ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2024 May 6; 12(13): 2138-2292

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 12 Number 13 May 6, 2024

EDITORIAL

ORIGINAL ARTICLE

Case Control Study

Retrospective Cohort Study

Retrospective Study

Clinical Trials Study

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 13 May 6, 2024

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 13 May 6, 2024

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Clinical Cases*, Konosuke Nakaji, FACP, MD, Doctor, Endoscopy Center, Aishinkai Nakae Hospital, Wakayama-shi 640-8461, Japan. parupurikopui@yahoo.co.jp

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJCC* as 1.1; IF without journal self cites: 1.1; 5-year IF: 1.3; Journal Citation Indicator: 0.26; Ranking: 133 among 167 journals in medicine, general and internal; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

PUBLICATION DATE

May 6, 2024

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2138-2142

DOI: 10.12998/wjcc.v12.i13.2138

ISSN 2307-8960 (online)

EDITORIAL

Parenteral iron therapy in children with iron deficiency anemia

Jelena Roganovic

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade C
Creativity or Innovation: Grade C
Scientific Significance: Grade C

P-Reviewer: Jiang MY, China

Received: December 12, 2023
Revised: February 10, 2024
Accepted: April 7, 2024
Published online: May 6, 2024

Jelena Roganovic, Department of Pediatric Hematology and Oncology, Children's Hospital Zagreb, 10000 Zagreb, Croatia

Jelena Roganovic, Faculty of Biotechnology and Drug Development, University of Rijeka, Rijeka 51000, Croatia

Corresponding author: Jelena Roganovic, MD, PhD, Adjunct Professor, Chief Doctor, Full Professor, Senior Researcher, Department of Pediatric Hematology and Oncology, Children's Hospital Zagreb, Klaiceva 16, 10000 Zagreb, Croatia. roganovic.kbcri@gmail.com

Abstract

Iron deficiency anemia (IDA) continues to be a global public health problem. Oral iron is the universally accepted first-line therapy, and most children have a prompt and favorable response to oral formulations. In subsets of children who fail to respond due to intolerance, poor adherence, or inadequate intestinal absorption, parenteral iron is indicated. Despite numerous studies in adults with IDA of diverse etiologies, pediatric studies on parenteral iron use are very limited. Although mostly retrospective and small, these studies have documented the efficacy and safety profile of intravenous iron formulations. In this editorial the author comments on the most important published data and underscores the need to seriously consider parenteral iron use in children unresponsive to oral therapy.

Key Words: Anemia; Iron deficiency; Intravenous iron; Iron deficiency anemia; Children

Core Tip: Intravenous iron is an important but underutilized therapy in children with iron deficiency anemia (IDA) who fail to respond to oral iron. Considering IDA-related long-term negative neurobehavioral effects, it is important to switch to intravenous iron timely and safely. Over the last decades there has been a remarkable improvement in the quality of intravenous iron formulations with greater efficacy, tolerability, and safety.

Citation: Roganovic J. Parenteral iron therapy in children with iron deficiency anemia. *World J Clin Cases* 2024; 12(13): 2138-2142
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2138.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2138

INTRODUCTION

Iron deficiency anemia (IDA) is a global public health problem, particularly affecting young children and women of childbearing age in low-income countries[1]. Despite worldwide prevention and control strategies, IDA is still common in developed countries, with an estimated prevalence of 20.1% in children under the age of 4 years[2]. Common risk factors for IDA in early childhood include poor dietary intake, prematurity, rapid growth, and gastrointestinal blood loss due to excessive consumption of cow's milk. The clinical presentation varies, ranging from asymptomatic to excessive irritability or lethargy, tachypnea, and heart failure. Symptoms and clinical signs depend on the age of the affected child, the underlying condition, the rate of onset, the duration and the severity of anemia, and comorbidities[3,4].

Regardless of the presence of symptoms, children with iron deficiency and IDA should receive timely treatment, because they are at risk for long-lasting neurocognitive impairments, altered motor functions, decreased school performance, and behavioral disorders[4]. The mainstay of the treatment includes iron supplementation, together with the investigation and correction of the underlying cause of IDA. Peroral iron substitution is the universally accepted first line therapy of IDA or iron deficiency without anemia. The excellent efficacy, safety and cost profile of oral formulations are well documented, but guidelines vary[5-7]. Oral iron should generally be taken at least 1 to 2 h before or after meals, to ensure better absorption. Children sometimes dislike oral iron preparations due to their metallic taste. Gastrointestinal side effects, such as abdominal pain, nausea, vomiting, diarrhea, or constipation, have been reported in up to 32% of patients and can lead to low compliance or discontinuation of therapy. To limit side effects and ameliorate adherence to treatment, some current therapeutic regimens favor lower dosages and less frequent administration (alternate-day dosing) of oral iron[5]. Other strategies include formulations with higher bioavailability and fewer adverse gastrointestinal effects, such as bis-glycinate chelate iron and liposomal iron[5,8]. Detailed education of the family about possible side effects is recommended from the beginning of treatment to improve adherence.

Despite these efforts, there is a small proportion of children who do not tolerate or are refractory to oral iron administration. Moreover, oral iron therapy frequently fails in children who present with gastrointestinal tract disorders, such as intestinal failure, inflammatory bowel disease, coeliac disease, *Helicobacter pylori* infection, chronic gastrointestinal bleeding, or tropical parasitosis[9,10]. Besides, pediatric patients may have iron absorption defects due to prolonged use of medications, such as proton pump inhibitors and histamine-2 receptor antagonists[11]. Finally, oral iron therapy is inadequate when a rapid increase in iron levels is required to avoid blood transfusion, such as severe perioperative IDA related to surgery with high blood loss[12].

In all the above pediatric conditions, parenteral iron therapy should be considered. However, the available pediatric experience with intravenous iron products as an alternative to oral iron is very limited outside the context of chronic kidney disease, where the patient is mainly hemodialysis-dependent and receiving recombinant erythropoiesis-stimulating agents[13-15]. There is a widespread belief among pediatricians that parenteral iron is avoided in children with IDA unless severe malabsorption or a serious condition is present. Major concerns about adverse reactions such as life-threatening hypersensitivity further contribute to the avoidance of parenteral iron therapy in pediatric practice[16].

Due to the wide range of underlying IDA-associated etiologies that could benefit from parenteral iron administration, some small but noteworthy pediatric studies have documented the safety and efficacy of parenteral iron. As intramuscular iron injections have long been avoided due to local pain, skin pigmentation, and the potential risk for rhabdomyolysis and sarcoma arising at the injection site, intravenous iron formulations are the only alternative to oral administration[17].

The first-generation intravenous iron products in the form of high molecular weight iron dextran were associated with unfavorable safety profiles, and have been abandoned in pediatric use[18]. Pinsk *et al*[19] first reported the second-generation intravenous iron product - iron sucrose - as an effective and safe means in 45 children with IDA who did not respond to oral iron therapy. They observed a statistically significant rise in hemoglobin concentrations 14 d after the first iron dose and 6 months following completion of therapy, and only one severe side effect with transient hypotension. Similar results with second-generation formulations were consecutively confirmed in several studies that included limited numbers of children with IDA, from 11 to 38[20-23]. The largest study was conducted by Kaneva *et al*[24], who reported a moderate increase in hemoglobin and a substantial improvement in iron after administration of intravenous iron sucrose in 142 patients with IDA (aged 7 months to 22 years), not compliant with oral formulations or with malabsorption. Broader experience across various specialties (excluding nephrology) incorporated 194 patients who received a total of 1088 intravenous iron doses. No severe infusion-associated reactions occurred. Although lacking standardization in the indications, formulations, or dosing, the data supported previous findings that intravenous iron should be considered as an efficacious and extremely safe alternative for IDA treatment in children in whom oral iron had been either unsuccessful or was contraindicated[25].

The next challenge was to address the issue of reducing the need for repeated intravenous infusions and administering larger amounts of iron in a shorter period. The third-generation intravenous iron product ferric carboxymaltose was approved for pediatric patients over the age of 14, having the advantage of being administered not only as a single shot and without a test dose, but in a lower dosage and with a shorter infusion time than second-generation preparations[5,10]. Several reports have provided evidence for the excellent efficacy and safety profile of intravenous ferric carboxymaltose in children and adolescents with IDA of diverse etiologies[26-30].

The main benefits of intravenous iron compared to oral iron administration are the reduction in non-adherence related to gastrointestinal side effects, and the bypassing of the intestinal absorption, thereby avoiding further mucosal damage. In addition, parenteral iron is indicated in cases of intolerance or refractoriness to oral formulations in children with severe IDA with ongoing bleeding, where the iron loss is greater than oral iron can supply, and in children with chronic kidney diseases who are on hemodialysis. Nevertheless, current practice provides evidence of the underuse of parenteral iron in children. Safety concerns frequently cause physicians and parents to be reluctant to switch to intravenous iron.

Although adverse reactions are rare with careful patient monitoring in a hospital setting with experienced staff, the potential disadvantages of parenteral iron include lower availability, higher cost, and the greater impact on the child due to venipunctures and the clinical environment. Furthermore, the risk of iron overload, burdened by a potential proinflammatory effect, should always be considered.

There are insufficient data on the pharmacokinetics and pharmacodynamics of different iron preparations in the pediatric population. Repeated administration of iron sucrose, the most frequently used intravenous iron preparation in children, was effective in raising hemoglobin concentrations to normal in all children with IDA within 31-42 d after the first infusion[22]. Administration of a single dose of intravenous ferric carboxymaltose in children unresponsive to oral iron therapy showed a complete hematological response in 49% of patients with IDA and 85% of all patients reached the target ferritin level within 12 wk post-treatment[30]. Likewise, dose-related increases in ferritin and transferrin saturation and clinically meaningful increases in mean hemoglobin concentration were observed from baseline to 35 d after a single intravenous dose of ferric carboxymaltose in children with IDA[31]. These pharmacokinetic studies provide useful information regarding the optimal dosing regimen and potential adverse events, but more detailed investigation is required to better understand and predict the bioavailability of iron preparations[32].

Oral iron therapy with standard ferric salts is by far the lowest cost option and is readily available, but often of limited efficacy, with frequent gastrointestinal side effects and poor adherence. Conversely, intravenous iron formulations are associated with significant cost, yet have been previously shown to replenish hemoglobin levels more effectively than oral iron[33,34]. Older-generation intravenous iron products have lower prices than newer-generation products. However, the latter may be associated with a reduction in total cost of care, mainly due to the lower number of venipunctures, better adherence, lower cumulative chance of infusion reactions or extravasations, and increased convenience for physicians and patients[35]. For all these reasons, physicians should consider the underlying disorder, the therapy goal, the response to prior therapy, patient tolerance and adherence, the cost, and the ease of access to the treating center when deciding on which formulation to use.

High oral iron doses or rapid iron release from intravenous formulations can saturate the iron transport system, resulting in oxidative stress, with adverse clinical and subclinical consequences[32]. A common concern is that intravenous iron may promote or exacerbate inflammation in anemic patients by triggering macrophage activation. While some studies have shown a transient increase in the circulating inflammatory cytokines interleukin (IL)-6, tumor necrosis factor-alpha, chemokine ligand 2 and interferon gamma[36], others observed no effect on the inflammatory markers IL-6 and IL-10[37]. Further research is required to better understand the pro-oxidant and proinflammatory potential of intravenous iron.

Altogether, clinical studies have clearly demonstrated that the benefits of parenteral iron strongly outweigh any potential harm. With the growing evidence supporting a wider range of indications for parenteral iron in children, and with the availability of new iron formulations, randomized prospective trials are needed to establish practical recommendations for the most appropriate strategies in pediatric practice.

CONCLUSION

Intravenous iron has become a major therapeutic modality for IDA in pediatrics when oral iron preparations are unsuccessful. Proper utilization of intravenous iron offers significant clinical benefits by reducing morbidity from many IDA-related pathological conditions in children.

FOOTNOTES

Author contributions: Roganovic J designed and wrote the article.

Conflict-of-interest statement: The author has nothing to disclose.

Country/Territory of origin: Croatia

ORCID number: Jelena Roganovic 0000-0002-7960-6069.

S-Editor: Che XX
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **World Health Organization**. Anaemia in Women and Children. Geneva: World Health Organization. WHO Global Anaemia estimates; 2021. [Cited 11 December 2023]. Available from: https://www.who.int/data/gho/data/themes/topics/anaemia_in_women_and_children

2 **Martinez-Torres V**, Torres N, Davis JA, Corrales-Medina FF. Anemia and Associated Risk Factors in Pediatric Patients. *Pediatric Health Med Ther* 2023; **14**: 267-280 [PMID: 37691881 DOI: 10.2147/PHMT.S389105]

3 **Roganović J**, Starinac K. Iron Deficiency Anemia in Children. In: Khan J. Current Topics in Anemia. InTech; 2018: 47-71. Available from: https://www.intechopen.com/chapters/56773

4 **Mattiello V**, Schmugge M, Hengartner H, von der Weid N, Renella R; SPOG Pediatric Hematology Working Group. Diagnosis and management of iron deficiency in children with or without anemia: consensus recommendations of the SPOG Pediatric Hematology Working Group. *Eur J Pediatr* 2020; **179**: 527-545 [PMID: 32020331 DOI: 10.1007/s00431-020-03597-5]

5 **Moscheo C**, Licciardello M, Samperi P, La Spina M, Di Cataldo A, Russo G. New Insights into Iron Deficiency Anemia in Children: A Practical Review. *Metabolites* 2022; **12** [PMID: 35448476 DOI: 10.3390/metabo12040289]

6 **Powers JM**, McCavit TL, Buchanan GR. Management of iron deficiency anemia: a survey of pediatric hematology/oncology specialists. *Pediatr Blood Cancer* 2015; **62**: 842-846 [PMID: 25663613 DOI: 10.1002/pbc.25433]

7 **Powers JM**, Daniel CL, McCavit TL, Buchanan GR. Deficiencies in the Management of Iron Deficiency Anemia During Childhood. *Pediatr Blood Cancer* 2016; **63**: 743-745 [PMID: 26728130 DOI: 10.1002/pbc.25861]

8 **Name JJ**, Vasconcelos AR, Valzachi Rocha Maluf MC. Iron Bisglycinate Chelate and Polymaltose Iron for the Treatment of Iron Deficiency Anemia: A Pilot Randomized Trial. *Curr Pediatr Rev* 2018; **14**: 261-268 [PMID: 30280670 DOI: 10.2174/1573396314666181002170040]

9 **Powers JM**, O'Brien SH. How I approach iron deficiency with and without anemia. *Pediatr Blood Cancer* 2019; **66**: e27544 [PMID: 30393941 DOI: 10.1002/pbc.27544]

10 **Mantadakis E**. Advances in Pediatric Intravenous Iron Therapy. *Pediatr Blood Cancer* 2016; **63**: 11-16 [PMID: 26376214 DOI: 10.1002/pbc.25752]

11 **Lam JR**, Schneider JL, Quesenberry CP, Corley DA. Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use and Iron Deficiency. *Gastroenterology* 2017; **152**: 821-829.e1 [PMID: 27890768 DOI: 10.1053/j.gastro.2016.11.023]

12 **Gómez-Ramírez S**, Bisbe E, Shander A, Spahn DR, Muñoz M. Management of Perioperative Iron Deficiency Anemia. *Acta Haematol* 2019; **142**: 21-29 [PMID: 30970362 DOI: 10.1159/000496965]

13 **Albaramki J**, Hodson EM, Craig JC, Webster AC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database Syst Rev* 2012; **1**: CD007857 [PMID: 22258974 DOI: 10.1002/14651858.CD007857.pub2]

14 **Warady BA**, Zobrist RH, Wu J, Finan E; Ferrlecit Pediatric Study Group. Sodium ferric gluconate complex therapy in anemic children on hemodialysis. *Pediatr Nephrol* 2005; **20**: 1320-1327 [PMID: 15971073 DOI: 10.1007/s00467-005-1904-y]

15 **Ambarsari CG**, Trihono PP, Kadaristiana A, Rachmadi D, Andriastuti M, Puspitasari HA, Tambunan T, Pardede SO, Mangunatmadja I, Hidayati EL. Low-Dose Maintenance Intravenous Iron Therapy Can Prevent Anemia in Children with End-Stage Renal Disease Undergoing Chronic Hemodialysis. *Int J Nephrol* 2020; **2020**: 3067453 [PMID: 32566294 DOI: 10.1155/2020/3067453]

16 **Camaschella C**. Iron deficiency: new insights into diagnosis and treatment. *Hematology Am Soc Hematol Educ Program* 2015; **2015**: 8-13 [PMID: 26637694 DOI: 10.1182/asheducation-2015.1.8]

17 **Caimmi S**, Crisafulli G, Franceschini F, Liotti L, Bianchi A, Bottau P, Mori F, Triggiano P, Paglialunga C, Saretta F, Giannetti A, Ricci G, Caffarelli C. Hypersensitivity to Intravenous Iron Preparations. *Children (Basel)* 2022; **9** [PMID: 36291409 DOI: 10.3390/children9101473]

18 **Bircher AJ**, Auerbach M. Hypersensitivity from intravenous iron products. *Immunol Allergy Clin North Am* 2014; **34**: 707-723, x [PMID: 25017687 DOI: 10.1016/j.iac.2014.04.013]

19 **Pinsk V**, Levy J, Moser A, Yerushalmi B, Kapelushnik J. Efficacy and safety of intravenous iron sucrose therapy in a group of children with iron deficiency anemia. *Isr Med Assoc J* 2008; **10**: 335-338 [PMID: 18605353]

20 **Crary SE**, Hall K, Buchanan GR. Intravenous iron sucrose for children with iron deficiency failing to respond to oral iron therapy. *Pediatr Blood Cancer* 2011; **56**: 615-619 [PMID: 21298748 DOI: 10.1002/pbc.22930]

21 **Akin M**, Atay E, Oztekin O, Karadeniz C, Karakus YT, Yilmaz B, Erdogan F. Responsiveness to parenteral iron therapy in children with oral iron-refractory iron-deficiency anemia. *Pediatr Hematol Oncol* 2014; **31**: 57-61 [PMID: 24087940 DOI: 10.3109/08880018.2013.829540]

22 **Mantadakis E**, Tsouvala E, Xanthopoulou V, Chatzimichael A. Intravenous iron sucrose for children with iron deficiency anemia: a single institution study. *World J Pediatr* 2016; **12**: 109-113 [PMID: 25754747 DOI: 10.1007/s12519-015-0010-x]

23 **Roganovic J**. Parenteral iron therapy in children with iron deficiency anemia. *World J Pediatr* 2016; **12**: 122 [PMID: 26782343 DOI: 10.1007/s12519-016-0002-5]

24 **Kaneva K**, Chow E, Rosenfield CG, Kelly MJ. Intravenous Iron Sucrose for Children With Iron Deficiency Anemia. *J Pediatr Hematol Oncol* 2017; **39**: e259-e262 [PMID: 28562517 DOI: 10.1097/MPH.0000000000000879]

25 **Boucher AA**, Pfeiffer A, Bedel A, Young J, McGann PT. Utilization trends and safety of intravenous iron replacement in pediatric specialty care: A large retrospective cohort study. *Pediatr Blood Cancer* 2018; **65**: e26995 [PMID: 29369486 DOI: 10.1002/pbc.26995]

26 **Powers JM**, Shamoun M, McCavit TL, Adix L, Buchanan GR. Intravenous Ferric Carboxymaltose in Children with Iron Deficiency Anemia Who Respond Poorly to Oral Iron. *J Pediatr* 2017; **180**: 212-216 [PMID: 27776750 DOI: 10.1016/j.jpeds.2016.09.053]

27 **Mantadakis E**, Roganovic J. Safety and efficacy of ferric carboxymaltose in children and adolescents with iron deficiency anemia. *J Pediatr* 2017; **184**: 241 [PMID: 28196681 DOI: 10.1016/j.jpeds.2017.01.041]

28 **Panagopoulou P**, Alexiadou S, Ntoumpara M, Papazoglou A, Makis A, Tragiannidis A, Fotoulaki M, Mantadakis E. Safety of Ferric Carboxymaltose in Children: Report of a Case Series from Greece and Review of the Literature. *Paediatr Drugs* 2022; **24**: 137-146 [PMID: 35083718 DOI: 10.1007/s40272-022-00491-5]

29 **Carman N**, Muir R, Lewindon P. Ferric carboxymaltose in the treatment of iron deficiency in pediatric inflammatory bowel disease. *Transl Pediatr* 2019; **8**: 28-34 [PMID: 30881896 DOI: 10.21037/tp.2019.01.01]

30 **Ozsahin H**, Schaeppi M, Bernimoulin M, Allard M, Guidard C, van den Ouweland F. Intravenous ferric carboxymaltose for iron deficiency anemia or iron deficiency without anemia after poor response to oral iron treatment: Benefits and risks in a cohort of 144 children and adolescents. *Pediatr Blood Cancer* 2020; **67**: e28614 [PMID: 32729200 DOI: 10.1002/pbc.28614]

31 **Korczowski B**, Farrell C, Falone M, Blackman N, Rodgers T. Safety, pharmacokinetics, and pharmacodynamics of intravenous ferric carboxymaltose in children with iron deficiency anemia. *Pediatr Res* 2023; **94**: 1547-1554 [PMID: 37208431 DOI:

10.1038/s41390-023-02644-9]

