarget* 2018; **9**: 28691-28701 [PMID: 29983889 DOI: 10.18632/oncotarget.25611]

17 **McCracken J**, Neff J. Discordant IHC/PCR test results for mismatch repair status in colorectal adenocarcinoma. *CAP Today* 2018; 1-4 [DOI: 10.26226/morressier.578f37f9d462b8028d88f705]

18 **Lin CH**, Lin JK, Chang SC, Chang YH, Chang HM, Liu JH, Li LH, Chen YT, Tsai SF, Chen WS. Molecular profile and copy number analysis of sporadic colorectal cancer in Taiwan. *J Biomed Sci* 2011; **18**: 36 [PMID: 21645411 DOI: 10.1186/1423-0127-18-36]

19 **Lindor NM**, Burgart LJ, Leontovich O, Goldberg RM, Cunningham JM, Sargent DJ, Walsh-Vockley C, Petersen GM, Walsh MD, Leggett BA, Young JP, Barker MA, Jass JR, Hopper J, Gallinger S, Bapat B, Redston M, Thibodeau SN. Immunohistochemistry *vs* microsatellite instability testing in phenotyping colorectal tumors. *J Clin Oncol* 2002; **20**: 1043-1048 [PMID: 11844828 DOI: 10.1200/JCO.2002.20.4.1043]

20 **Bartley AN**, Luthra R, Saraiya DS, Urbauer DL, Broaddus RR. Identification of cancer patients with Lynch syndrome: clinically significant discordances and problems in tissue-based mismatch repair testing. *Cancer Prev Res (Phila)* 2012; **5**: 320-327 [PMID: 22086678 DOI: 10.1158/1940-6207.CAPR-11-0288]

21 **Goldstein JB**, Wu W, Borras E, Masand G, Cuddy A, Mork ME, Bannon SA, Lynch PM, Rodriguez-Bigas M, Taggart MW, Wu J, Scheet P, Kopetz S, You YN, Vilar E. Can Microsatellite Status of Colorectal Cancer Be Reliably Assessed after Neoadjuvant Therapy? *Clin Cancer Res* 2017; **23**: 5246-5254 [PMID: 28522602 DOI: 10.1158/1078-0432.CCR-16-2994]

22 **Zhang L**. Immunohistochemistry *vs* microsatellite instability testing for screening colorectal cancer patients at risk for hereditary nonpolyposis colorectal cancer syndrome. Part II. The utility of microsatellite instability testing. *J Mol Diagn*

2008; **10**: 301-307 [PMID: 18556776 DOI: 10.2353/jmoldx.2008.080062]

23 **Stadler ZK**, Battaglin F, Middha S, Hechtman JF, Tran C, Cercek A, Yaeger R, Segal NH, Varghese AM, Reidy-Lagunes DL, Kemeny NE, Salo-Mullen EE, Ashraf A, Weiser MR, Garcia-Aguilar J, Robson ME, Offit K, Arcila ME, Berger MF, Shia J, Solit DB, Saltz LB. Reliable Detection of Mismatch Repair Deficiency in Colorectal Cancers Using Mutational Load in Next-Generation Sequencing Panels. *J Clin Oncol* 2016; **34**: 2141-2147 [PMID: 27022117 DOI: 10.1200/JCO.2015.65.1067]

24 **Shimozaki K**, Hayashi H, Tanishima S, Horie S, Chida A, Tsugaru K, Togasaki K, Kawasaki K, Aimono E, Hirata K, Nishihara H, Kanai T, Hamamoto Y. Concordance analysis of microsatellite instability status between polymerase chain reaction based testing and next generation sequencing for solid tumors. *Sci Rep* 2021; **11**: 20003 [PMID: 34625576 DOI: 10.1038/s41598-021-99364-z]

25 **Smithgall MC**, Remotti H, Hsiao SJ, Mansukhani M, Liu-Jarin X, Fernandes H. Investigation of discrepant mismatch repair immunohistochemistry and microsatellite instability polymerase chain reaction test results for gynecologic cancers using next-generation sequencing. *Hum Pathol* 2022; **119**: 41-50 [PMID: 34666078 DOI: 10.1016/j.humpath.2021.10.004]

26 **Vanderwalde A**, Spetzler D, Xiao N, Gatalica Z, Marshall J. Microsatellite instability status determined by next-generation sequencing and compared with PD-L1 and tumor mutational burden in 11,348 patients. *Cancer Med* 2018; **7**: 746-756 [PMID: 29436178 DOI: 10.1002/cam4.1372]

27 **Chalmers ZR**, Connelly CF, Fabrizio D, Gay L, Ali SM, Ennis R, Schrock A, Campbell B, Shlien A, Chmielecki J, Huang F, He Y, Sun J, Tabori U, Kennedy M, Lieber DS, Roels S, White J, Otto GA, Ross JS, Garraway L, Miller VA, Stephens PJ, Frampton GM. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med* 2017; **9**: 34 [PMID: 28420421 DOI: 10.1186/s13073-017-0424-2]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com