32 **Geisser P**, Burckhardt S. The pharmacokinetics and pharmacodynamics of iron preparations. *Pharmaceutics* 2011; **3**: 12-33 [PMID: 24310424 DOI: 10.3390/pharmaceutics3010012]

33 **Kumar A**, Sharma E, Marley A, Samaan MA, Brookes MJ. Iron deficiency anaemia: pathophysiology, assessment, practical management. *BMJ Open Gastroenterol* 2022; **9** [PMID: 34996762 DOI: 10.1136/bmjgast-2021-000759]

34 **Lucas S**, Garg M. Intravenous iron: an update. *Intern Med J* 2024; **54**: 26-34 [PMID: 37490496 DOI: 10.1111/imj.16184]

35 **Polson MK**, Bahrain H, Ogden JF, Utkina K, Bucco RA, Khan N. Financial burden associated with discordance to intravenous iron therapies in US patients with iron deficiency anemia. *J Manag Care Spec Pharm* 2023; **29**: 818-824 [PMID: 37133430 DOI: 10.18553/jmcp.2023.22407]

36 **Vinchi F**, Castagna A, Costa da Silva M, Busti F, Marchi G, Sparla R, Muckenthaler MU, Girelli D. Intravenous Iron Promotes Low-Grade Inflammation in Anemic Patients By Triggering Macrophage Activation. *Blood* 2019; **134**: 957 [DOI: 10.1182/blood-2019-132235]

37 **Kassianides X**, Allgar V, Macdougall IC, Kalra PA, Bhandari S. Analysis of oxidative stress, inflammation and endothelial function following intravenous iron in chronic kidney disease in the Iron and Heart Trial. *Sci Rep* 2022; **12**: 6853 [PMID: 35477731 DOI: 10.1038/s41598-022-10717-8]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2143-2146

DOI: 10.12998/wjcc.v12.i13.2143

ISSN 2307-8960 (online)

EDITORIAL

Treatment-induced neuroendocrine prostate cancer and *de novo* neuroendocrine prostate cancer: Identification, prognosis and survival, genetic and epigenetic factors

Mohamed Wishahi

Specialty type: Oncology

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

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade C

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade B, Grade B

P-Reviewer: Ji Y, China; Zhang Z, China

Received: December 18, 2023

Revised: February 10, 2024

Accepted: April 7, 2024

Published online: May 6, 2024

Mohamed Wishahi, Department of Urology, Theodor Bilharz Research Institute, Cairo 12411, Egypt

Corresponding author: Mohamed Wishahi, MD, PhD, Professor, Surgical Oncologist. Department of Urology, Theodor Bilharz Research Institute, Giza, Cairo 12411, Egypt. moh.weshahy@gmail.com

Abstract

Neuroendocrine prostate cancer (NEPC) shows an aggressive behavior compared to prostate cancer (PCa), also known as prostate adenocarcinoma. Scanty foci in PCa can harbor genetic alternation that can arise in a heterogeneity of prostate cancer. NEPC may arise *de novo* or develop following androgen deprivation therapy (ADT). NEPC that arise following ADT has the nomenclature "treatment-emerging/induced NEPC (t-NEPC)". t-NEPC would be anticipated in castration resistant prostate cancer (CRPC) and metastatic PCa. t-NEPC is characterized by low or absent androgen receptor (AR) expression, independence of AR signaling, and gain of neuroendocrine phenotype. t-NEPC is an aggressive metastatic tumor, develops from PCa in response to drug induced ADT, and shows very short response to conventional therapy. t-NEPC occurs in 10%-17% of patients with CRPC. *De novo* NEPC is rare and is accounting for less than 2% of all PCa. The molecular mechanisms underlying the trans-differentiation from CRPC to t-NEPC are not fully elucidated. Sphingosine kinase 1 plays a significant role in t-NEPC development. Although neuroendocrine markers: Synaptophysin, chromogranin A, and insulinoma associated protein 1 (*INSM1*) are expressed in t-NEPC, they are non-specific for diagnosis, prognosis, and follow-up of therapy. t-NEPC shows enriched genomic alteration in tumor protein P53 (*TP53*) and retinoblastoma 1 (*RB1*). There are evidences suggest that t-NEPC might develop through epigenetic evolution. There are genomic, epigenetic, and transcriptional alterations that are reported to be involved in development of t-NEPC. Knock-outs of *TP53* and *RB1* were found to contribute in development of t-NEPC. PCa is resistant to immuno-therapy, and at present there are running trials to approach immunotherapy for PCa, CRPC, and t-NEPC.

Key Words: Prostate cancer; Neuroendocrine carcinoma; Treatment induced neuro-endocrine prostate cancer; Androgen deprivation therapy; Genetic and epigenetic factors;

Castration resistant prostate cancer; *De novo* neuroendocrine prostate cancer

Core Tip: Neuroendocrine prostate cancer (NEPC) are aggressive metastatic tumors, and there are two distinct types. *De novo* NEPC, which is less than 2% of all prostate cancer, is categorized as an entity of the endocrine tumors. The other type is the treatment induced NEPC (t-NEPC) that develops in castration resistant prostate cancer (CRPC) following androgen deprivation therapy, and it is an aggressive metastatic tumor occurs in 10%-17% of patients with CRPC and metastatic cancer, with median survival of 7 months after diagnosis. Genomic, epigenetic, and transcriptional alternation has been reported to be involved in its development. Future expectations for treatment would be tumor-directed immunotherapy.

Citation: Wishahi M. Treatment-induced neuroendocrine prostate cancer and *de novo* neuroendocrine prostate cancer: Identification, prognosis and survival, genetic and epigenetic factors. *World J Clin Cases* 2024; 12(13): 2143-2146
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2143.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2143

INTRODUCTION

Neuroendocrine prostate cancer (NEPC) shows an aggressive biological behavior compared to prostate cancer (PCa), also known as prostate adenocarcinoma (PRAD). Recently, there has been extensive research on NEPC to elucidate its aggressive lethal characteristics. Prostatic adenocarcinoma foci can harbor genomic alterations that can arise in heterogeneity of prostate cancer.

Prostate cancer is not always adenocarcinoma with an elevated prostate specific antigen (PSA), and considerations of rare aggressive variants of NEPC should be born in mind. NEPC may arise *de novo* or develop after castration-resistant prostate cancer (CRPC) following androgen deprivation therapy (ADT). This type of tumor is more common than the *de novo* type and has the nomenclature "treatment-emergent NEPC" (t-NEPC). t-NEPC represents a challenge in early diagnosis by the urologist and pathologist and would be anticipated in CRPC and in metastatic PCa.

Recently, Weng *et al*[1] published an article on an aggressive variant PCa. They described a case of NEPC that was diagnosed as PRAD that received ADT, and 4 months later the patients had metastases and poor prognosis, finally the case was considered NEPC. In this work recognition of the variant of NEPC would be of significance.

The WHO fifth edition has joined together neuroendocrine tumors from different sites in each system into a separate chapter. This new classification is applied to the genitourinary system with specific consideration of *de novo* NEPC. t-NEPC has its own section in the PCa chapter with detailed description. Moreover, t-NEPC has its distinctive clinical and biological behavior differ from *de novo* NEPC[2,3]. t-NEPC develops in 10%-17% in patients with PRAD who received ADT and are CRPC[4,5]. *De novo* NEPC accounts for less than 2% of all PCa[6,7].

The second highest incidence of carcinomas in men worldwide is PCa[1]. While 90%-95% of PCa are adenocarcinoma which is characterized by strong androgen receptor (AR) and PSA expression. The tumor depends on the AR mediated signalling for maintenance and growth. Standard treatment of localized PCa is surgery or radiotherapy. For advanced PCa, ADT is the first-line treatment. In rare cases the PCa tumor can adapt to ADT leading to CRPC.

A subset CRPC, is the t-NEPC that differs from PRAD by low expression or absent AR and/or signaling, and it acquires neuroendocrine phenotype. Furthermore, t-NEPC is an aggressive metastatic subtype of PCa, it develops from prostate adenocarcinoma in response to drug induced ADT. The incidence rate of t-NEPC has increased in the last 2 decades in the United States. Median overall survival of t-NEPC after initial diagnosis of PCa is 53.5 months, and median survival is 7 months after diagnosis of t-NEPC[8,9]. The t-NEPC shows *P53* positive immunostaining, while PSA and prostatic acid phosphatase are negative[9].

The molecular mechanisms underlying the trans-differentiation from CRPC to t-NEPC are not fully distinguished. Sphingosine kinase 1 (SphK1) plays a significant role in t-NEPC development. SphK1 is transcriptionally repressed by AR-RE1-silencing transcription factor (REST). SPHK1 produces sphingosine 1phosphate that modulate REST protein turnover. Also, the decreased REST protein levels enhance the expression of neuroendocrine markers in CRPC, leading to the transition to t-NEPC[10]. t-NEPC is disguised by loss of AR activities and the expression of chromatin, chromogranin A, synaptophysin, CD56 and INSM1 which are neuroendocrine markers[11,12]. t-NEPC shows dysregulated cytokine function. Tumor-plasticity is characteristic of t-NEPC that leads to dedifferentiate into different cell lineages. Tumor plasticity and epithelial-to-mesenchymal transition-induced cellular-plasticity and stem-cell signaling pathways lead to the progression of NEPC[13-16]. Genomic, epigenetic, and transcriptional alterations have been reported to be involved in the development of t-NEPC[17].

Combinatorial knock-outs (KO) of *TP53* and *RB1* have induced the growth of an AR-low neuroendocrine-like tumor. A triple KO model with *PTEN* loss has exhibited multiple metastases. Aberrations of these three genes mediated increased lineage plasticity. t-NEPC exhibits genomic aberrations that include the amplification of aurora kinase A (AURKA) and N-MYC (encoded by MYCN). N-MYC is highly enriched in t-NEPC tumors (40% *vs* 5% in PRAD). AURKA and N-MYC expression increased by reduced protein degradation mediated by *TP53* mutation and microRNA[9]. Transforming

growth factor-beta is expressed in PCa tumor cells and stromal cells are enriched in stromal cells of CRPC and bone metastases.

Recently there is data on the features of trans-differentiating from adenocarcinoma to neuroendocrine phenotype. t-NEPC shows enriched genomic alterations in *RB1* and *TP53*, in addition to epigenetic changes, these findings suggest that t-NEPC might develop through epigenetic changes evolution[18].

The difficulties in the clinical study of t-NEPC are presence of focal neuroendocrine differentiation detected with immunohistochemistry among the standard acinar adenocarcinoma of the prostate without any clinical evidence or circulating markers. PRAD expresses varying degrees of neuroendocrinal differentiation, consequently the WHO fifth edition and other authors do not recommend routine application of immunohistochemistry to detect synaptophysin and chromogranin. Moreover, these markers are insignificant in diagnosis or prognosis of t-NEPC[19-23].

The prediction of patients who will develop t-NEPC necessitates serial prostate biopsies at different timing from the initiation of ADT to achieve surveillance on development of CRPC and possible development of t-NEPC[13].

The origin of t-NEPC is postulated to arise from basal or neuroendocrine cells which are scanty, small in number and distributed in the normal prostate. Induction of ADT leads to inhibition of AR resulting in development of t-NEPC[10, 18]. Prostate cancers are often resistant to immunotherapies. There are running research trials to approach immunotherapy for PCa, CRPC, and t-NEPC[24].

CONCLUSION

NEPC shows an aggressive biological behavior compared to PRAD. NEPC represents a challenge in early diagnosis by the urologist and pathologist. NEPC may arise *de novo* or develop after CRPC following treatment with ADT. t-NEPC is reported to arise in 10%-17% of patients with CRPC. *De novo* NEPC is rare, it accounts for less than 2% of PCa. t-NEPC develops from PRAD in response to drug induced ADT to AR signaling inhibition, it would be anticipated in CRBC and in metastatic PCa. Genetic, epigenetic, and transcriptional alternation has been reported to be involved in the development of t-NEPC. The molecular mechanism underlying the trans-differentiation from CRPC to t-NEPC is not fully elucidated. PCa are often resilient to immunotherapy. There are running research trials to approach tumor-immunotherapy for PCa, CRPC, and t-NEPC.

FOOTNOTES

Author contributions: Wishahi M conceived the design; analyzed published data; wrote, reviewed, and edited the manuscript; and revised and approved the final version.

Conflict-of-interest statement: The author confirms that he has no conflict of interest of any kind.

Country/Territory of origin: Egypt

ORCID number: Mohamed Wishahi 0000-0002-4559-619X.

S-Editor: Che XX
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Weng XT**, Lin WL, Pan QM, Chen TF, Li SY, Gu CM. Aggressive variant prostate cancer: A case report and literature review. *World J Clin Cases* 2023; **11**: 6213-6222 [PMID: 37731555 DOI: 10.12998/wjcc.v11.i26.6213]

2 **Kench JG**, Amin MB, Berney DM, Compérat EM, Cree IA, Gill AJ, Hartmann A, Menon S, Moch H, Netto GJ, Raspollini MR, Rubin MA, Tan PH, Tsuzuki T, Turjalic S, van der Kwast TH, Zhou M, Srigley JR. WHO Classification of Tumours fifth edition: evolving issues in the classification, diagnosis, and prognostication of prostate cancer. *Histopathology* 2022; **81**: 447-458 [PMID: 35758185 DOI: 10.1111/his.14711]

3 **Netto GJ**, Amin MB, Berney DM, Compérat EM, Gill AJ, Hartmann A, Menon S, Raspollini MR, Rubin MA, Srigley JR, Hoon Tan P, Tickoo SK, Tsuzuki T, Turajlic S, Cree I, Moch H. The 2022 World Health Organization Classification of Tumors of the Urinary System and Male Genital Organs-Part B: Prostate and Urinary Tract Tumors. *Eur Urol* 2022; **82**: 469-482 [PMID: 35965208 DOI: 10.1016/j.eururo.2022.07.002]

4 **Aggarwal R**, Huang J, Alumkal JJ, Zhang L, Feng FY, Thomas GV, Weinstein AS, Friedl V, Zhang C, Witte ON, Lloyd P, Gleave M, Evans CP, Youngren J, Beer TM, Rettig M, Wong CK, True L, Foye A, Playdle D, Ryan CJ, Lara P, Chi KN, Uzunangelov V, Sokolov A, Newton Y, Beltran H, Demichelis F, Rubin MA, Stuart JM, Small EJ. Clinical and Genomic Characterization of Treatment-Emergent Small-Cell

Neuroendocrine Prostate Cancer: A Multi-institutional Prospective Study. *J Clin Oncol* 2018; **36**: 2492-2503 [PMID: 29985747 DOI: 10.1200/JCO.2017.77.6880]

5 **Bluemn EG**, Coleman IM, Lucas JM, Coleman RT, Hernandez-Lopez S, Tharakan R, Bianchi-Frias D, Dumpit RF, Kaipainen A, Corella AN, Yang YC, Nyquist MD, Mostaghel E, Hsieh AC, Zhang X, Corey E, Brown LG, Nguyen HM, Pienta K, Ittmann M, Schweizer M, True LD, Wise D, Rennie PS, Vessella RL, Morrissey C, Nelson PS. Androgen Receptor Pathway-Independent Prostate Cancer Is Sustained through FGF Signaling. *Cancer Cell* 2017; **32**: 474-489.e6 [PMID: 29017058 DOI: 10.1016/j.ccell.2017.09.003]

6 **Zaffuto E**, Pompe R, Zanaty M, Bondarenko HD, Leyh-Bannurah SR, Moschini M, Dell'Oglio P, Gandaglia G, Fossati N, Stabile A, Zorn KC, Montorsi F, Briganti A, Karakiewicz PI. Contemporary Incidence and Cancer Control Outcomes of Primary Neuroendocrine Prostate Cancer: A SEER Database Analysis. *Clin Genitourin Cancer* 2017; **15**: e793-e800 [PMID: 28506524 DOI: 10.1016/j.clgc.2017.04.006]

7 **Vlachostergios PJ**, Puca L, Beltran H. Emerging Variants of Castration-Resistant Prostate Cancer. *Curr Oncol Rep* 2017; **19**: 32 [PMID: 28361223 DOI: 10.1007/s11912-017-0593-6]

8 **Wang HT**, Yao YH, Li BG, Tang Y, Chang JW, Zhang J. Neuroendocrine Prostate Cancer (NEPC) progressing from conventional prostatic adenocarcinoma: factors associated with time to development of NEPC and survival from NEPC diagnosis-a systematic review and pooled analysis. *J Clin Oncol* 2014; **32**: 3383-3390 [PMID: 25225419 DOI: 10.1200/JCO.2013.54.3553]

9 **Merkens L**, Sailer V, Lessel D, Janzen E, Greimeier S, Kirfel J, Perner S, Pantel K, Werner S, von Amsberg G. Aggressive variants of prostate cancer: underlying mechanisms of neuroendocrine transdifferentiation. *J Exp Clin Cancer Res* 2022; **41**: 46 [PMID: 35109899 DOI: 10.1186/s13046-022-02255-y]

10 **Lee CF**, Chen YA, Hernandez E, Pong RC, Ma S, Hofstad M, Kapur P, Zhau H, Chung LW, Lai CH, Lin H, Lee MS, Raj GV, Hsieh JT. The central role of Sphingosine kinase 1 in the development of neuroendocrine prostate cancer (NEPC): A new targeted therapy of NEPC. *Clin Transl Med* 2022; **12**: e695 [PMID: 35184376 DOI: 10.1002/ctm2.695]

11 **Epstein JI**, Amin MB, Beltran H, Lotan TL, Mosquera JM, Reuter VE, Robinson BD, Troncoso P, Rubin MA. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. *Am J Surg Pathol* 2014; **38**: 756-767 [PMID: 24705311 DOI: 10.1097/PAS.0000000000000208]

12 **Quintanal-Villalonga Á**, Chan JM, Yu HA, Pe'er D, Sawyers CL, Sen T, Rudin CM. Lineage plasticity in cancer: a shared pathway of therapeutic resistance. *Nat Rev Clin Oncol* 2020; **17**: 360-371 [PMID: 32152485 DOI: 10.1038/s41571-020-0340-z]

13 **Wang Y**, Wang Y, Ci X, Choi SYC, Crea F, Lin D. Molecular events in neuroendocrine prostate cancer development. *Nat Rev Urol* 2021; **18**: 581-596 [PMID: 34290447 DOI: 10.1038/s41585-021-00490-0]

14 **Soundararajan R**, Paranjape AN, Maity S, Aparicio A, Mani SA. EMT, stemness and tumor plasticity in aggressive variant neuroendocrine prostate cancers. *Biochim Biophys Acta Rev Cancer* 2018; **1870**: 229-238 [PMID: 29981816 DOI: 10.1016/j.bbcan.2018.06.006]

15 **Pérez-González A**, Bévant K, Blanpain C. Cancer cell plasticity during tumor progression, metastasis and response to therapy. *Nat Cancer* 2023; **4**: 1063-1082 [PMID: 37537300 DOI: 10.1038/s43018-023-00595-y]

16 **Beltran H**, Hruszkewycz A, Scher HI, Hildesheim J, Isaacs J, Yu EY, Kelly K, Lin D, Dicker A, Arnold J, Hecht T, Wicha M, Sears R, Rowley D, White R, Gulley JL, Lee J, Diaz Meco M, Small EJ, Shen M, Knudsen K, Goodrich DW, Lotan T, Zoubeidi A, Sawyers CL, Rudin CM, Loda M, Thompson T, Rubin MA, Tawab-Amiri A, Dahut W, Nelson PS. The Role of Lineage Plasticity in Prostate Cancer Therapy Resistance. *Clin Cancer Res* 2019; **25**: 6916-6924 [PMID: 31363002 DOI: 10.1158/1078-0432.CCR-19-1423]

17 **Abida W**, Cyrta J, Heller G, Prandi D, Armenia J, Coleman I, Cieslik M, Benelli M, Robinson D, Van Allen EM, Sboner A, Fedrizzi T, Mosquera JM, Robinson BD, De Sarkar N, Kunju LP, Tomlins S, Wu YM, Nava Rodrigues D, Loda M, Gopalan A, Reuter VE, Pritchard CC, Mateo J, Bianchini D, Miranda S, Carreira S, Rescigno P, Filipenko J, Vinson J, Montgomery RB, Beltran H, Heath EI, Scher HI, Kantoff PW, Taplin ME, Schultz N, deBono JS, Demichelis F, Nelson PS, Rubin MA, Chinnaiyan AM, Sawyers CL. Genomic correlates of clinical outcome in advanced prostate cancer. *Proc Natl Acad Sci USA* 2019; **116**: 11428-11436 [PMID: 31061129 DOI: 10.1073/pnas.1902651116]

18 **Labrecque MP**, Coleman IM, Brown LG, True LD, Kollath L, Lakely B, Nguyen HM, Yang YC, da Costa RMG, Kaipainen A, Coleman R, Higano CS, Yu EY, Cheng HH, Mostaghel EA, Montgomery B, Schweizer MT, Hsieh AC, Lin DW, Corey E, Nelson PS, Morrissey C. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. *J Clin Invest* 2019; **129**: 4492-4505 [PMID: 31361600 DOI: 10.1172/JCI128212]

19 **Shehabeldin AN**, Ro JY. Neuroendocrine tumors of genitourinary tract: Recent advances. *Ann Diagn Pathol* 2019; **42**: 48-58 [PMID: 31306859 DOI: 10.1016/j.anndiagpath.2019.06.009]

20 **Priemer DS**, Montironi R, Wang L, Williamson SR, Lopez-Beltran A, Cheng L. Neuroendocrine Tumors of the Prostate: Emerging Insights from Molecular Data and Updates to the 2016 World Health Organization Classification. *Endocr Pathol* 2016; **27**: 123-135 [PMID: 26885643 DOI: 10.1007/s12022-016-9421-z]

21 **Santoni M**, Conti A, Burattini L, Berardi R, Scarpelli M, Cheng L, Lopez-Beltran A, Cascinu S, Montironi R. Neuroendocrine differentiation in prostate cancer: novel morphological insights and future therapeutic perspectives. *Biochim Biophys Acta* 2014; **1846**: 630-637 [PMID: 25450825 DOI: 10.1016/j.bbcan.2014.10.008]

22 **Aggarwal R**, Zhang T, Small EJ, Armstrong AJ. Neuroendocrine prostate cancer: subtypes, biology, and clinical outcomes. *J Natl Compr Canc Netw* 2014; **12**: 719-726 [PMID: 24812138 DOI: 10.6004/jnccn.2014.0073]

23 **Conteduca V**, Oromendia C, Eng KW, Bareja R, Sigouros M, Molina A, Faltas BM, Sboner A, Mosquera JM, Elemento O, Nanus DM, Tagawa ST, Ballman KV, Beltran H. Clinical features of neuroendocrine prostate cancer. *Eur J Cancer* 2019; **121**: 7-18 [PMID: 31525487 DOI: 10.1016/j.ejca.2019.08.011]

24 **Meng L**, Yang Y, Mortazavi A, Zhang J. Emerging Immunotherapy Approaches for Treating Prostate Cancer. *Int J Mol Sci* 2023; **24**: 14347 [PMID: 37762648 DOI: 10.3390/ijms241814347]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2147-2150

DOI: 10.12998/wjcc.v12.i13.2147

ISSN 2307-8960 (online)

EDITORIAL

Perioperative cardiac risks in myasthenia gravis

Deb Sanjay Nag, Abhishek Chatterjee, Pratap Rudra Mahanty, Merina Sam, Murari Kumar Bharadwaj

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A
Novelty: Grade A
Creativity or Innovation: Grade A
Scientific Significance: Grade A

P-Reviewer: Xavier-Elsas P, Brazil

Received: December 19, 2023
Revised: February 23, 2024
Accepted: April 7, 2024
Published online: May 6, 2024

Deb Sanjay Nag, Abhishek Chatterjee, Pratap Rudra Mahanty, Merina Sam, Murari Kumar Bharadwaj, Department of Anaesthesiology, Tata Main Hospital, Jamshedpur 831001, India

Abhishek Chatterjee, Pratap Rudra Mahanty, Department of Anaesthesiology, Manipal Tata Medical College, Jamshedpur 831017, India

Corresponding author: Deb Sanjay Nag, MBBS, MD, Doctor, Department of Anaesthesiology, Tata Main Hospital, C Road West, Northern Town, Bistupur, Jamshedpur 831001, India. ds.nag@tatasteel.com

Abstract

Myasthenia gravis (MG) is an autoimmune disorder that affects the neuromuscular junction. The primary pathology in MG involves the presence of autoantibodies to acetylcholine receptors (AChRs), which results in qualitative and quantitative reductions in the availability of functional AChRs. Cardiac muscles are also affected, resulting in various perioperative cardiac complications. Antistriational antibodies are commonly reported in MG cases with cardiac involvement. In the presence of thymoma, the prevalence of cardiac manifestations in patients with MG increases to approximately 10%-15%. Cardiac involvement in MG may range from asymptomatic electrocardiogram changes to ventricular tachycardia, myocarditis, conduction disorders, heart failure, and sudden death. Increased incidence of atrial fibrillation, ventricular and supraventricular extra systoles, and prolonged QTc have also been reported in patients with MG. Clinicians should consider the evaluation of autonomic dysfunction and risk of cardiovascular disease in patients with MG.

Key Words: Myasthenia Gravis; Perioperative period; Receptors; Cholinergic; Anesthesia

Core Tip: Current evidence shows that elderly patients with myasthenia gravis (MG) are more prone to developing perioperative cardiac complications. As healthcare professionals refine and evolve screening methods to identify patients with MG at risk of developing perioperative cardiac events due to autonomic dysfunction, the integration of screening for antistriational antibodies becomes crucial. In addition, assessing left ventricular function in the preoperative period may result in successful outcomes in these patients.

Citation: Nag DS, Chatterjee A, Mahanty PR, Sam M, Bharadwaj MK. Perioperative cardiac risks in myasthenia gravis. *World J Clin Cases* 2024; 12(13): 2147-2150
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2147.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2147

INTRODUCTION

Myasthenia gravis (MG) leads to fatigue and progressive muscular weakness due to an autoimmune disorder affecting the neuromuscular junction[1]. With a maximal prevalence in the second-third decade in females and fifth-sixth decade in males, the approximate prevalence of MG is 1:7500[2].

The primary pathology in MG involves the presence of autoantibodies to acetylcholine receptors (AChRs)[1], which disrupts the function of AChRs by blocking the receptors, making conformational changes, activation of complements, and crosslinking. This leads to increased degradation of these receptors[1]. The qualitative and quantitative reductions in the availability of functional AChRs result in decreased motor endplate potential amplitude and failure in the initiation of muscle fiber contraction[1]. Skeletal muscles are primarily involved in MG. However, numerous studies[3-5] have shown that cardiac muscles are also affected, resulting in various perioperative cardiac complications. In the presence of thymoma, the prevalence of cardiac manifestations in patients with MG increases to around 10%-15%[3]. The AChRs autoantibodies do not bind to cardiac muscle receptors. Studies[5,6] have revealed that 48% of patients with MG and 97% of patients in whom MG is present along with thymoma, have antibodies against cardiac muscles[5]. The antistriational antibodies[6] (antititin antibodies, antiryanodine receptor antibodies, and anti-Kv 1.4 antibodies) are commonly reported in MG cases with cardiac involvement[5,6].

Cardiac involvement in MG may range from a normal sinus rhythm on an electrocardiogram (ECG) to various other pathologies myocarditis or heart failure and ventricular tachycardia to conduction disorders, with at times can lead to sudden death[2].

Myocarditis

Myocarditis has been reported in 37.5% of patients with MG who possess antistriational antibodies[4]. Suzuki *et al*[7] observed that anti-Kv 1.4 antibody influences cardiac function by complement activation and T cell proliferation; therefore, it can be a potential marker for the development of lethal autoimmune myocarditis. Giant cell myocarditis is frequently reported in patients with MG and is evidenced by the presence of myonecrosis[5] with increased age and thymoma being identified as risk factors[8].

Cardiomyopathy

Studies[5] have shown takotsubo cardiomyopathy, a stress-induced reversible and transient left ventricular dysfunction is often associated with MG, which is in the absence of significant coronary stenosis, takotsubo cardiomyopathy frequently presents as acute coronary syndrome and is aggravated by anything which causes a catecholamine surge, like emotional or physical stress, and suppresses myocardial function[9]. Mayor-Gomez *et al*[10] reported a case of heart failure with difficulty in weaning a patient off the ventilator after mitral valve replacement, which was retrospectively diagnosed as a myasthenia crisis. Similarly, Shukla *et al*[11] observed that with every episode of myasthenia crisis in an elderly female, she had recurrent takotsubo cardiomyopathy.

Cardiac arrhythmias

Increased in the incidence of atrial fibrillation, ventricular or supraventricular extra systoles, or prolonged QTc have been reported in different studies[5,12] in patients with MG and thymoma. Peric *et al*[12], in his study of patients with MG, observed that autonomic dysfunction was present in 20% of cases with thymoma and about 3% of cases without thymoma. He also concluded that antibodies to ganglionic AChRs were responsible for autonomic dysfunction in these patients[12]. Chiavistelli *et al*[13] showed that patients with MG had associated nonspecific changes in T waves, prolongations in QT interval and increase in the incidence of first-degree atrioventricular (AV) block during the perioperative period. Several other studies[2,14,15] have documented a positive correlation between anti-Kv1.4 antibody and perioperative fatal arrhythmias, which include sick sinus syndrome, ventricular tachycardias, complete AV block, and sudden cardiac death.

Coronary artery spasm

Various cases of coronary artery spasm have been reported in patients with MG. Yanagihashi *et al*[16] reported a case of intravenous immunoglobulin coronary spastic angina (CSA) that was relieved by glyceryl trinitrate. Hsu *et al*[17] also reported a case of diffuse coronary artery spasm with three vessels. Intracoronary isosorbide dinitrate and adenosine relieved the symptoms. Chuapakdee *et al*[18] also reported a case of CSA after pyridostigmine dose up-titration. Sublingual nitrate immediately relieved symptoms concomitantly with the resolution of abnormal electrocardiograph findings.

CONCLUSION

The heart, like other organs, is a potential target for immune attack in autoimmune disorders such as MG. The exact incidence of perioperative major adverse cardiac events in patients suffering from MG is not known, perhaps due to similar symptoms such as fatigue, dyspnea, and poor exercise tolerance, leading to lesser appreciation of cardiac manifestations. The current evidence mostly consists of retrospective case-control studies or case reports; these suggest that cardiac involvement in MG is often associated with thymoma, anti-Kv 1.4 antibodies, and advancing age. Therefore, it is necessary to conduct prospective studies before recommending cardiac screening in MG. However, antistriational antibodies highlight a fascinating potential connection between MG and cardiac diseases.

FOOTNOTES

Author contributions: Nag DS and Chatterjee A designed the overall concept and outline of the manuscript; Mahanty PR, Sam M, and Bharadwaj MK contributed to the discussion and design of the manuscript; All authors contributed to the writing, and editing the manuscript and review of literature.

Conflict-of-interest statement: The authors declare no conflict of interest.

Country/Territory of origin: India

ORCID number: Deb Sanjay Nag 0000-0003-2200-9324.

S-Editor: Che XX
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Daum P**, Smelt J, Ibrahim IR. Perioperative management of myasthenia gravis. *BJA Educ* 2021; **21**: 414-419 [PMID: 34707886 DOI: 10.1016/j.bjae.2021.07.001]
2 **Călin C**, Savu O, Dumitru D, Ghiorghiu I, Călin A, Capraru C, Popescu BA, Croitoru M, Vîlciu C, Ginghină C. Cardiac involvement in myasthenia gravis--is there a specific pattern? *Rom J Intern Med* 2009; **47**: 179-189 [PMID: 20067169]
3 **Suzuki S**, Baba A, Kaida K, Utsugisawa K, Kita Y, Tsugawa J, Ogawa G, Nagane Y, Kuwana M, Suzuki N. Cardiac involvements in myasthenia gravis associated with anti-Kv1.4 antibodies. *Eur J Neurol* 2014; **21**: 223-230 [PMID: 23829303 DOI: 10.1111/ene.12234]
4 **Suzuki S**, Utsugisawa K, Yoshikawa H, Motomura M, Matsubara S, Yokoyama K, Nagane Y, Maruta T, Satoh T, Sato H, Kuwana M, Suzuki N. Autoimmune targets of heart and skeletal muscles in myasthenia gravis. *Arch Neurol* 2009; **66**: 1334-1338 [PMID: 19752287 DOI: 10.1001/archneurol.2009.229]
5 **Shivamurthy P**, Parker MW. Cardiac manifestations of myasthenia gravis: a systematic review. *IJC Metab Endocr* 2014; **5**: 3-6 [DOI: 10.1016/j.ijcme.2014.08.003]
6 **Meriggioli MN**, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. *Lancet Neurol* 2009; **8**: 475-490 [PMID: 19375665 DOI: 10.1016/S1474-4422(09)70063-8]
7 **Suzuki S**, Utsugisawa K, Nagane Y, Suzuki N. Three types of striational antibodies in myasthenia gravis. *Autoimmune Dis* 2011; **2011**: 740583 [PMID: 21785709 DOI: 10.4061/2011/740583]
8 **Kon T**, Mori F, Tanji K, Miki Y, Kimura T, Wakabayashi K. Giant cell polymyositis and myocarditis associated with myasthenia gravis and thymoma. *Neuropathology* 2013; **33**: 281-287 [PMID: 22989101 DOI: 10.1111/j.1440-1789.2012.01345.x]
9 **Wong CP**, Chia PL. Recurrent takotsubo cardiomyopathy precipitated by myasthenic crisis. *Int J Cardiol* 2012; **155**: e11-e12 [PMID: 21767885 DOI: 10.1016/j.ijcard.2011.06.129]
10 **Mayor-Gomez S**, Lacruz F, Ezpeleta D. [Myasthenic crisis and Takotsubo syndrome: a non-chance relationship]. *Rev Neurol* 2012; **55**: 725-728 [PMID: 23233140]
11 **Shukla G**, Gupta S, Goyal V, Singh S, Srivastava A, Behari M. Abnormal sympathetic hyper-reactivity in patients with myasthenia gravis: a prospective study. *Clin Neurol Neurosurg* 2013; **115**: 179-186 [PMID: 22676958 DOI: 10.1016/j.clineuro.2012.05.013]
12 **Peric S**, Rakocevic-Stojanovic V, Nisic T, Pavlovic S, Basta I, Popovic S, Damjanovic S, Lavrnic D. Cardiac autonomic control in patients with myasthenia gravis and thymoma. *J Neurol Sci* 2011; **307**: 30-33 [PMID: 21658726 DOI: 10.1016/j.jns.2011.05.028]
13 **Chiavistelli P**, Cei M, Carmignani G, Bartolomei C, Mumoli N. Pseudoischemic electrocardiogram in myasthenia gravis with thymoma: reversibility after thymectomy. *Clin Cardiol* 2009; **32**: E75-E78 [PMID: 19330853 DOI: 10.1002/clc.20309]
14 **Asensio E**, Gómez M, Narváez R, Castillo L, Oseguera J, Dorantes J, Orea A, Hernández P, Rebollar V. [Description of the resting electrocardiogram in a series of patients with myasthenia gravis]. *Rev Invest Clin* 2003; **55**: 270-275 [PMID: 14515671]
15 **Tsugawa J**, Tsuboi Y, Inoue H, Suzuki S, Yamada T. [Recurrent syncope due to sick sinus syndrome in a patient with myasthenia gravis associated with thymoma]. *Rinsho Shinkeigaku* 2011; **51**: 32-34 [PMID: 21387697 DOI: 10.5692/clinicalneurol.51.32]

16 **Yanagihashi M**, Okamoto R, Morioka H, Sawada M, Matsumoto S, Ikeda T, Kano O. Coronary spastic angina after the administration of intravenous immunoglobulin in myasthenia gravis: a case report. *BMC Neurol* 2020; **20**: 319 [PMID: 32859168 DOI: 10.1186/s12883-020-01901-2]

17 **Hsu CW**, Chang CC, Lin CS. Intraoperative cardiogenic shock induced by refractory coronary artery spasm in a patient with myasthenia gravis: A case report. *World J Clin Cases* 2023; **11**: 8589-8594 [PMID: 38188219 DOI: 10.12998/wjcc.v11.i36.8589]

18 **Chuapakdee O**, Layangkool T, Theerasuwipakorn N. Pyridostigmine-induced coronary artery spasm in early-onset myasthenia gravis: a case presentation and review of the literature. *BMJ Case Rep* 2022; **15**: e249819 [PMID: 36104035 DOI: 10.1136/bcr-2022-249819]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2151-2156

DOI: 10.12998/wjcc.v12.i13.2151

ISSN 2307-8960 (online)

EDITORIAL

Management of geriatric acetabular fractures: Contemporary treatment strategies

Theodoros Tosounidis, Byron Chalidis

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
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ueda H, Japan

Received: December 29, 2023
Peer-review started: December 29, 2023
First decision: February 9, 2024
Revised: February 15, 2024
Accepted: March 28, 2024
Article in press: March 28, 2024
Published online: May 6, 2024

Theodoros Tosounidis, Academic Department of Orthopaedic Surgery, Heraklion University Hospital, University of Crete, Greece, Heraklion 71500, Greece

Byron Chalidis, 1st Department of Orthopaedic, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki 57010, Greece

Corresponding author: Byron Chalidis, MD, PhD, Assistant Professor, 1st Department of Orthopaedic, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, G. Papanikolaou Hospital, Exohi, Thessaloniki 57010, Greece.
byronchalidis@gmail.com

Abstract

Acetabular fractures in the geriatric population are typically low-energy fractures resulting from a fall from standing height. Compromised bone quality in the elderly, as well as this population's concomitant medical comorbidities, render the management of such fractures challenging and controversial. Non-operative management remains the mainstay of treatment, although such a choice is associated with numerous and serious complications related to both the hip joint as well as the general condition of the patient. On the other hand, operatively treating acetabular fractures (*e.g.*, with osteosynthesis or total hip arthroplasty) is gaining popularity. Osteosynthesis can be performed with open reduction and internal fixation or with minimally invasive techniques. Total hip arthroplasty could be performed either in the acute phase combined with osteosynthesis or as a delayed procedure after a period of non-operative management or after failed osteosynthesis of the acetabulum. Regardless of the implemented treatment, orthogeriatric co-management is considered extremely crucial, and it is currently one of the pillars of a successful outcome after an acetabular fracture.

Key Words: Acetabular fractures; Geriatric fractures; Fracture fixation; Total hip arthroplasty; Mortality; Morbidity

Core Tip: Treatment of geriatric acetabular fractures is a challenging clinical problem that has recently gained significant attention within the orthopaedic community. Whilst non-operative management is a used treatment strategy, surgery in the form of either osteosynthesis or combination of osteosynthesis and acute total hip arthroplasty is currently extensively performed. The orthogeriatric co-management of the fragile patients who have sustained an acetabular fracture is essential and of paramount importance.

Citation: Tosounidis T, Chalidis B. Management of geriatric acetabular fractures: Contemporary treatment strategies. *World J Clin Cases* 2024; 12(13): 2151-2156
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2151.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2151

INTRODUCTION

The incidence of acetabular fractures in the elderly population has significantly increased over the last years[1]. There are substantial differences that make these fractures different from the ones occurring in the younger counterparts. First, they are low-energy fractures; second the configuration/type of the fracture is different with a significant prevalence of anteriorly based fractures; third, their management includes the option of hip arthroplasty, which is not the case in young patients; and last but not least the co-existing medical comorbidities constitute both the decision making and the overall management more challenging.

Variation in decision-making

The degree of controversy surrounding the issue and the lack of validated management guidelines are vividly depicted in a recent survey that was conducted in 15 level-I Trauma Centers in the United States and included more than 250 patients over the age of 60 years [2]. The study showed that operative treatment was implemented in only 60% of the cases. Age less than 80 years, high-energy fractures, concomitant femoral head lesions, and hip incongruency were the main factors that were taken into consideration by the treating surgeons to decide on the operative management. The vast majority (90%) of the surgically treated patients were managed with open reduction and internal fixation (ORIF) whilst total hip arthroplasty (THA) was performed in the remainder of the cases. From the known risk factors associated with poor outcomes, only dome impaction was significantly associated with receiving surgery. The authors concluded that these results reflected the lack of clear guidelines for management. In general, the decision for surgical intervention is a multifactorial endeavor that takes into account the type of fracture, the physiology and the age of the patients, the expertise of the surgical team, and the logistics of the healthcare setup.

Mortality

Mortality resulting from geriatric acetabular fractures is a matter that has been recently revisited by many scholars. There is a tendency in the contemporary literature to compare the mortality of acetabular fractures to that of hip fractures that occur in the same age cohorts. Khoshbin *et al*[3] from the University of Toronto in a matched cohort study that included patients older than 60 years, concluded that acetabular fractures had a much higher risk of early mortality compared to hip fractures. On the other hand, Stetzelberger *et al*[4] from Switzerland documented that whilst there was no difference in mortality between the acetabular and hip fracture patients at the first 30 postinjury days, the 1-year mortality was double for hip fracture patients (18% acetabular *vs* 36% hip fractures). Mortality has also been studied by comparing operative *vs* no-operative management. Firoozabadi *et al*[5] demonstrated that operative treatment had significantly lower mortality compared to conservative management whilst at the same time more than 80% of the deaths in the no-surgically treated patients occurred within one year from the injury. Gary *et al*[6] in a larger group of patients also indicated that the 1-year mortality was higher in non-operatively treated patients but when this was adjusted for comorbidities, gender, age, and mechanism of injury, no difference between them was observed. Another interesting parameter that has been recently added and investigated in the long catalog of factors that could potentially strongly affect and predict mortality after acetabular fractures is sarcopenia, which in simple words can be understood as age-related bone loss[7,8]. Considering the increased interest related to sarcopenia and orthopaedic trauma, it is to be expected that in the near future, there will be more studies shedding light on this issue.

Non-operative management

Non-operative management used to be the standard of care for these injuries up to the recent past. In the contemporary era despite the fact the surgical management of these injuries is on the rise, there is still a role for the so-called "conservative management"[9]. This by no means should be interpreted as complete bed rest. The latter is fraud with devastating and potentially fatal complications namely pulmonary and/or urinary infections, thromboembolic disease, and recumbency ulcers. Non-operative management should include early mobilization of the patient out of bed, musculoskeletal conditioning, and respiratory physiotherapy. Taking this into consideration, long periods of skeletal traction have no place in the modern management of acetabular fractures in the elderly. Traction should only be applied with caution and only for a few days (maximum 7-10 d). Early and safe mobilization of the patients is a priority and every effort should be made in that direction.

The outcomes of non-operative management have not extensively been studied in the current era. They remain contradictive, with Ryan *et al*[10] reporting good outcomes at a 2-year follow-up in a cohort of 27 patients that were treated non-operatively even though the patients met at least one of the surgical indications. On the contrary, Baker *et al*[11] studied 49 patients with associated fracture types and reported significantly reduced mobility and living independence at 1-year follow-up.

Osteosynthesis

Osteosynthesis of acetabular fractures in the elderly is challenging and frequently yields suboptimal results[12]. Several criteria should be considered when a surgeon is choosing osteosynthesis as the mode of surgical management. Chronological age should not be taken into account in isolation. No clear cut-off is used in the contemporary literature to discriminate between elderly *vs* younger patients. Nevertheless, most of the studies use the age of 60 years as the cut-off point.

Biological age is a more appropriate parameter to be considered. Consequently, the physical condition as well as the comorbidities should be considered when a decision for osteosynthesis is made.

The type of fractures encountered in the elderly are more frequently anterior-based[9] and have a concomitant anteromedial dome impaction[13,14] (Figure 1). This configuration of fracture along with the associated osteopenia make the osteosynthesis quite cumbersome and prone to secondary failure even if intra-operatively a good result has been achieved. In recent days the anterior intrapelvic approach[15] is most frequently used when addressing anterior-based fractures through a typical ORIF technique. Additionally, the pararectus approach introduced by the Bernese group[16], is an option that offers direct access to the superior and anteromedial dome of the acetabulum and is more atraumatic to the soft tissues compared to other surgical approaches. Although optimal outcomes have been documented with its application, the pararectus approach is not widely used and worldwide, the Anteriorly Intrapelvic Approach is still the most commonly used approach to surgically treat anteriorly based acetabular fractures.

At this juncture, it should be emphasized that perfect anatomic reduction of acetabular fractures is not always feasible in elderly patients and oftentimes the surgeon should accept a less perfect reduction keeping in mind that especially in octogenarians, early and pain-free mobilization is the goal of management.

In a recent systematic review, Capone *et al*[17] found that the conversion to a THA after an ORIF was performed at a mean of 25.5 months. Anatomical reduction was achieved in 11.6% of cases and imperfect and poor reduction in 22.3%. In the same study, ORIF was associated with longer operative time, more blood loss, higher secondary surgery rate, and higher 1-year mortality when compared to a THA performed in the acute setting. On the contrary, in another systematic review, Daurka *et al*[18] demonstrated better functional outcomes in the patients treated with ORIF compared to those with THA.

Minimally invasive percutaneous osteosynthesis is advocated by some surgeons to stabilize only the columnar elements of a fracture. Minimal invasion fracture osteosynthesis with closed reduction and percutaneous fixation is an attractive option for acetabular fracture fixation as it may be associated with less blood loss, shorter operative time, and decreased risk for infection, particularly in geriatric populations with low cardiac reserve[10]. The technique has gained popularity not only in simple fractures of the anterior or posterior column but also in displaced fractures that can be reduced with traction, manipulation, and percutaneous leverage under fluoroscopy and can be subsequently fixed with screws[19]. Percutaneous fracture fixation of pelvis and acetabulum is a technically demanding procedure that requires a high level of surgical skills and expertise to perform accurately and safely. Despite the clear advantages of stabilizing the fracture by closed means, the long-term functional outcome and the incidence of conversion to THA are similar[10] or even higher[20] when compared to open fixation techniques.

THA

THA should be considered for the elderly in a threefold perspective: (1) Acute THA along with ORIF; (2) Delayed THA after non-operative management; and (3) THA after failed ORIF of the acetabulum.

The combination of ORIF and acute THA is a complex surgical procedure that requires a mixed and advanced skillset from the orthopaedic surgeon[21,22]. The purpose of the ORIF in this clinical scenario is to restore the anatomy of the columns and thus create a stable bed for the subsequent implantation of the acetabular cup. The ORIF should be applied in a timely and efficient manner to minimize the surgical time, the blood loss, and the physiological stress of the patient. The ORIF can be performed utilizing an anterior-based approach (anterior intrapelvic or pararectus) and then followed by a THA using the posterior approach. Another option is to perform a posterior approach to perform both the ORIF and the THA. A third alternative is to perform a Smith-Petersen-type approach followed by an anteriorly performed THA. The choice depends on the type of fracture and the skillset of the surgeon. In regards to the implant selection for the THA, an uncemented cup is preferred. The option of a big multi-hole cup size should be strongly considered. Trabecular metal offers great initial stabilization of the cup and is an option preferred by many surgeons. Dual mobility articulation should also be considered based on the same rationale that dictates its use during THA after a femoral neck fracture. Acetabular cages must be considered when needed. The critical point of the surgical technique is that the surgeon should be prepared to perform a complex primary THA having implants that are usually used in the revision THA setting.

In recent years, acute THA has yielded optimal clinical outcomes. In a recent systematic review that included 642 patients from 10 observational studies, comparing ORIF *vs* limited ORIF combined with THA, Tu *et al*[23] noticed that acute THA was associated with higher hip Harris score (HHS), improved physical function and better SF-36 physical component summary and mental component summary scores after 1-year postoperatively. Moreover, lesser complication and reoperation rates, and greater bodily pain were also recorded. According to a meta-analysis from Jauregui *et al*[24], acute THA provided a good functional outcome (HSS: 83) and was associated with a revision rate of 4.3% and a complication rate of 20%.

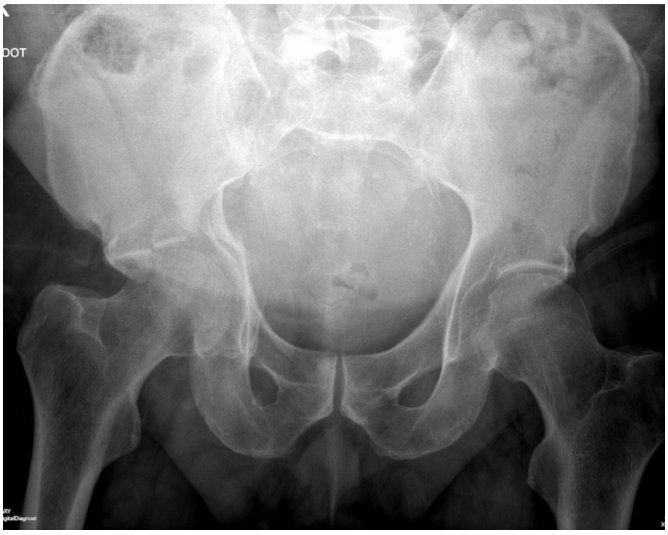

Figure 1 Anteroposterior radiograph of the pelvis showing a right acetabular fracture with anteromedial dome impaction.

THA after a non-operative acetabular fracture can be either relatively straightforward or very technically demanding [25,26] (Figure 2). If the initial and subsequent displacement is minimal then the technical difficulties are not usually of great extent. On the other hand, if the displacement is significant the distorted anatomy can be very problematic and should be addressed accordingly. The same facts stand true for a delayed THA after ORIF. Although the literature is very scant upon this subject, it suggests that the outcomes are generally inferior to those observed after primary THA.

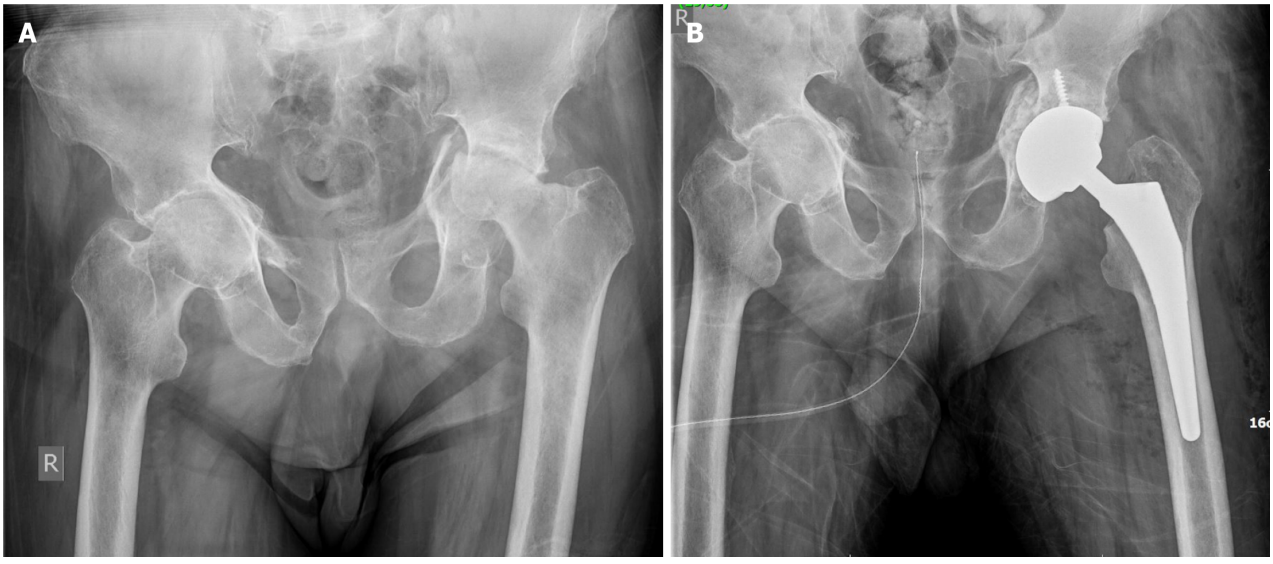

Figure 2 Surgical treatment of post-traumatic hip osteoarthritis after displaced acetabular fracture. A: Preoperative anteroposterior radiograph showing a left acetabular fracture in a 90-year-old patient. The patient did not follow the non-weight bearing instructions and developed symptomatic hip arthritis 5 months post-injury; B: Immediate postoperative radiograph. Autograft from the femoral head was taken to address the cavitary acetabular defect. A dual mobility cup was used for the reconstruction of the acetabulum.

Orthogeriatric co-management

The proper and optimal management of acetabular fractures in the elderly also encompasses the collaboration of different medical specialties and the application of specific individualized protocols based on patients' physical and mental status [19]. Orthogeriatric involvement and co-management is a well-established concept and is currently the standard of care for hip fractures worldwide[27,28]. Although fracture liaison service efficiency has not been studied in this subgroup of elderly patients it is logical to assume that this approach should be also implemented in elderly patients with acetabular fractures[29]. Further involvement of anesthesiologists and nurses can additionally decrease the mortality rates and improve the treatment efficacy[20]. Older patients should be acknowledged as a special cohort with diminished physiologic reserve and resistance to stressors. Thus, their immune, pulmonary, and cardiovascular responses to an injury with a significant impact on elderly mortality and morbidity, such as acetabular fracture, could be significantly altered

compared to younger patients[30].

CONCLUSION

In summary, the contemporary literature is devoid of robust evidence to guide the most appropriate management of acetabular fractures in the elderly. There is currently a wide variation of management practices even amongst high-volume, experienced surgeons. The decision should be guided by the physiologic age and the comorbidities of the patient, the fracture configuration as well as the expertise and experience of the surgeon. Non-operative management is appropriate for particular patients, but prolonged bed rest should be avoided. Osteosynthesis is associated with good outcomes in selected patients but there is currently a trend toward a same-setting ORIF in combination with THA. Orthogeriatric co-management is essential and of paramount importance to achieve an overall optimal outcome in the fragile group of elderly patients who have sustained an acetabular fracture.

FOOTNOTES

Author contributions: Tosounidis T and Chalidis B designed the research, analyzed the data and wrote the paper; Both authors read and approved the final manuscript.

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

Country/Territory of origin: Greece

ORCID number: Theodoros Tosounidis 0000-0003-3939-0643; Byron Chalidis 0000-0003-1305-2734.

S-Editor: Che XX
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Fritz A**, Gericke L, Höch A, Josten C, Osterhoff G. Time-to-treatment is a risk factor for the development of pressure ulcers in elderly patients with fractures of the pelvis and acetabulum. *Injury* 2020; **51**: 352-356 [PMID: 31843198 DOI: 10.1016/j.injury.2019.12.007]
2 **Manson TT**, Reider L, O'Toole RV, Scharfstein DO, Tornetta P 3rd, Gary JL; Major Extremity Trauma Research Consortium (METRC). Variation in Treatment of Displaced Geriatric Acetabular Fractures Among 15 Level-I Trauma Centers. *J Orthop Trauma* 2016; **30**: 457-462 [PMID: 27218694 DOI: 10.1097/BOT.0000000000000632]
3 **Khoshbin A**, Atrey A, Chaudhry H, Nowak L, Melo LT, Stavrakis A, Schemitsch EH, Nauth A. Mortality Rate of Geriatric Acetabular Fractures Is High Compared With Hip Fractures. A Matched Cohort Study. *J Orthop Trauma* 2020; **34**: 424-428 [PMID: 32168201 DOI: 10.1097/BOT.0000000000001758]
4 **Stetzelberger VM**, Brouze IF, Steppacher SD, Bastian JD, Schwab JM, Tannast M. Lower 1-Year Postoperative Mortality After Acetabular Versus Proximal Femoral Fractures in Elderly Patients. *J Bone Joint Surg Am* 2021; **103**: 1807-1816 [PMID: 34019495 DOI: 10.2106/JBJS.20.01805]
5 **Firoozabadi R**, Cross WW, Krieg JC, Routt MLC. Acetabular Fractures in the Senior Population- Epidemiology, Mortality and Treatments. *Arch Bone Jt Surg* 2017; **5**: 96-102 [PMID: 28497099]
6 **Gary JL**, Paryavi E, Gibbons SD, Weaver MJ, Morgan JH, Ryan SP, Starr AJ, O'Toole RV. Effect of surgical treatment on mortality after acetabular fracture in the elderly: a multicenter study of 454 patients. *J Orthop Trauma* 2015; **29**: 202-208 [PMID: 25233162 DOI: 10.1097/BOT.0000000000000223]
7 **Deren ME**, Babu J, Cohen EM, Machan J, Born CT, Hayda R. Increased Mortality in Elderly Patients with Sarcopenia and Acetabular Fractures. *J Bone Joint Surg Am* 2017; **99**: 200-206 [PMID: 28145950 DOI: 10.2106/JBJS.16.00734]
8 **Mitchell PM**, Collinge CA, O'Neill DE, Bible JE, Mir HR. Sarcopenia Is Predictive of 1-Year Mortality After Acetabular Fractures in Elderly Patients. *J Orthop Trauma* 2018; **32**: 278-282 [PMID: 29533306 DOI: 10.1097/BOT.0000000000001159]
9 **Albrektsson M**, Möller M, Wolf O, Wennergren D, Sundfeldt M. Acetabular fractures: Epidemiology and mortality based on 2,132 fractures from the Swedish Fracture Register. *Bone Jt Open* 2023; **4**: 652-658 [PMID: 37652452 DOI: 10.1302/2633-1462.49.BJO-2023-0085.R1]
10 **Ryan SP**, Manson TT, Sciadini MF, Nascone JW, LeBrun CT, Castillo RC, Muppavarapu R, Schurko B, O'Toole RV. Functional Outcomes of Elderly Patients With Nonoperatively Treated Acetabular Fractures That Meet Operative Criteria. *J Orthop Trauma* 2017; **31**: 644-649 [PMID: 28742787 DOI: 10.1097/BOT.0000000000000990]
11 **Baker G**, McMahon SE, Warnock M, Johnston A, Cusick LA. Outcomes of conservatively managed complex acetabular fractures in the frail and elderly one year post injury. *Injury* 2020; **51**: 347-351 [PMID: 31843199 DOI: 10.1016/j.injury.2019.12.008]
12 **Tosounidis TH**, Giannoudis PV. What is new in acetabular fracture fixation? *Injury* 2015; **46**: 2089-2092 [PMID: 26515109 DOI:

10.1016/j.injury.2015.10.012]
13 **Manson T**, Schmidt AH. Acetabular Fractures in the Elderly: A Critical Analysis Review. *JBJS Rev* 2016; **4** [PMID: 27792674 DOI: 10.2106/JBJS.RVW.15.00090]
14 **Tosounidis TH**, Stengel D, Giannoudis PV. Anteromedial dome impaction in acetabular fractures: Issues and controversies. *Injury* 2016; **47**: 1605-1607 [PMID: 27499274 DOI: 10.1016/j.injury.2016.07.020]
15 **Sagi HC**, Afsari A, Dziadosz D. The anterior intra-pelvic (modified rives-stoppa) approach for fixation of acetabular fractures. *J Orthop Trauma* 2010; **24**: 263-270 [PMID: 20418730 DOI: 10.1097/BOT.0b013e3181dd0b84]
16 **Keel MJB**, Siebenrock KA, Tannast M, Bastian JD. The Pararectus Approach: A New Concept. *JBJS Essent Surg Tech* 2018; **8**: e21 [PMID: 30588366 DOI: 10.2106/JBJS.ST.17.00060]
17 **Capone A**, Peri M, Mastio M. Surgical treatment of acetabular fractures in the elderly: a systematic review of the results. *EFORT Open Rev* 2017; **2**: 97-103 [PMID: 28507782 DOI: 10.1302/2058-5241.2.160036]
18 **Daurka JS**, Pastides PS, Lewis A, Rickman M, Bircher MD. Acetabular fractures in patients aged > 55 years: a systematic review of the literature. *Bone Joint J* 2014; **96-B**: 157-163 [PMID: 24493178 DOI: 10.1302/0301-620X.96B2.32979]
19 **Antell NB**, Switzer JA, Schmidt AH. Management of Acetabular Fractures in the Elderly. *J Am Acad Orthop Surg* 2017; **25**: 577-585 [PMID: 28737617 DOI: 10.5435/JAAOS-D-15-00510]
20 **McCormick BP**, Serino J, Orman S, Webb AR, Wang DX, Mohamadi A, Mortensen S, Weaver MJ, Von Keudell A. Treatment modalities and outcomes following acetabular fractures in the elderly: a systematic review. *Eur J Orthop Surg Traumatol* 2022; **32**: 649-659 [PMID: 34076747 DOI: 10.1007/s00590-021-03002-3]
21 **Manson TT**. Open Reduction and Internal Fixation Plus Total Hip Arthroplasty for the Acute Treatment of Older Patients with Acetabular Fracture: Surgical Techniques. *Orthop Clin North Am* 2020; **51**: 13-26 [PMID: 31739876 DOI: 10.1016/j.ocl.2019.08.006]
22 **Giustra F**, Cacciola G, Pirato F, Bosco F, De Martino I, Sabatini L, Rovere G, Camarda L, Massè A. Indications, complications, and clinical outcomes of fixation and acute total hip arthroplasty for the treatment of acetabular fractures: A systematic review. *Eur J Orthop Surg Traumatol* 2024; **34**: 47-57 [PMID: 37640795 DOI: 10.1007/s00590-023-03701-z]
23 **Tu TY**, Chen CY, Lin PC, Hsu CY, Lin KC. Comparison of primary total hip arthroplasty with limited open reduction and internal fixation vs open reduction and internal fixation for geriatric acetabular fractures: a systematic review and meta-analysis. *EFORT Open Rev* 2023; **8**: 532-547 [PMID: 37395715 DOI: 10.1530/EOR-21-0099]
24 **Jauregui JJ**, Weir TB, Chen JF, Johnson AJ, Sardesai NR, Maheshwari AV, Manson TT. Acute total hip arthroplasty for older patients with acetabular fractures: A meta-analysis. *J Clin Orthop Trauma* 2020; **11**: 976-982 [PMID: 33191999 DOI: 10.1016/j.jcot.2020.01.003]
25 **Sermon A**, Broos P, Vanderschot P. Total hip replacement for acetabular fractures. Results in 121 patients operated between 1983 and 2003. *Injury* 2008; **39**: 914-921 [PMID: 18599057 DOI: 10.1016/j.injury.2007.12.004]
26 **Nicol GM**, Sanders EB, Kim PR, Beaulé PE, Gofton WT, Grammatopoulos G. Outcomes of Total Hip Arthroplasty After Acetabular Open Reduction and Internal Fixation in the Elderly-Acute vs Delayed Total Hip Arthroplasty. *J Arthroplasty* 2021; **36**: 605-611 [PMID: 32919846 DOI: 10.1016/j.arth.2020.08.022]
27 **De Vincentis A**, Behr AU, Bellelli G, Bravi M, Castaldo A, Galluzzo L, Iolascon G, Maggi S, Martini E, Momoli A, Onder G, Paoletta M, Pietrogrande L, Roselli M, Ruggeri M, Ruggiero C, Santacaterina F, Tritapepe L, Zurlo A, Antonelli Incalzi R; Società Italiana Geriatria e Gerontologia (SIGG); Associazione Italiana di Psicogeriatria (AIP); Società Italiana di Geriatria Ospedale e Territorio (SIGOT); Società Italiana di Medicina Generale (SIMG); Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva (SIAARTI); Società Italiana di Ortopedia e Traumatologia (SIOT); Fragility Fracture Network-Italia (FFN-I); Società Italiana di Medicina Fisica e Riabilitativa (SIMFER); Società Italiana di Fisioterapia (SIF); Consiglio Nazionale delle Ricerche (CNR); Associazione Italiana di Fisioterapia (AIFI); Istituto Superiore Sanità (ISS). Orthogeriatric co-management for the care of older subjects with hip fracture: recommendations from an Italian intersociety consensus. *Aging Clin Exp Res* 2021; **33**: 2405-2443 [PMID: 34287785 DOI: 10.1007/s40520-021-01898-9]
28 **Fluck B**, Yeong K, Lisk R, Watters H, Robin J, Fluck D, Fry CH, Han TS. Changes in Characteristics and Outcomes of Patients Undergoing Surgery for Hip Fractures Following the Initiation of Orthogeriatric Service: Temporal Trend Analysis. *Calcif Tissue Int* 2022; **110**: 185-195 [PMID: 34448887 DOI: 10.1007/s00223-021-00906-4]
29 **Javaid MK**, Sami A, Lems W, Mitchell P, Thomas T, Singer A, Speerin R, Fujita M, Pierroz DD, Akesson K, Halbout P, Ferrari S, Cooper C. A patient-level key performance indicator set to measure the effectiveness of fracture liaison services and guide quality improvement: a position paper of the IOF Capture the Fracture Working Group, National Osteoporosis Foundation and Fragility Fracture Network. *Osteoporos Int* 2020; **31**: 1193-1204 [PMID: 32266437 DOI: 10.1007/s00198-020-05377-1]
30 **Bradburn E**, Rogers FB, Krasne M, Rogers A, Horst MA, Beelen MJ, Miller JA. High-risk geriatric protocol: improving mortality in the elderly. *J Trauma Acute Care Surg* 2012; **73**: 435-440 [PMID: 22846952 DOI: 10.1097/TA.0b013e31825c7cf4]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2157-2159

DOI: 10.12998/wjcc.v12.i13.2157

ISSN 2307-8960 (online)

EDITORIAL

Pioneering role of machine learning in unveiling intensive care unit-acquired weakness

Silvano Dragonieri

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): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Juneja D, India

Received: February 21, 2024
Peer-review started: February 23, 2024
First decision: March 6, 2024
Revised: March 7, 2024
Accepted: March 27, 2024
Article in press: March 27, 2024
Published online: May 6, 2024

Silvano Dragonieri, Department of Respiratory Diseases, University of Bari, Bari 70124, Italy

Corresponding author: Silvano Dragonieri, MD, PhD, Associate Professor, Department of Respiratory Diseases, University of Bari, Piazza Giulio Cesare 11, Bari 70124, Italy. silvano.dragonieri@uniba.it

Abstract

In the research published in the *World Journal of Clinical Cases*, Wang and Long conducted a quantitative analysis to delineate the risk factors for intensive care unit-acquired weakness (ICU-AW) utilizing advanced machine learning methodologies. The study employed a multilayer perceptron neural network to accurately predict the incidence of ICU-AW, focusing on critical variables such as ICU stay duration and mechanical ventilation. This research marks a significant advancement in applying machine learning to clinical diagnostics, offering a new paradigm for predictive medicine in critical care. It underscores the importance of integrating artificial intelligence technologies in clinical practice to enhance patient management strategies and calls for interdisciplinary collaboration to drive innovation in healthcare.

Key Words: Intensive care unit-acquired weakness; Machine learning; Multilayer perceptron neural network; Predictive medicine; Interdisciplinary collaboration

Core Tip: This editorial leverages machine learning, specifically a multilayer perceptron neural network, to pinpoint key risk factors for intensive care unit-acquired weakness (ICU-AW), emphasizing the critical roles of ICU stay duration and mechanical ventilation. It heralds a paradigm shift towards data-driven, predictive medicine in critical care, advocating for the integration of artificial intelligence in clinical practices and interdisciplinary collaboration to enhance patient care outcomes.

Citation: Dragonieri S. Pioneering role of machine learning in unveiling intensive care unit-acquired weakness. *World J Clin Cases* 2024; 12(13): 2157-2159
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2157.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2157

INTRODUCTION

In the groundbreaking study published in the *World Journal of Clinical Cases*, Wang and Long[1] embark on an exploratory journey through the complex landscape of intensive care unit-acquired weakness (ICU-AW), employing the sophisticated lens of machine learning to uncover its hidden contours. This investigation illuminates the significant risk factors associated with ICU-AW, utilizing the robust capabilities of a multilayer perceptron neural network model to forecast the onset of this debilitating condition with remarkable precision[2]. The meticulous analysis presented in this study not only sheds light on the pivotal factors such as the duration of ICU stay and the extent of mechanical ventilation but also heralds a new era in the application of iterative machine learning within the realm of clinical diagnostics and therapeutic strategies.

The integration of machine learning algorithms in this research signifies a monumental stride towards the advancement of medical science, particularly within the critical care domain. The data-driven approach adopted by the researchers permits a nuanced understanding of the myriad factors influencing the development of ICU-AW, a condition that profoundly impacts the recovery trajectory of patients[2]. The construction of a predictive model through this study stands as a testament to the transformative potential of artificial intelligence, marking a significant departure from traditional diagnostic and prognostic methods in medicine.

Furthermore, this research extends an invitation to the global medical community to embrace the integration of machine learning and artificial intelligence technologies into everyday clinical practices[3]. The insights garnered from such predictive models can significantly enhance decision-making processes, offering the potential to mitigate the incidence of ICU-AW through timely and targeted interventions. This study also underscores the critical importance of fostering interdisciplinary collaboration across the fields of clinical medicine, data science, and machine learning, paving the way for holistic advancements in healthcare delivery.

CONCLUSION

As we delve into the details of this study, we uncover the profound implications it holds for the prevention and management of ICU-AW. The research by Wang and Long[1] stands as a beacon of innovation, exemplifying the immense promise machine learning holds in redefining healthcare. Through the lens of precision medicine and predictive healthcare models, this study not only contributes invaluable insights to the field of critical care medicine but also sets the stage for the future integration of advanced technologies in enhancing patient care and outcomes. As the healthcare landscape continues to evolve, the role of machine learning in shaping the future of medical interventions and patient management becomes increasingly indispensable[3].

This study, therefore, is not merely an academic exercise but a clarion call for the medical community to venture beyond the conventional boundaries and explore the vast expanse of possibilities that machine learning and artificial intelligence offer. In doing so, it beckons a paradigm shift in the approach to patient care, emphasizing the need for a more predictive, personalized, and proactive healthcare ecosystem. The journey embarked upon by Wang and Long[1] through this study is a testament to the inventiveness and foresight necessary to navigate the complexities of modern medicine, heralding a new dawn in the fight against ICU-AW and beyond.

FOOTNOTES

Author contributions: Dragonieri S conceived and wrote the entire manuscript.

Conflict-of-interest statement: The author has no conflicts of interest to declare.

Country/Territory of origin: Italy

ORCID number: Silvano Dragonieri 0000-0003-1563-6864.

S-Editor: Zheng XM
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Wang L**, Long DY. Significant risk factors for intensive care unit-acquired weakness: A processing strategy based on repeated machine

learning. *World J Clin Cases* 2024; **12**: 1235-1242 [DOI: 10.12998/wjcc.v12.i7.1235]

2 **MacEachern SJ**, Forkert ND. Machine learning for precision medicine. *Genome* 2021; **64**: 416-425 [PMID: 33091314 DOI: 10.1139/gen-2020-0131]

3 **Haug CJ**, Drazen JM. Artificial Intelligence and Machine Learning in Clinical Medicine, 2023. *N Engl J Med* 2023; **388**: 1201-1208 [PMID: 36988595 DOI: 10.1056/NEJMra2302038]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2160-2172

DOI: 10.12998/wjcc.v12.i13.2160

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Case Control Study

Detection and analysis of serum bile acid profile in patients with colonic polyps

Xin Ji, Hong Chen

Specialty type: Gastroenterology and hepatology

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: Wu YH, Taiwan

Received: December 14, 2023
Peer-review started: December 14, 2023
First decision: February 12, 2024
Revised: February 21, 2024
Accepted: March 28, 2024
Article in press: March 28, 2024
Published online: May 6, 2024

Xin Ji, School of Medicine, Southeast University, Nanjing 210009, Jiangsu Province, China

Hong Chen, Department of Gastroenterology, Zhongda Hospital Southeast University, Nanjing 210009, Jiangsu Province, China

Corresponding author: Hong Chen, Doctor, Professor, Department of Gastroenterology, Zhongda Hospital Southeast University, No. 87 Dingjiaqiao, Gulou District, Nanjing 210009, Jiangsu Province, China. njchenhong66@163.com

Abstract

BACKGROUND

Analyzing the variations in serum bile acid (BA) profile can provide a certain biological basis for early warning and prevention of various diseases. There is currently no comprehensive study on the relationship between the serum BA profile and colonic polyps.

AIM

To study the serum BA profile detection results of patients with colonic polyps, and analyze the correlation between BA and colonic polyps.

METHODS

From January 1, 2022, to June 1, 2023, 204 patients with colonic polyps who were diagnosed and treated at Zhongda Hospital Southeast University were chosen as the study subjects, and 135 non-polyp people who underwent physical examination were chosen as the control group. Gathering all patients' clinical information, typical biochemical indicators, and BA profile.

RESULTS

Compared with the control group, the serum levels of taurocholic acid, glycocholic acid, glycochenodeoxycholic acid, and taurochenodeoxycholic acid in the colonic polyp group were significantly higher than those in the control group, while the content of deoxycholic acid (DCA) was lower than that in the control group ($P < 0.05$). When colonic polyps were analyzed as subgroups, it was shown that there was a strong correlation between changes in the BA profile and polyp diameter, location, morphology, pathological kind, *etc.*

CONCLUSION

The serum BA profile showed significant changes in patients with colonic polyps,

with a significant increase in primary conjugated BA content and a decrease in secondary free bile acid DCA content. There is a certain correlation between primary free BA and pathological parameters of polyps.

Key Words: Serum; Bile acid profile; Colonic polyps; Bile acid metabolism

Core Tip: This study shows that the serum primary conjugated bile acid (BA) levels in the colonic polyp group were significantly higher than those in the control group ($P < 0.05$), while the secondary free BA, deoxycholic acid content was lower than that in the control group. Patients with various polyp sizes, locations, morphologies, and pathological types had variable serum BA profile, according to subgroup study of colonic polyps. Therefore, analyzing the changes in serum BA profile may provide new ideas for finding new targets for the treatment of colonic tumors.

Citation: Ji X, Chen H. Detection and analysis of serum bile acid profile in patients with colonic polyps. *World J Clin Cases* 2024; 12(13): 2160-2172
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2160.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2160

INTRODUCTION

Colonic polyps are lesions that protrude from the mucosal surface into the large intestine lumen, and they can be further classified into adenomatous polyps and non-adenomatous polyps based on their pathology[1]. The second-highest death rate of all malignancies is associated with colon cancer, which is the third most frequent malignancy worldwide[2]. Colonic polyps are precancerous lesions of colonic cancer, especially adenomatous polyps. Over 50% of colonic cancer is derived from adenomas, which make up about two-thirds of colonic polyps[3]. Early-stage colon cancer is typically found *via* a colonoscopy and does not typically present with any overt clinical symptoms. The incidence of colonic cancer can be decreased and the survival rate increased by early detection of precancerous lesions, early diagnosis, and early treatment. At present, the initial diagnosis of the disease mainly relies on endoscopic examination, further diagnosis requires pathological biopsy[4]. Therefore, finding ways to lessen them and enhancing the degree of non-invasive colonic polyp identification and treatment can help to some extent reduce the incidence of colonic cancer.

Bile acid (BA) is a major component of bile, synthesized by cholesterol in the liver and stored in the gallbladder. It is secreted into the small intestine after eating to promote the digestion and absorption of lipids and lipophilic vitamins[5]. Meanwhile, as a cellular signaling molecule, BA also regulates biological processes by stimulating various signaling pathways, participating in the regulation of glucose metabolism, energy homeostasis, and immune response in the body. Analyzing the variations in serum BA profile can provide a certain biological basis for early warning and prevention of various diseases. There is currently no comprehensive study on the relationship between the serum bile acid profile and colonic polyps, despite the fact that numerous studies have demonstrated that high levels of total bile acid (TBA) are a risk factor for colonic cancer[6]. In this study, the levels of 15 serum BA components were compared between patients with colonic polyps and healthy people. Additionally, alterations in the serum BA profile of patients with colonic polyps were initially explored, and the relationship between BA components and colonic polyps was analyzed.

MATERIALS AND METHODS

Research object

204 individuals who were hospitalized and diagnosed with colonic polyps at Zhongda Hospital Southeast University between January 1, 2022, and June 1, 2023 were chosen as the colonic polyp group by reviewing the electronic medical record system. There were 114 men and 90 women in this group, with an average age of (57.19 ± 9.43) years. Inclusion criteria: (1) Patients with pathological diagnosis of colonic polyps through colonoscopy, aged between 30 and 75 years old; and (2) Routine biochemical tests and serum BA profile have been completed before undergoing colonoscopy. Exclusion criteria: (1) Previous history of inflammatory bowel disease; (2) Previous intestinal surgery (excluding appendectomy); (3) Previous liver and biliary system diseases, such as viral liver disease, cirrhosis, autoimmune hepatitis, sclerosing cholangitis, *etc*.; (4) Severe cardiopulmonary and renal dysfunction; (5) Patients with other malignant tumors; and (6) Patients who have received chemotherapy or immunotherapy. The control group consisted of up of 135 healthy people who were examined by colonoscopy in our institution throughout the same time period but were not found to have any significant abnormalities. They had an average age of (55.35 ± 8.79) years, with 61 men and 74 women. The exclusion criteria are the same as those for the colonic polyp group. This study was approved by the Ethics Committee of Zhongda Hospital (2021ZDSYLL297-P01). Retrospective study without informed consent.

Research methods

Gathering demographic data and clinical test results about the research subjects, such as age, gender, body mass index (BMI), alanine transaminase (ALT), aspartate transaminase (AST), total cholesterol (TC), and serum BA profile. Additionally, gathering the pathological characteristics of colonic polyps, including their number, size, location, and whether or not they have a pedicle. 15 different types of BA were identified in the BA profile using high-performance liquid chromatography tandem mass spectrometry (LC-MS/MS), including: (1) Primary free BAs: cholic acid (CA), chenodeoxycholic acid (CDCA); (2) Primary conjugated BAs: Taurocholic acid (TCA), glycocholic acid (GCA), taurochenodeoxycholic acid (TCDCA), glycochenodeoxycholic acid (GCDCA); (3) Secondary free BAs: Deoxycholic acid (DCA), ursodeoxycholic acid (UDCA), lithocholic acid (LCA); and (4) Secondary conjugated BAs: Tauroursodeoxycholic acid (TDCA), glycodeoxycholic acid (GDCA), tauroursodeoxycholic acid (TUDCA), glycoursodeoxycholic acid (GUDCA), taurolithocholic acid (TLCA), and glycolithocholic acid (GLCA).

Statistical analysis

Statistical analysis was conducted using SPSS 26.0 software. The normality test of the data was conducted using the Kolmogorov-Smirnon test. The measurement data of normal distribution was expressed by mean ± SD, and the comparison between the two groups is conducted using independent sample *t*-test. The measurement data of skewed distribution were represented by median and interquartile spacing [M (P25, P75)]. The independent sample non parametric Mann Whitney *U* test is used for comparison between the two groups, and the Kruskal-Wallis *H* rank sum test is used for comparison between multiple groups. Chi-square test was used for counting data between groups. The risk factors for colonic polyps were analyzed using univariate and multivariate logistic regression analysis, and the results were expressed using odds ratio (OR) and 95% Confidence Interval (95%CI). P values < 0.05 were considered statistically significant. Using the MetaboAnalyst platform to draw heat maps, perform orthogonal partial least squares discriminant analysis (OPLS-DA), and calculate the variable importance in projection (VIP) of predicted variables; And combined with SPSS 26.0 software for analysis, differential BA components were screened under conditions of P < 0.05 and VIP > 1.

RESULTS

Comparison of research subjects' overall situations

In this retrospective analysis, 204 people made up the colonic polyp group and 135 people made up the control group. Age, BMI, gender, ALT, AST, and TC did not statistically differ between the two groups (P > 0.05), demonstrating comparability (Table 1).

Comparison of serum TBA levels between colonic polyp group and control group

The TBA content did not differ statistically significantly between the colonic polyp group and the control group, according to an analysis of the 15 different forms of BA present in the serum of the two groups (Colonic polyp group: 2990.100 (1384.950, 5489.750), Control group: 2490.500 (1337.300, 4519.400), P = 0.138).

Comparison of differences in serum BA composition between colonic polyp group and control group

The results of two sets of BA profile detection are shown in Table 2. Using the OPLS-DA model to search for differential metabolites between the colonic polyp group and the control group, it can be observed from the score chart (Figure 1A) that the sample points of the two groups are relatively concentrated, and the differences between the data groups are not significant. To further screen for BA with discrepancies, use VIP values (Figure 1B). It is evident that the two groups' BAs differ in the following ways: GDCA, DCA, GCA, GCDCA, TCA, TCDCA (VIP > 1). DCA, GCA, GCDCA, TCA, and TCDCA were all statistically different (P < 0.05) between the two groups, according to SPSS software analysis. While the concentration of DCA was lower than that of the control group, it was significantly greater than that of GCDCA, GCA, TCA, and TCDCA in the colonic polyp group. The other BA components (Table 2) showed no statistically significant change (P > 0.05). Differential BA components GCA, GCDCA, TCA, TCDCA, and DCA were screened under the conditions of P < 0.05 and VIP > 1. Additionally, the heat map (Figure 2) can be used to reference the expression of BA profiles in distinct samples.

Analysis of the relationship between serum BA levels and clinical pathological parameters of colonic polyps

Colonic polyps can be classified using subgroup analysis in accordance with different pathological types, numbers, sizes, locations, and shapes (Table 3). Through subgroup analysis, we found that: (1) In terms of CA, CDCA, UDCA, and TUDCA, there was a statistically difference (P < 0.05) between the adenomatous colonic group and the non-adenomatous polyp group. In comparison to the non-adenomatous polyp group, the CA, CDCA, UDCA, and TUDCA content in the adenomatous polyp group was lower (Table 4); (2) There is no statistical difference in the composition of BA between the single and multiple groups (P > 0.05) (Table 5); (3) There was a statistical difference (P < 0.05) between the two groups with polyp diameter < 1 cm and ≥ 1 cm in CA, CDCA, UDCA, GUDCA, and TUDCA, and the content of CA, CDCA, UDCA, GUDCA, and TUDCA in the group with polyp diameter ≥ 1cm was higher than that in the group with polyp diameter < 1 cm (Table 6); (4) There were statistical differences (P < 0.05) among CA, CDCA, GCA, and GCDCA in the left colon group, right colon group, and total colon group (Table 7). Through pairwise analysis, it was found that there was a significant statistical difference in GCDCA between the left and right colon groups (P = 0.008), and the GCDCA content in the right colon group was significantly higher than that in the left colon group; There was a significant statistical di-

Table 1 Comparison of general conditions between the colonic polyp group and the control group, *n* (%)

General information	Colonic polyp group (*n* = 204)	Control group (*n* = 135)	*P* value
Age (year)	57.19 ± 9.43	55.35 ± 8.79	0.072
BMI (kg/m^2)	23.82 ± 2.28	23.52 ± 2.37	0.244
Gender			0.054
Males	114 (55.88)	61 (45.19)	
Females	90 (44.12)	74 (54.81)	
ALT (U/L)	18.00 (13.00, 26.00)	17.00 (13.00, 24.00)	0.277
AST (U/L)	20.00 (17.00, 24.00)	19.00 (16.00, 23.00)	0.155
TC (mmol/L)	4.49 ± 0.84	4.56 ± 0.91	0.463

BMI: Body mass index; ALT: Alanine transaminase; AST: Aspartate transaminase; TC: Total cholesterol; Reference value range: ALT 9-50U/L; AST 15-40U/L; TC 0.00-6.20 mmol/L.

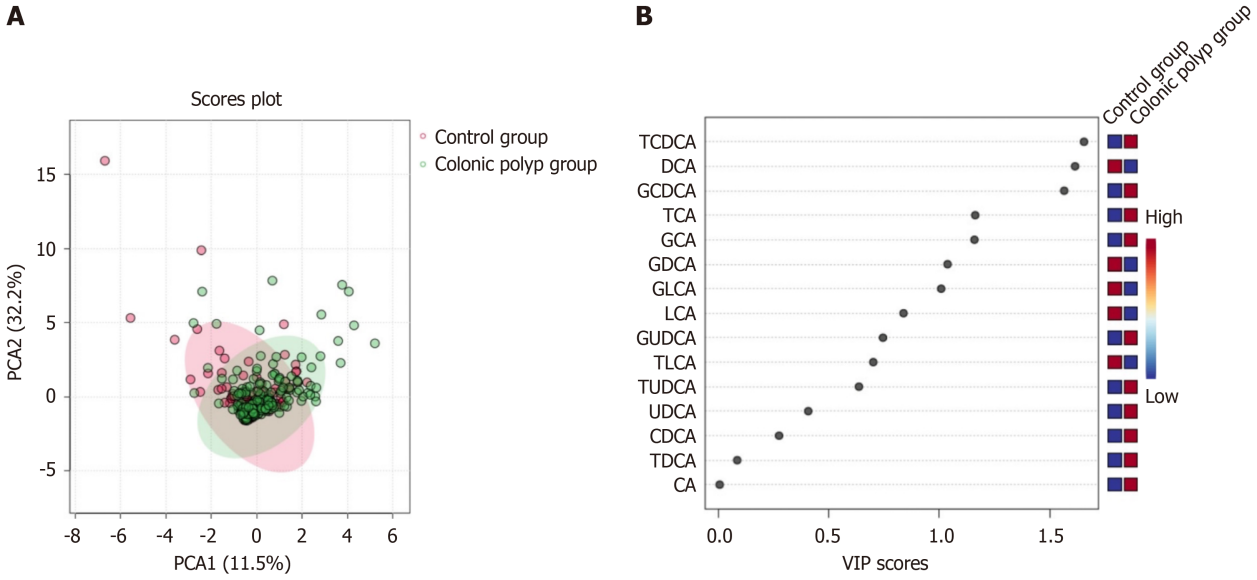

Figure 1 Orthogonal partial least squares discriminant analysis of the control group and colonic polyp group. A: Score map; B: Variable importance in projection score map. PCA: Principal Component Analysis; CA: Cholic acid; CDCA: Chenodeoxycholic acid; TCA: Taurocholic acid; GCA: Glycocholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; DCA: Deoxycholic acid; UDCA: Ursodeoxycholic acid; LCA: Lithocholic acid; TDCA: Tauroursodeoxycholic acid; GDCA: Glycodeoxycholic acid; TUDCA: Tauroursodeoxycholic acid; GUDCA: Glycoursodeoxycholic acid; TLCA: Taurolithocholic acid; GLCA: Glycolithocholic acid.

fference (P = 0.000) between the left colon group and the whole colon group in terms of CA content. The content of CA in the left colon group was significantly higher than that in the whole colon group; There is a statistical difference between the right colon group and the whole colon group in terms of CA (P = 0.008), GCA (P = 0.005), and GCDCA (P = 0.015). The content of CA, GCA, and GCDCA in the right colon group is significantly higher than that in the whole colon group; and (5) There was a statistical difference (P < 0.05) between the pedicle polyp group and the sessile polyp group in terms of CA, CDCA, UDCA, and GUDCA. The content of CA, CDCA, UDCA, and GUDCA in the pedicle polyp group was significantly higher than that in the sessile polyp group (Table 8). Therefore, we speculate that the changes in BA profile are closely related to polyp diameter, polyp site, polyp morphology, pathological type, *etc.*

Logistic regression model analysis of risk factors for colonic polyps

A univariate logistic regression analysis using the presence or absence of colonic polyps as the dependent variable and other indicators as the independent variables was carried out to evaluate the risk factors for colonic polyps. The results showed that CDCA (B = 0.000, OR = 1.000), GCDCA (B = 0.000, OR = 1.000), and primary BA (B = 0.000, OR = 1.000) were associated with the risk of colonic polyps and were risk factors for colonic polyps (P < 0.05), as shown in Table 9. The results of multivariate logistic regression analysis using the statistically differences in the aforementioned univariate analysis indicators revealed that CDCA, GCDCA and primary BA were not independent risk factors for the development of colonic polyps (P > 0.05).

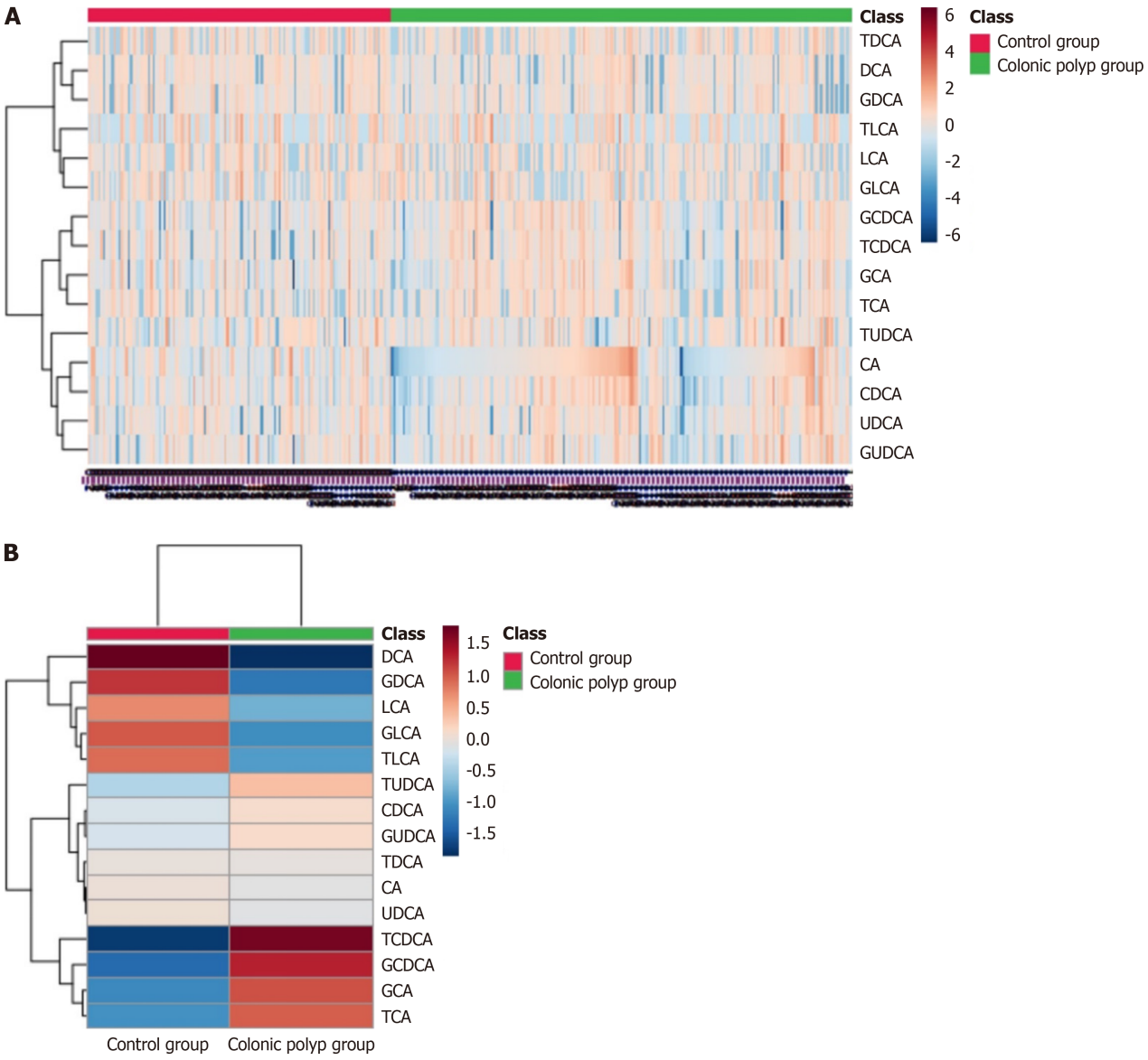

Figure 2 Heat map analysis of the serum bile acid profile of the subjects. A: The values of each sample; B: The average values of each group. The abscissa represents the sample size, and the ordinate represents the bile acid (BA) profile. The main part represents the expression of BA profile in the sample, and the color in the heat map reflects the changes in the content of BA profile. Figure 2A shows the values of each sample, while Figure 2B shows the average values of each group. CA: Cholic acid; CDCA: Chenodeoxycholic acid; TCA: Taurocholic acid; GCA: Glycocholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; DCA: Deoxycholic acid; UDCA: Ursodeoxycholic acid; LCA: Lithocholic acid; TDCA: Tauroursodeoxycholic acid; GDCA: Glycodeoxycholic acid; TUDCA: Tauroursodeoxycholic acid; GUDCA: Glycoursodeoxycholic acid; TLCA: Taurolithocholic acid; GLCA: Glycolithocholic acid.

DISCUSSION

This study found that compared with the control group, the serum primary conjugated BAs, TCA, GCA, GCDCA, and TCDCA levels in the colonic polyp group were significantly higher than those in the control group ($P < 0.05$), while the secondary free BAs, DCA content was lower than that in the control group. Kühn *et al*[7] included 581 cases of primary colonic cancer diagnosed between 1993 and 2008, found that five primary conjugated BAs, GCA, TCA, GCDCA, TCDCA, and GHCA, as well as two secondary conjugated BAs, GDCA and TDCA were positively correlated with colonic cancer risk. Experts believed that an increase in primary conjugated BAs can promote the occurrence of colonic cancer, and the outcomes of this investigation supported those of our study. The concentration of fecal BA is the main subject of several relevant investigations. Sun *et al*[8] demonstrated that CDCA, DCA, and LCA increased in the feces of colon cancer patients whereas GCDCA decreased. By comparing the Alaskan aboriginals (AN) with the highest incidence rate of colonic cancer and the African rural people (RA) with the lowest incidence rate, Ocvirk *et al*[9] discovered that the detection rate of colonic polyps in the AN population was higher than that in the RA population, and the concentration of DCA, CA, and CDCA in the AN population's feces was also significantly higher than that of the RA sample. Kawano *et al*[10] compared the concentration of BA in fecal samples from 366 patients who underwent endoscopic resection of colonic tumors (tumor group) and 24 control groups (control group) with no abnormalities in the large intestine, and followed up the tumor group. The findings revealed that while there was no change in CA levels between the two groups, the fecal

Table 2 Detection results of serum bile acid profiles in the colonic polyp group and the control group (nmol/L)

BA components	Colonic polyp group (*n* = 204)	Control group (*n* = 135)	*P* value
Primary free BAs			
CA	62.75 (24.33, 232.00)	53.80 (27.60, 149.00)	0.571
CDCA	382.50 (105.50, 851.50)	294.00 (130.00, 625.00)	0.164
Primary conjugated BAs			
TCA	21.85 (5.50, 50.50)	12.70 (1.50, 32.30)	0.015[a]
GCA	166.50 (76.60, 330.00)	126.00 (52.90, 234.00)	0.025[a]
GCDCA	935.50 (430.50, 1967.50)	708.00 (298.00, 1250.00)	0.005[a]
TCDCA	74.35 (27.20, 164.50)	41.60 (18.30, 119.00)	0.006[a]
Secondary free BAs			
DCA	142.00 (30.90, 424.25)	234.00 (82.60, 502.00)	0.011[a]
LCA	6.20 (0.13, 17.10)	6.40 (0.60, 21.00)	0.539
UDCA	73.70 (23.03, 221.50)	70.70 (19.00, 199.00)	0.545
Secondary conjugated BAs			
TDCA	8.50 (0.05, 32.65)	7.70 (0.00, 35.30)	0.615
GDCA	113.50 (12.08, 248.50)	125.00 (34.60, 335.00)	0.274
TLCA	0.00 (0.00, 2.40)	0.10 (0.00, 4.00)	0.255
GLCA	4.60 (0.00, 16.35)	5.40 (0.00, 18.10)	0.399
TUDCA	7.65 (3.15, 15.00)	8.20 (2.50, 15.00)	0.369
GUDCA	137.50 (47.25, 343.00)	122.00 (63.80, 283.00)	0.604

[a]$P < 0.05$, there is a statistical difference in this indicator between the two groups.

BA: Bile acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid; TCA: Taurocholic acid; GCA: Glycocholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; DCA: Deoxycholic acid; UDCA: Ursodeoxycholic acid; LCA: Lithocholic acid; TDCA: Tauroursodeoxycholic acid; GDCA: Glycodeoxycholic acid; TUDCA: Tauroursodeoxycholic acid; GUDCA: Glycoursodeoxycholic acid; TLCA: Taurolithocholic acid; GLCA: Glycolithocholic acid.

DCA levels in the tumor group were considerably greater than those in the control group. In the tumor group, the subgroup with high fecal DCA levels is more likely than the subgroup with low DCA levels to experience a recurrence of large adenomas (> 3 mm) after four years. On the basis of the aforementioned studies, we discovered that DCA may be linked to the development of colonic cancers, particularly when fecal DCA concentration rises and serum DCA concentration falls. On the pattern of alterations in other BA components in colon cancer patients, there is yet no unified conclusion. The outcomes of various research detection and analysis varies substantially. However, it is evident that colon cancer patients' serum BA profiles have changed from those of healthy people, and that these alterations in the BA spectrum are somewhat correlated with the formation and progression of colon cancer.

Previous studies have analyzed the role and mechanism of BA profile in the occurrence and development of colonic tumors. The commonly accepted theory holds that while increasing the concentration of UDCA may restrict the onset and development of cancers, increasing the concentration of DCA in the BA profile may promote the emergence of colonic malignancies[11,12]. In 1940, DCA was first proven to be a carcinogen capable of causing mouse colonic cancer[11]. It can induce excessive proliferation of colonic epithelium, disrupt cell membranes, promote excessive production of reactive oxygen species and reactive nitrogen species, cause oxidative stress, damage DNA, induce gene mutations, and nuclear factor kappa B (NF-κB) activation by activating epidermal growth factor receptor and protein kinase C leads to pathological changes in the tissue[13]. The activation of NF-κB in intestinal inflammation can induce the expression of cytokines to support inflammation related tissue damage, such as tumor necrosis factor alpha, interleukin-6, and other chemokines. Therefore, NF-κB may also promote the occurrence of colonic cancer by maintaining a continuous inflammatory process in the intestinal tissue[14]. In addition, studies[15] have found that DCA induces β-catenin signaling increases the expression of cyclin D1 involved in cell cycle progression, degrades tumor suppressor p53, promotes resistance to cell apoptosis, increases cell proliferation and invasion, ultimately leads to the development and further malignant transformation of adenomas[16]. The study by Liu *et al*[17] provides a new perspective that DCA plays a role in intestinal tumors by regulating the intestinal barrier. By feeding DCA to $Apc^{min/+}$ mice, it was found that the number and size of adenomas in their intestines increased, and the adenoma adenocarcinoma sequence increased. In addition, cytoplasmic tight adhesin-1 and intestinal cells, such as goblet cells and Paneth cells, were found to be decreased in the intestinal mucosa of mice treated with DCA. Secretory immunoglobulin A levels were also shown to be significantly

Table 3 Clinical and pathological parameters of colonic polyps in the polyp group

Group	Cases, *n* (%)
Pathological type	
Adenomatous polyp	
Tubular adenoma	30 (14.71)
Villous tubular adenoma	109 (53.43)
High grade intraepithelial neoplasia	6 (2.94)
Non adenomatous polyp	
Hyperplastic polyp	59 (28.92)
Number of polyps	
Single polyp	73 (35.78)
Multiple polyps	131 (64.22)
Size of polyp	
Diameter < 1 cm	169 (82.84)
Diameter ≥ 1 cm	35 (17.16)
Location of polyp	
Left colon	114 (55.88)
Right colon	48 (23.53)
Total colon	42 (20.59)
The polyp is pedicled or not	
Pedicled polyp	22 (10.78)
Sessile polyp	182 (89.22)

If the patient has multiple polyps in the colon, the grouping of polyp size is based on the maximum polyp diameter in the colon; If there is a pedunculated polyp, it will be classified as a pedunculated group. Polyps can be seen in the ascending colon, transverse colon, descending colon, and sigmoid colon in the whole colon group. If proliferative polyps and adenomatous polyps coexist in the pathological report of polyps, they are classified as adenomatous polyps.

reduced. According to the findings, DCA can damage the intestinal mucosa's mechanical and immune defenses, promote cell proliferation, prevent cell apoptosis, and exacerbate the occurrence of intestinal tumors. UDCA is believed to inhibit the occurrence of colonic cancer[12]. Patients with colonic adenomas who have taken UDCA for a long time have a lower probability of recurrence after resection of colonic adenomas, and the proliferation of colonic epithelium is significantly reduced[18]. In the azoxymethane (AOM) model of experimental rodent colonic cancer, Khare *et al*[19] discovered that DCA greatly promotes tumor formation, but UDCA can inhibit DCA-induced p38 activation and reduce CCAAT/enhancer binding protein beta upregulation of cyclooxygenase-2, hence limiting the carcinogenesis of AOM. In addition, activator protein 1 (AP-1) and NF-κB activation caused by DCA can likewise be inhibited by UDCA[20]. Interventions targeting NF-κB and AP-1 may play an important role in inhibiting the growth of colonic cancer. The Hippo/Yes Associated Protein (YAP) pathway plays an important role in the development of cancer. In AOM/dextran sodium sulfate induced colonic cancer models, UDCA can be found to reduce YAP expression in a concentration dependent manner, inhibiting tumor growth[21]. In this study, the serum DCA content of patients with colonic polyps was lower than that of the control group (colonic polyp group: 142.00 (30.90424.25), control group: 234.00 (82.60502.00), P = 0.011), while the UDCA content in the colonic polyp group was higher than that in the control group (colonic polyp group: 73.70 (23.03221.50), control group: 70.70 (19.00199.00), P = 0.545). In other words, it can be considered that in this situation, the DCA content in the intestinal contents of colonic polyp patients increases, while the UDCA content decreases, which is consistent with the above mechanism. However, this study did not actually analyze the BA levels in the feces of colonic polyp patients and healthy control groups, and this part of the study can be added in future studies.

This study went on to conduct grouping analysis based on a comparison of the BA profile detection results between the colonic polyp group and the control group. The results showed that the CA, CDCA, UDCA, and TUDCA contents of the adenomatous polyp group were lower than those of the non adenomatous polyp group. The content of CA, CDCA, UDCA, GUDCA, TUDCA in the group with polyp diameter ≥ 1 cm was higher than that in the group with polyp diameter < 1 cm. The GCDCA content in the right colon group was significantly higher than that in the left colon group, and the CA content in the left colon group was significantly higher than that in the whole colon group. The CA, GCA, and GCDCA content in the right colon group was significantly higher than that in the whole colon group. The content of CA,

Table 4 Bile acid levels in colonic polyps of different pathological types (nmol/L)

	Non adenomatous polyp group	Adenomatous polyp group	*P* value
Primary free BAs			
CA	107.00 (39.50, 357.00)	53.20 (20.35, 185.50)	0.003[a]
CDCA	408.00 (191.00, 1130.00)	373.00 (80.50, 785.00)	0.034[a]
Primary conjugated BAs			
TCA	24.80 (8.90, 71.50)	20.10 (5.45, 45.80)	0.189
GCA	160.00 (81.70, 423.00)	174.00 (72.60, 326.00)	0.676
GCDCA	866.00 (458.00, 2190.00)	961.00 (397.00, 1785.00)	0.465
TCDCA	113.00(40.70, 185.00)	64.50 (24.60, 152.50)	0.060
Secondary free BAs			
DCA	182.00 (38.50, 448.00)	118.00 (21.25, 401.00)	0.226
LCA	5.30 (0.00, 16.80)	6.70 (0.50, 17.20)	0.588
UDCA	107.00 (49.00, 311.00)	64.00 (16.15, 190.00)	0.003[a]
Secondary conjugated BAs			
TDCA	17.90 (2.50, 39.10)	6.80 (0.00, 24.35)	0.078
GDCA	135.00 (7.40, 398.00)	107.00 (19.25, 229.00)	0.593
TLCA	0.00 (0.00, 2.10)	0.00 (0.00, 2.55)	0.566
GLCA	4.40 (0.00, 20.30)	4.60 (0.00, 15.50)	0.646
TUDCA	11.70 (4.50, 20.10)	6.50 (2.95, 15.00)	0.023[a]
GUDCA	220.00 (58.10, 543.00)	114.00 (43.55, 303.00)	0.067

[a]$P < 0.05$, there is a statistical difference in this indicator between the two groups.

BA: Bile acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid; TCA: Taurocholic acid; GCA: Glycocholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; DCA: Deoxycholic acid; UDCA: Ursodeoxycholic acid; LCA: Lithocholic acid; TDCA: Tauroursodeoxycholic acid; GDCA: Glycodeoxycholic acid; TUDCA: Tauroursodeoxycholic acid; GUDCA: Glycoursodeoxycholic acid; TLCA: Taurolithocholic acid; GLCA: Glycolithocholic acid.

CDCA, UDCA, and GUDCA in the group with pedicle polyps was significantly higher than that in the group without pedicle polyps. In the study by Kawano *et al*[10], they monitored the tumor group and discovered that, compared to the subgroup with low DCA levels, the high DCA subgroup had a higher risk of large adenomas (> 3 mm) recurring after four years, and this trend was more pronounced in the left colon. According to Cai *et al*[22], right colon tumors had much higher levels of the 12 bile acids than left colon tumors did. In addition, in male patients, the secondary bile acids (DCA, LCA, UDCA) of the right colonic tumor increased compared to the left colonic tumor, but no difference in tumor location was observed in women. Research has shown that the distribution of BA abundance in cancer patients is specific to tumor location, age, and gender, and is related to patient prognosis. From the perspective of pathological characteristics of polyps, this study found that the changes in BA profile are closely related to polyp diameter, polyp site, polyp morphology, pathological type, *etc*. However, the specific role relationship is still unclear, which may be related to the small sample size included in this study. Due to the retrospective nature of this study, additional confounding factors such as inconsistent colonoscopy operators, inconsistent current gastrointestinal symptoms, inconsistent past medical histories of patients, and mismatched colonic polyp group and control group may also have an effect on the research results. However, by taking into account the pathological characteristics of colonic polyps, this study offers new suggestions for the treatment of individuals with colonic cancer.

In summary, the serum BA profile showed significant changes in patients with colonic polyps. The etiology of colon cancers may be intimately associated with secondary bile acid DCA, one of them. At present, the widely recognized view on the role of serum BA metabolism in the occurrence and development of colon polyps is that BA can induce changes in the colon environment by activating various signaling pathways in the body, thereby promoting the occurrence of colonic polyps and even colonic cancer. Among them, a large number of studies have shown that DCA can induce NF-κB activation, β-catenin signaling and regulation of intestinal barrier to promote the development of adenomas and the formation of adenocarcinoma. And UDCA can inhibit tumor growth by inhibiting DCA induced NF-κB activation and inhibiting YAP signaling. However, there is still controversy about whether other components in the BA spectrum can become therapeutic targets for colonic tumors, and further research is needed. This study indicates that controlling the content and composition of serum BA in the absence of intestinal abnormalities, even during the stage of colonic polyps, can to some extent reduce the production of polyps and prevent them from further developing into cancer. In addition,

Table 5 Bile acid levels in single polyp group and multiple polyps group (nmol/L)

	Single polyp group	Multiple polyps group	*P* value
Primary free BAs			
CA	92.40 (35.40, 275.50)	59.70 (23.50, 170.00)	0.067
CDCA	492.00 (193.50, 905.50)	357.00 (84.80, 836.00)	0.185
Primary conjugated BAs			
TCA	23.50 (8.70, 47.35)	20.20 (5.00, 52.10)	0.809
GCA	203.00 (93.35, 330.00)	157.00 (60.90, 342.00)	0.363
GCDCA	1050.00 (506.50, 1945.00)	881.00 (354.00, 2030.00)	0.346
TCDCA	80.70 (29.70, 170.50)	69.10 (25.10, 165.00)	0.707
Secondary free BAs			
DCA	119.00 (10.90, 401.00)	145.00 (32.30, 437.00)	0.588
LCA	5.50 (0.25, 15.50)	6.70 (0.00, 17.60)	0.715
UDCA	74.90 (33.15, 210.00)	73.70 (17.20, 253.00)	0.540
Secondary conjugated BAs			
TDCA	7.60 (0.00, 24.70)	11.20 (0.70, 36.10)	0.371
GDCA	116.00 (10.60, 239.00)	113.00 (12.70, 253.00)	0.991
TLCA	0.00 (0.00, 2.10)	0.00 (0.00, 2.80)	0.520
GLCA	2.70 (0.00, 16.70)	5.50 (0.00, 16.20)	0.340
TUDCA	9.10 (3.05, 15.00)	6.90 (3.30, 15.00)	0.865
GUDCA	169.00 (47.20, 399.50)	115.00 (47.10, 340.00)	0.482

BA: Bile acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid; TCA: Taurocholic acid; GCA: Glycocholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; DCA: Deoxycholic acid; UDCA: Ursodeoxycholic acid; LCA: Lithocholic acid; TDCA: Tauroursodeoxycholic acid; GDCA: Glycodeoxycholic acid; TUDCA: Tauroursodeoxycholic acid; GUDCA: Glycoursodeoxycholic acid; TLCA: Taurolithocholic acid; GLCA: Glycolithocholic acid.

Table 6 Bile acid levels in colonic polyps of different sizes (nmol/L)

	Diameter < 1cm group	Diameter ≥ 1 cm group	*P* value
Primary free BAs			
CA	55.80 (22.70, 200.00)	155.00 (32.30, 343.00)	0.005[a]
CDCA	365.00 (85.20, 835.00)	586.00 (278.00, 1130.00)	0.015[a]
Primary conjugated BAs			
TCA	21.70 (5.50, 46.85)	22.00 (11.50, 75.50)	0.391
GCA	167.00 (84.05, 329.50)	166.00 (57.50, 416.00)	0.927
GCDCA	961.00 (389.00, 1845.00)	900.00 (556.00, 2410.00)	0.333
TCDCA	69.10 (24.05, 152.50)	90.20 (40.70, 262.00)	0.060
Secondary free BAs			
DCA	127.00 (21.90, 389.00)	274.00 (77.30, 525.00)	0.063
LCA	5.50 (0.00, 16.15)	8.50 (2.10, 21.60)	0.163
UDCA	64.50 (16.75, 182.50)	196.00 (52.70, 421.00)	0.003[a]
Secondary conjugated BAs			
TDCA	8.20 (0.00, 29.80)	13.30 (3.10, 37.10)	0.317

GDCA	108.00 (12.65, 235.00)	144.00 (10.80, 324.00)	0.610
TLCA	0.00 (0.00, 2.30)	0.80 (0.00, 3.20)	0.189
GLCA	4.60 (0.00, 15.80)	2.50 (0.00, 21.20)	0.736
TUDCA	7.00 (3.00, 15.00)	14.10 (3.90, 34.60)	0.034[a]
GUDCA	122.00 (42.95, 315.50)	234.00 (59.00, 556.00)	0.030[a]

[a]$P < 0.05$, there is a statistical difference in this indicator between the two groups.
BA: Bile acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid; TCA: Taurocholic acid; GCA: Glycocholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; DCA: Deoxycholic acid; UDCA: Ursodeoxycholic acid; LCA: Lithocholic acid; TDCA: Tauroursodeoxycholic acid; GDCA: Glycodeoxycholic acid; TUDCA: Tauroursodeoxycholic acid; GUDCA: Glycoursodeoxycholic acid; TLCA: Taurolithocholic acid; GLCA: Glycolithocholic acid.

Table 7 Bile acid levels in different parts of polyps (nmol/L)

	Left colon group	Right colon group	Total colon group	*P* value
Primary free BAs				
CA	108.00 (24.53, 334.00)	65.60 (48.23, 126.00)	23.20 (11.05, 157.48)	0.000[a]
CDCA	447.00 (130.25, 1000.00)	448.00 (191.00, 813.00)	135.50 (41.43, 678.00)	0.047[a]
Primary conjugated BAs				
TCA	20.75 (4.88, 53.78)	34.70 (12.73, 58.85)	15.00 (4.15, 39.43)	0.148
GCA	156.50 (65.53, 342.25)	257.00 (136.00, 373.00)	134.00 (42.95, 204.00)	0.006[a]
GCDCA	812.50 (334.00, 1822.50)	1420.00 (764.00, 2387.50)	655.50 (290.50, 1622.50)	0.005[a]
TCDCA	73.95 (23.68, 154.25)	110.00 (45.63, 257.00)	64.20 (28.18, 125.50)	0.060
Secondary free BAs				
DCA	185.00 (48.85, 466.25)	105.50 (3.18, 383.75)	110.50 (18.08, 280.75)	0.098
LCA	6.20 (0.68, 15.08)	8.85 (0.00, 17.20)	5.50 (0.00, 28.83)	0.963
UDCA	73.55 (27.00, 209.50)	102.50 (29.80, 212.75)	46.45 (9.78, 252.75)	0.314
Secondary conjugated BAs				
TDCA	8.50 (1.25, 34.63)	8.50 (0.00, 22.825)	7.55 (0.00, 30.33)	0.635
GDCA	122.50 (20.03, 278.50)	118.00 (6.48, 242.00)	86.70 (7.18, 213.75)	0.464
TLCA	0.00 (0.00, 2.30)	0.45 (0.00, 3.00)	0.65 (0.00, 2.48)	0.478
GLCA	4.60 (0.00, 15.90)	3.35 (0.00, 18.25)	5.85 (0.38, 19.28)	0.555
TUDCA	9.10 (2.20, 15.00)	6.40 (4.13, 15.00)	6.75 (3.83, 15.00)	0.933
GUDCA	113.00 (34.43, 341.00)	228.50 (83.25, 514.50)	112.00 (47.55, 308.75)	0.064

[a]$P < 0.05$, there is a statistical difference in this indicator between the two groups.
BA: Bile acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid; TCA: Taurocholic acid; GCA: Glycocholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; DCA: Deoxycholic acid; UDCA: Ursodeoxycholic acid; LCA: Lithocholic acid; TDCA: Tauroursodeoxycholic acid; GDCA: Glycodeoxycholic acid; TUDCA: Tauroursodeoxycholic acid; GUDCA: Glycoursodeoxycholic acid; TLCA: Taurolithocholic acid; GLCA: Glycolithocholic acid.

Table 8 Bile acid levels in colonic polyps with or without pedicle (nmol/L)

	Pedicled polyp group	Sessile polyp group	*P* value
Primary free BAs			
CA	420.00 (32.48, 791.00)	59.80 (24.08, 173.00)	0.006[a]
CDCA	711.00 (214.75, 2845.00)	373.50 (94.68, 834.50)	0.016[a]

Primary conjugated BAs			
TCA	17.90 (11.00, 94.98)	22.10 (5.30, 49.90)	0.635
GCA	166.50 (92.35, 491.25)	168.50 (73.75, 330.00)	0.709
GCDCA	1230.00 (625.25, 2775.00)	900.00 (413.25, 1860.00)	0.096
TCDCA	111.50 (44.68, 307.50)	68.15 (25.35, 162.00)	0.075
Secondary free BAs			
DCA	155.50 (0.68, 806.00)	142.00 (34.03, 418.25)	0.976
LCA	3.50 (0.00, 22.13)	6.45 (0.50, 15.93)	0.662
UDCA	228.00 (64.38, 454.75)	64.90 (19.63, 196.50)	0.003[a]
Secondary conjugated BAs			
TDCA	13.90 (0.00, 56.58)	8.15 (0.50, 30.33)	0.539
GDCA	118.15 (0.00, 494.50)	113.50 (18.50, 238.00)	0.595
TLCA	0.25 (0.00, 3.78)	0.00 (0.00, 2.30)	0.540
GLCA	3.40 (0.00, 30.45)	4.65 (0.00, 16.05)	0.723
TUDCA	7.20 (4.15, 24.43)	7.65 (3.08, 15.00)	0.472
GUDCA	330.50 (133.75, 573.00)	114.50 (44.40, 314.75)	0.008[a]

[a]$P < 0.05$, there is a statistical difference in this indicator between the two groups.
BA: Bile acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid; TCA: Taurocholic acid; GCA: Glycocholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; DCA: Deoxycholic acid; UDCA: Ursodeoxycholic acid; LCA: Lithocholic acid; TDCA: Tauroursodeoxycholic acid; GDCA: Glycodeoxycholic acid; TUDCA: Tauroursodeoxycholic acid; GUDCA: Glycoursodeoxycholic acid; TLCA: Taurolithocholic acid; GLCA: Glycolithocholic acid.

Table 9 Risk factors for colonic polyps: Univariate and multivariate logistic regression analysis

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
TBA	1.000 (1.000, 1.000)	0.104		
CA	1.000 (1.000, 1.001)	0.181		
CDCA	1.000 (1.000, 1.000)	0.046	1.001 (1.000, 1.001)	0.073
DCA	1.000 (1.000, 1.000)	0.799		
LCA	1.000 (0.999, 1.001)	0.636		
UDCA	1.000 (1.000, 1.001)	0.329		
GCA	1.000 (1.000, 1.001)	0.512		
GCDCA	1.000 (1.000, 1.000)	0.027	1.001 (1.000, 1.001)	0.074
GDCA	1.000 (0.999, 1.000)	0.080		
GLCA	1.000 (0.999, 1.001)	0.394		
GUDCA	1.000 (1.000, 1.001)	0.154		
TCA	1.000 (0.998, 1.002)	0.927		
TCDCA	1.00 1(0.999, 1.002)	0.328		
TDCA	0.998 (0.995, 1.002)	0.310		
TLCA	0.999 (0.989, 1.009)	0.900		
TUDCA	1.005 (0.993, 1.018)	0.413		
primary BA	1.000 (1.000, 1.000)	0.018	1.000 (0.999, 1.000)	0.182
primary free BA	1.000 (1.000, 1.000)	0.053		

primary conjugated BA	1.000 (1.000, 1.000)	0.071
secondary BA	1.000 (1.000, 1.000)	0.720
secondary free BA	1.000 (1.000, 1,000)	0.710
secondary conjugated BA	1.000 (1.000, 1.000)	0.363

BA: Bile acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid; TCA: Taurocholic acid; GCA: Glycocholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; DCA: Deoxycholic acid; UDCA: Ursodeoxycholic acid; LCA: Lithocholic acid; TDCA: Tauroursodeoxycholic acid; GDCA: Glycodeoxycholic acid; TUDCA: Tauroursodeoxycholic acid; GUDCA: Glycoursodeoxycholic acid; TLCA: Taurolithocholic acid; GLCA: Glycolithocholic acid.

this study provides a new and effective approach for disease screening and postoperative follow-up of colonic polyps from the perspective of characteristic changes in serum BA profile. There are also many shortcomings in this study, and further improvement is needed in future experimental design. Further in-depth research can be conducted by expanding the sample size, collecting fecal samples, and collaborating with other hospitals to conduct multicenter studies, providing a basis for finding effective targets to reduce the production of colonic polyps and the incidence of colonic cancer.

CONCLUSION

This study shows that the serum BA profile of patients with colonic polyps has changed compared to normal individuals. The serum GCA, GCDCA, TCA, and TCDCA levels in the colonic polyp group are significantly higher than those in the control group ($P < 0.05$), while the DCA content is lower than that in the control group. Patients with various polyp sizes, locations, morphologies, and pathological types had variable serum BA profile, according to subgroup study of colonic polyps. Therefore, analyzing the changes in serum BA profile may provide new ideas for finding new targets for the treatment of colonic tumors.

FOOTNOTES

Author contributions: Ji X and Chen H provided the conception and design of the research; Ji X collected and analyzed the data, wrote the manuscript.

Institutional review board statement: This study was reviewed and approved by the Zhongda Hospital Institutional Review Board (Approval No.2021ZDSYLL297-P01).

Informed consent statement: This study was a retrospective study that collected existing clinical data from relevant populations through the hospital's electronic case system for statistical analysis. Therefore, we apologize that we are unable to provide informed consent.

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

Data sharing statement: Data supporting the research article are available from the corresponding author or first 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: Xin Ji 0009-0000-2625-9035; Hong Chen 0000-0001-8354-3980.

S-Editor: Liu JH
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Sullivan BA**, Noujaim M, Roper J. Cause, Epidemiology, and Histology of Polyps and Pathways to Colorectal Cancer. *Gastrointest Endosc Clin N Am* 2022; **32**: 177-194 [PMID: 35361330 DOI: 10.1016/j.giec.2021.12.001]

2 **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]

3 **Cao PX**, Shen YZ, Huang YQ, Jiang CX, Ma HQ, Wang ZY. Clinical characteristics and pathological types of 7408 cases of intestinal lesions found in colorectal cancer screening. *Zhonghua Xiaohua Neijing Zazhi* 2018; **35**: 630-633

4 **Shaukat A**, Levin TR. Current and future colorectal cancer screening strategies. *Nat Rev Gastroenterol Hepatol* 2022; **19**: 521-531 [PMID: 35505243 DOI: 10.1038/s41575-022-00612-y]

5 **Marin JJ**, Macias RI, Briz O, Banales JM, Monte MJ. Bile Acids in Physiology, Pathology and Pharmacology. *Curr Drug Metab* 2015; **17**: 4-29 [PMID: 26526836 DOI: 10.2174/1389200216666151103115454]

6 **Qi L**, Chen Y. Circulating Bile Acids as Biomarkers for Disease Diagnosis and Prevention. *J Clin Endocrinol Metab* 2023; **108**: 251-270 [PMID: 36374935 DOI: 10.1210/clinem/dgac659]

7 **Kühn T**, Stepien M, López-Nogueroles M, Damms-Machado A, Sookthai D, Johnson T, Roca M, Hüsing A, Maldonado SG, Cross AJ, Murphy N, Freisling H, Rinaldi S, Scalbert A, Fedirko V, Severi G, Boutron-Ruault MC, Mancini FR, Sowah SA, Boeing H, Jakszyn P, Sánchez MJ, Merino S, Colorado-Yohar S, Barricarte A, Khaw KT, Schmidt JA, Perez-Cornago A, Trichopoulou A, Karakatsani A, Thriskos P, Palli D, Agnoli C, Tumino R, Sacerdote C, Panico S, Bueno-de-Mesquita B, van Gils CH, Heath AK, Gunter MJ, Riboli E, Lahoz A, Jenab M, Kaaks R. Prediagnostic Plasma Bile Acid Levels and Colon Cancer Risk: A Prospective Study. *J Natl Cancer Inst* 2020; **112**: 516-524 [PMID: 31435679 DOI: 10.1093/jnci/djz166]

8 **Sun L**, Zhang Y, Cai J, Rimal B, Rocha ER, Coleman JP, Zhang C, Nichols RG, Luo Y, Kim B, Chen Y, Krausz KW, Harris CC, Patterson AD, Zhang Z, Takahashi S, Gonzalez FJ. Bile salt hydrolase in non-enterotoxigenic Bacteroides potentiates colorectal cancer. *Nat Commun* 2023; **14**: 755 [PMID: 36765047 DOI: 10.1038/s41467-023-36089-9]

9 **Ocvirk S**, Wilson AS, Posma JM, Li JV, Koller KR, Day GM, Flanagan CA, Otto JE, Sacco PE, Sacco FD, Sapp FR, Newton K, Brouard F, DeLany JP, Behnning M, Appolonia CN, Soni D, Bhatti F, Methé B, Fitch A, Morris A, Gaskins HR, Kinross J, Nicholson JK, Thomas TK, O'Keefe SJD. A prospective cohort analysis of gut microbial co-metabolism in Alaska Native and rural African people at high and low risk of colorectal cancer. *Am J Clin Nutr* 2020; **111**: 406-419 [PMID: 31851298 DOI: 10.1093/ajcn/nqz301]

10 **Kawano A**, Ishikawa H, Kamano T, Kanoh M, Sakamoto K, Nakamura T, Otani T, Sakai T, Kono K. Significance of fecal deoxycholic acid concentration for colorectal tumor enlargement. *Asian Pac J Cancer Prev* 2010; **11**: 1541-1546 [PMID: 21338194]

11 **Cook J**, Kennaway E, Kennaway N. Production of Tumours in Mice by Deoxycholic Acid. *Nature* 1940; **145**: 627 [DOI: 10.1038/145627a0]

12 **Fang Y**, Yan C, Zhao Q, Xu J, Liu Z, Gao J, Zhu H, Dai Z, Wang D, Tang D. The roles of microbial products in the development of colorectal cancer: a review. *Bioengineered* 2021; **12**: 720-735 [PMID: 33618627 DOI: 10.1080/21655979.2021.1889109]

13 **Di Ciaula A**, Wang DQ, Molina-Molina E, Lunardi Baccetto R, Calamita G, Palmieri VO, Portincasa P. Bile Acids and Cancer: Direct and Environmental-Dependent Effects. *Ann Hepatol* 2017; **16**: s87-s105 [PMID: 29080344 DOI: 10.5604/01.3001.0010.5501]

14 **Wang S**, Liu Z, Wang L, Zhang X. NF-kappaB signaling pathway, inflammation and colorectal cancer. *Cell Mol Immunol* 2009; **6**: 327-334 [PMID: 19887045 DOI: 10.1038/cmi.2009.43]

15 **Jia W**, Xie G, Jia W. Bile acid-microbiota crosstalk in gastrointestinal inflammation and carcinogenesis. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 111-128 [PMID: 29018272 DOI: 10.1038/nrgastro.2017.119]

16 **Ocvirk S**, O'Keefe SJD. Dietary fat, bile acid metabolism and colorectal cancer. *Semin Cancer Biol* 2021; **73**: 347-355 [PMID: 33069873 DOI: 10.1016/j.semcancer.2020.10.003]

17 **Liu L**, Dong W, Wang S, Zhang Y, Liu T, Xie R, Wang B, Cao H. Deoxycholic acid disrupts the intestinal mucosal barrier and promotes intestinal tumorigenesis. *Food Funct* 2018; **9**: 5588-5597 [PMID: 30339173 DOI: 10.1039/c8fo01143e]

18 **Serfaty L**, De Leusse A, Rosmorduc O, Desaint B, Flejou JF, Chazouilleres O, Poupon RE, Poupon R. Ursodeoxycholic acid therapy and the risk of colorectal adenoma in patients with primary biliary cirrhosis: an observational study. *Hepatology* 2003; **38**: 203-209 [PMID: 12830003 DOI: 10.1053/jhep.2003.50311]

19 **Khare S**, Mustafi R, Cerda S, Yuan W, Jagadeeswaran S, Dougherty U, Tretiakova M, Samarel A, Cohen G, Wang J, Moore C, Wali R, Holgren C, Joseph L, Fichera A, Li YC, Bissonnette M. Ursodeoxycholic acid suppresses Cox-2 expression in colon cancer: roles of Ras, p38, and CCAAT/enhancer-binding protein. *Nutr Cancer* 2008; **60**: 389-400 [PMID: 18444174]

20 **Shah SA**, Volkov Y, Arfin Q, Abdel-Latif MM, Kelleher D. Ursodeoxycholic acid inhibits interleukin 1 beta [corrected] and deoxycholic acid-induced activation of NF-kappaB and AP-1 in human colon cancer cells. *Int J Cancer* 2006; **118**: 532-539 [PMID: 16106402 DOI: 10.1002/ijc.21365]

21 **Zhang H**, Xu H, Zhang C, Tang Q, Bi F. Ursodeoxycholic acid suppresses the malignant progression of colorectal cancer through TGR5-YAP axis. *Cell Death Discov* 2021; **7**: 207 [PMID: 34365464 DOI: 10.1038/s41420-021-00589-8]

22 **Cai Y**, Shen X, Lu L, Yan H, Huang H, Gaule P, Muca E, Theriot CM, Rattray Z, Rattray NJW, Lu J, Ahuja N, Zhang Y, Paty PB, Khan SA, Johnson CH. Bile acid distributions, sex-specificity, and prognosis in colorectal cancer. *Biol Sex Differ* 2022; **13**: 61 [PMID: 36274154 DOI: 10.1186/s13293-022-00473-9]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2173-2181

DOI: 10.12998/wjcc.v12.i13.2173

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Case Control Study

Clinical analysis of colistin sulfate in the treatment of pneumonia caused by carbapenem-resistant Gram-negative bacteria

Hai-Chang Xu, Yan Cui, Xue-Ying Wang, Hai-Bo Wu, Wei Li, Dan Wang, Na Lin, Lin Lin, Ying-Hui Zhang

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: Odhiambo A, Hungary

Received: January 25, 2024
Peer-review started: January 25, 2024
First decision: February 8, 2024
Revised: February 27, 2024
Accepted: March 25, 2024
Article in press: March 25, 2024
Published online: May 6, 2024

Hai-Chang Xu, Yan Cui, Xue-Ying Wang, Hai-Bo Wu, Wei Li, Dan Wang, Na Lin, Lin Lin, Ying-Hui Zhang, Department of Intensive Care Medicine, The General Hospital of the Northern Theater Command of the People's Liberation Army of China, Shenyang 110016, Liaoning Province, China

Corresponding author: Yan Cui, MM, Deputy Director, Department of Intensive Care Medicine, The General Hospital of the Northern Theater Command of the People's Liberation Army of China, No. 83 Wenhua Road, Shenhe District, Shenyang 110003, Liaoning Province, China. cyan9010@qq.com

Abstract

BACKGROUND

Multidrug-resistant Gram-negative bacteria, exacerbated by excessive use of antimicrobials and immunosuppressants, are a major health threat.

AIM

To study the clinical efficacy and safety of colistin sulfate in the treatment of carbapenem-resistant Gram-negative bacilli-induced pneumonia, and to provide theoretical reference for clinical diagnosis and treatment.

METHODS

This retrospective analysis involved 54 patients with Gram-negative bacilli pneumonia admitted to intensive care unit of The General Hospital of the Northern Theater Command of the People's Liberation Army of China from August 2020 to June 2022. After bacteriological culture, the patients' airway secretions were collected to confirm the presence of Gram-negative bacilli. The patients were divided into the experimental and control groups according to the medication used. The research group consisted of 28 patients who received polymyxin sulfate combined with other drugs through intravenous, nebulization, or intravenous combined with nebulization, with a daily dosage of 1.5–3.0 million units. The control group consisted of 26 patients who received standard dosages of other antibiotics (including sulbactam sodium for injection, cefoperazone sodium sulbactam for injection, tigecycline, meropenem, or vaborbactam).

RESULTS

Of the 28 patients included in the research group, 26 patients showed improvement, treatment was ineffective for two patients, and one patient died, with the treatment efficacy rate of 92.82%. Of the 26 patients in the control group, 18

patients improved, treatment was ineffective for eight patients, and two patients died, with the treatment efficacy rate of 54.9%; significant difference was observed between the two groups ($P < 0.05$). The levels of white blood cell (WBC), procalcitonin (PCT), and C-reactive protein (CRP) in both groups were significantly lower after treatment than before treatment ($P < 0.05$), and the levels of WBC, PCT, and CRP in the research group were significantly lower than those in the control group ($P < 0.05$). Compared with before treatment, there were no significant changes in aspartate aminotransferase, creatinine, and glomerular filtration rate in both groups, while total bilirubin and alanine aminotransferase decreased after treatment ($P < 0.05$) with no difference between the groups. In patients with good clinical outcomes, the sequential organ failure assessment (SOFA) score was low when treated with inhaled polymyxin sulfate, and specific antibiotic treatment did not improve the outcome. Sepsis and septic shock as well as a low SOFA score were independent factors associated with good clinical outcomes.

CONCLUSION

Polymyxin sulfate has a significant effect on the treatment of patients with multiple drug-resistant Gram-negative bacilli pneumonia and other infections in the lungs and is safe and reliable. Moreover, the administration route of low-dose intravenous injection combined with nebulization shows better therapeutic effects and lower adverse reactions, providing new ideas for clinical administration.

Key Words: Colistin sulfate; Extensively drug-resistant; Pneumonia; Intravenous combined with nebulization; Sepsis; Nephrotoxicity; Neurotoxicity

Core Tip: Multidrug-resistant Gram-negative bacteria, exacerbated by excessive use of antimicrobials and immunosuppressants, are a major health threat. Colistin sulfate provides comprehensive, highly sensitive coverage against these bacteria. For pulmonary infections, its use *via* intravenous and nebulization methods improves cure rates and reduces adverse reactions, including renal and neurotoxicity. It also significantly ameliorates clinical symptoms in sepsis patients, proving to be safe and reliable.

Citation: Xu HC, Cui Y, Wang XY, Wu HB, Li W, Wang D, Lin N, Lin L, Zhang YH. Clinical analysis of colistin sulfate in the treatment of pneumonia caused by carbapenem-resistant Gram-negative bacteria. *World J Clin Cases* 2024; 12(13): 2173-2181
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2173.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2173

INTRODUCTION

Polymyxin is a polypeptide antibiotic obtained from the culture solution of *Bacillus polymyxa*[1]. The components are named A, B, C, D, and E5 according to their chemical structures. Polymyxin B and Polymyxin E (sulfate polymyxin) were successfully developed in the 1950s and have been used in the treatment of infections caused by Gram-negative bacteria, particularly *Pseudomonas aeruginosa* (*P. aeruginosa*); however, they were abandoned in the 1970s owing to their narrow antibacterial spectrum and high nephrotoxicity[2]. With the extensive use of antimicrobial drugs and immunosuppressants, multidrug- or pandrug-resistant *Gram-negative bacteria*, particularly drug-resistant *Acinetobacter baumannii* (*A. baumannii*), *P. aeruginosa*, and *Klebsiella pneumoniae* (*K. pneumoniae*), pose a serious threat to human health. The number of drugs available for clinical use is decreasing, and the development and marketing of new antimicrobial drugs cannot keep pace with the rapidly increasing trend of drug resistance[3-4]. In recent years, the old drug polymyxin has achieved good results in infections caused by multidrug-resistant *Gram-negative bacteria*, including *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae*, and has therefore received renewed clinical attention[5]. Polymyxin has multiple antibacterial mechanisms, mainly through acting on the bacterial cell membrane and causing important intracellular substances to leak, thus exhibiting bactericidal effect. In nature, many microbes exhibit drug resistance; therefore, finding a novel and highly effective broad-spectrum antibacterial agent has become a hot topic in the field of medicine. Polycationic polymyxin can bind to the outer membrane of Gram-negative bacteria, disrupt bacterial integrity, increase the permeability of the bacterial cell membrane, resulting in the leakage and death of major bacterial cell components[6]. Simultaneously, polymyxin carrying positive charge forms electrostatic bonds/interactions with negatively charged lipopolysaccharides on the bacterial cell membrane[7]. This electrostatic action can cause replacement of calcium and magnesium ions, which have a stabilizing effect on lipopolysaccharide molecules, in the outer membrane. This study observed that electrostatic action (1) has a great impact on the structure and function of polymyxin biofilm; (2) alters cell membrane permeability, reduces intracellular osmotic pressure, and inhibits phosphatidylinositol kinase activity; and (3) connects the polymyxin fatty acid chain more closely to the cell membrane, destroying bacterial cell integrity[8]. Second, an important characteristic of polymyxin is its ability to bind to lipopolysaccharides. It can inhibit the interaction between lipid and protein molecules through various pathways, thereby protecting the body from damage. In addition, it can

effectively prevent bleeding caused by damage to vascular endothelial cells. Notably, the lipid components of polymyxin can specifically bind to and remove lipopolysaccharides, which plays a crucial role in the treatment of endotoxin shock[9, 10]. Endotoxins are the major components in the outer membrane of Gram-negative bacteria and can activate macrophages and neutrophils to release inflammatory mediators and induce sepsis, causing tissue destruction or death[11-13]. Currently, specific anti-endotoxin drugs are lacking in clinical practice. Owing to the its specific structure, polymyxin has been used as a lipopolysaccharide inactivator and adsorbent and clinically proven effective for the management of patients with sepsis[14]. Extensively drug-resistant *Gram-negative bacilli* (XDR-GNB) such as *Escherichia coli* (*E. coli*), *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* are clinically important human pathogens[15]. The mortality rate of pneumonia caused by XDR-GN pathogens is extremely high. Currently, only a few effective antimicrobial strategies are available against XDR-GN bacteria[16]. Sulfate polymyxin has been used as a rescue therapy for pneumonia caused by XDR-GNB[4]. In addition, emerging cephalosporin-class beta-lactamase inhibitors (ceftazidime-avibactam, cefepime-tazobactam, ceftolozane, and eravacycline) are active against XDR-GNB that cause pneumonia in intensive care unit (ICU) patients. In addition to sulfate polymyxin, new cephalosporins can be used to treat pneumonia caused by XDR-GNB[17]. However, owing to the high cost of new cephalosporin/beta-lactamase inhibitors, unavailability in middle-income countries, high antibiotic pressure in the ICU, and high risk of antibiotic resistance, polymyxin is considered the best treatment for pneumonia caused by XDR-GNB. Researchers have found that intravenous injection leads to poor distribution of sulfate polymyxin at the infection site, which may have a negative impact on the treatment of pneumonia and tracheobronchitis caused by multidrug-resistant XDR-GNB. Inhalation therapy has shown a wide prospect of expanding indications, including respiratory diseases such as lower respiratory tract infections[18] Theoretically, the inhalation route of administration is more appropriate for sulfate polymyxins to directly reach at the infection site and reduce systemic side effects[19]. Polymyxin sulfate is the first antibiotic independently developed by China, which is fermented by Bacillus polymyxa. Its main components are polymyxin E1 (also known as colistin A) and polymyxin E2 (also known as polymyxin B). It is an active drug that does not require hydrolysis in the body to exert antibacterial activity. Studies have found that as an important choice for combined or single treatment of intravenous antimicrobial drugs, the adjunctive nebulization route can improve the clinical effect and microbial eradication rate of patients with XDR-GNB pneumonia, and its safety is relatively high. However, it does not affect the overall mortality rate of patients with hospital-acquired pneumonia/ventilator-associated pneumonia[20-23].

MATERIALS AND METHODS

Subjects

This is a retrospective study involving 105 patients with pneumonia caused by XDR-GN who were admitted to the ICU of The General Hospital of the Northern Theater Command of the People's Liberation Army of China between August 2020 and June 2022. Since it is a retrospective study, the informed consent is waived. The inclusion criteria were as follows: Age 18–80 years; confirmed diagnosis of pneumonia caused by XDR *E. coli*, *K. pneumoniae*, *P. aeruginosa*, or *A. baumannii*; at least two consecutive samples on different d (minimum time interval of 24 h) showing the presence of XDR-GNB in bronchial secretions or bronchoalveolar lavage samples; and at least six doses of inhaled or intravenous sulfate polymyxin. Patients under 18 years or over 80 years of age, with polymicrobial pneumonia, cystic fibrosis, or lung transplantation were excluded.

Relevant diagnostic criteria

Antimicrobial susceptibility testing was performed *in vitro*, following the norms used in the clinical and laboratory standard studies. Resistance was evaluated based on the minimum inhibitory concentration (MIC), which is widely recognized for guiding rational drug use. Currently, MIC is one of the most commonly used international indicators for evaluating the efficacy and safety of antimicrobial drugs. XDR-GNB are defined as a class of bacteria that are only relatively sensitive to polymyxin, and mainly include *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii*, as detected in the laboratory[24].

Clinical outcomes were divided into three stages: Clinical cure (symptoms and signs related to the infection disappeared after the administration of sulfate polymyxin), clinical improvement (improved when compared with before the administration of sulfate polymyxin), and clinical failure (continued or worsened symptoms and signs related to the infection even after the administration of sulfate polymyxin and/or death). Infection recurrence was defined as the appearance of symptoms, such as fever and shortness of breath, within 72 h after stopping sulfate polymyxin; laboratory indicators indicating bacterial infection, such as CRP, procalcitonin (PCT), and white blood cell (WBC) count; and no other infection foci. Favorable clinical outcomes include clinical cure or improvement, and unfavorable outcomes include clinical failure or recurrence[25]. Two physicians who were unaware of the study protocol independently analyzed the clinical outcomes. None of the participants underwent any examination or trial. There were no significant differences between the groups. In case of a discrepancy with the clinical outcome in patients, the reviewer will re-evaluate the information.

Treatment methods

The study involved 54 patients who were divided into experimental and control groups according to their medication status. In the research group, 28 patients were treated with sulfate polymyxin (National Medicine Approval Number H31020822, batch number 20180324) in combination with tigecycline at a daily dosage of 150–300 million units, administered intravenously, nebulized, or a combination of both. The efficacy and adverse reactions were observed in the

two groups. The control group of 26 patients received the standard dosage of another antibiotic (tigecycline). To avoid serious side effects caused by inhaled polymyxin B, inhaled glucocorticoids and bronchodilators were administered 30 min before treatment. A vibrating mesh nebulizer was used to improve the nebulization performance of inhaled sulfate polymyxin. The vibrating mesh nebulizer is placed upstream of the inspiratory arm and a constant inspiratory flow volume control method is selected. The humidification system is removed during inhalation, and it is restored after nebulization. All patients receive the same nebulized dose of drug treatment: 125000 to 250000 units *per* use. Lung function was reviewed every two wk or one month. After nebulization, the expiratory filter was replaced. Each treatment group was implemented by one or two experienced physicians. Both treatment groups received the same treatment measures at each stage. All subjects were randomly divided into two groups for controlled trials. In both treatment groups, sulfate polymyxin was administered for more than 3 d.

Clinical efficacy evaluation

Referring to the "Technical Guiding Principles for Clinical Trials of Antimicrobial Drugs"[26], clinical efficacy of different treatments was analyzed in all patients. This includes general condition, clinical features, and non-microbiological indicators, including biochemical indicators and laboratory examinations. The clinical effectiveness in all patients was evaluated based on the WBC count, PCT level, and CRP level before and after the treatment. The SOFA scoring system was used to score the patients.

Liver and kidney function evaluation

The changes in the liver and kidney function indicators, such as total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and glomerular filtration rate, were recorded and analyzed. Microbiological diagnoses were performed using routine biochemical methods.

Neurotoxicity reaction diagnostic criteria[27]

Grade 0: No clinical manifestations; Grade 1: Sensory dullness, completely disappeared within one wk; Grade 2: Completely disappeared within 21 d; Grade 3: Did not completely disappear within 21 d; Grade 4: Accompanied by functional impairment.

Statistical analysis

Statistical analyses were performed using SPSS 22.0. Continuous data were expressed as mean ± SD, and independent sample *t*-test was used for comparison between groups; discrete data were expressed as percentages, and chi-square test (χ^2 test) was used for comparison between groups. $P < 0.05$ indicated that the difference was statistically significant. The study explores the clinical effectiveness of sulfate polymyxin and its impact on in-hospital mortality: With or without sepsis; *A. baumannii* drug-resistant bacteria and *E. coli* drug-resistant bacteria and *P. aeruginosa* XDR bacteria; with or without immunosuppression as indicators; the median SOFA score was used to assess patients' conditions.

RESULTS

General patient information

A total of 54 patients diagnosed with pneumonia caused by XDR-GN bacteria, who were admitted to our hospital between August 2020 and June 2022, were included in the study. The clinical data mainly included the following aspects: The research group was comprised of 15 males and 13 females of age ranging from 24 to 75 years, with an average of (57.22 ± 11.07) years. The control group was comprised of 14 males and 12 females of age ranging from 28 to 78 years, *i.e.*, (57.22 ± 11.07) years. All patients had confirmed diagnosis of pneumonia caused by XDR-GN bacteria based on sputum culture and bacteriological examination. There was no statistically significant difference between the two groups, and all research subjects were diagnosed with pulmonary infectious diseases according to the standards of the National Institutes of Health in the United States. The hospitalized patients were randomly divided into experimental and control groups. The research group comprising 28 patients was administered polymyxin sulfate in combination with anti-infective therapy, of which 8 were administered intravenous medication, 10 were administered nebulized medication, and 10 were administered a combination of intravenous and nebulized medications. The duration of polymyxin sulfate medication was 3–55 (10.94 ± 1.86) d. The control group of 26 patients was treated with tigecycline in combination with anti-infective therapy, of which 6 were administered intravenous medication, 10 were administered nebulized medication, and 10 were administered a combination of intravenous and nebulized medications. The duration of antibiotic medication was 3–55 (11.43 ± 4.98) d.

Clinical efficacy

The research group included 28 patients, of which 26 patients showed clinical improvement, one patient showed clinical failure of the treatment, and another one patient died. The treatment efficacy rate was 92.82%. The control group included 26 patients, of which 18 showed clinical improvement, six patients showed clinical failure, and two patients died. The treatment efficacy rate was 69.23%. There was a significant difference in the treatment efficacy rate between the two groups ($P < 0.05$).

Comparison of laboratory test results before and after treatment in both groups

The comparison of laboratory test results before and after treatment in the two groups showed that the levels of WBC, PCT, and CRP significantly decreased after treatment compared with before treatment in both groups, and the difference was statistically significant ($P < 0.05$), as shown in Table 1. The levels of WBC and PCT significantly decreased after treatment in the research group, and CRP level significantly decreased in both groups.

Comparison of liver and kidney functions before and after treatment in both groups

There were no significant changes in AST, creatinine, and glomerular filtration rate before and after treatment in both groups, but total bilirubin and ALT levels decreased to varying degrees in control group ($P < 0.05$, Table 2). There were no significant differences in other indicators between the two groups.

Comparison of neurotoxicity before and after treatment in both groups

The incidence of neurotoxicity was as follows: Grade 0, 19 cases (67.85%); Grade 1, five cases (17.85%); Grade 2, three cases (10.71%); and Grade 3, one case (3.57%), with a total incidence of nine cases (32.14%) in the research group *vs* 15 (57.69%), 5 (19.23%), 5 (19.23%), 1 (3.84%), and 11 (42.30%), respectively, in the control group. There were no significant differences between the two groups ($\chi^2 = 3.02$, $P > 0.05$), as shown in Table 1.

Comparison of clinical features after treatment between the two groups

Univariate analysis of clinical features of 54 patients with pneumonia showed that patients treated with inhaled polymyxin sulfate had good clinical outcomes and lower SOFA scores (Table 3).

DISCUSSION

A. baumannii, *K. pneumoniae*, and *P. aeruginosa* are the most common Gram-negative bacilli causing pneumonia[28]. Pathogens present in ICU show antibiotic resistance[29]. The mortality rate of pneumonia caused by XDR-GNB is high (46%–60%)[30]. Because polymyxin sulfate has poor permeability through the lung parenchyma and causes systemic toxicity when administered intravenously, nebulized polymyxin sulfate is often used to treat pneumonia caused by multidrug-resistant or Gram-negative bacilli[31]. However, the lack of optimization of nebulization technology and dosage limitations restrict its clinical application[32]. Existing clinical and experimental evidence suggest that nebulized high-dose colistimethate sodium may be effective against multidrug resistance. Whether nebulized high-dose polymyxin sulfate is therapeutically equivalent or better compared to intravenous ceftazidime (cephalosporin)/β-lactamase (lactamase) inhibitor is not yet known. Nebulized polymyxin sulfate is also used to treat pneumonia caused by multidrug-resistant bacilli. However, there have been few reports on its safety when used to treat respiratory infections. This article reviews the results of the related clinical trials and discusses these issues. Previous studies have shown that the clearance rate of *K. pneumoniae* infection when treated with intravenous and nebulized polymyxin sulfate is higher than that with polymyxin sulfate alone. The combined use of intravenous injection and nebulization can also reduce the average intubation time and amount of polymyxin sulfate used during ICU hospitalization[33]. The main side effects of polymyxin include nephrotoxicity and neurotoxicity[34]. Polymyxin exhibits certain degree of damaging effect on various systems of the human body. The most common clinically used are β-lactam antibiotics (such as ampicillin). Polymyxin can enter various organs of the body through the blood; the most significant toxicity of polymyxin is renal toxicity. Most drug-induced nephrotoxicity is caused by at least one pathogenic mechanism, including changes in glomerular hemodynamics, tubular cell toxicity, inflammation, oxidative damage, crystal nephropathy, or thrombotic microangiopathy[35]. Renal tubular epithelial cells are the main target cells of polymyxin. The accumulation of high concentrations of polymyxin in the renal tubules causes severe apoptosis and necrosis of the epithelial cells[36]. Polymyxin binds to glycoproteins on the apical cell membrane, resulting in increased cell membrane permeability, excretion of cations, anions, and cell fluids, and continuous cell damage[37]; at the same time, some *in vitro* animal experiments have also proven that the nephrotoxicity caused by polymyxin can increase reactive oxygen species due to the inhibition or damage of the body's existing antioxidant defense system by the drug, thereby causing tissue cell oxidative damage and renal function damage[38].

The incidence of neurotoxicity associated with polymyxin sulfate in the past 20 years has not been high, and the condition is mild, with no severe symptoms, of muscle relaxation and respiratory paralysis. However, damage to the central nervous system, particularly acute cerebral ischemic attack, has attracted widespread attention. This article reviews the neurotoxic effects of polymyxin sulfate and the underlying mechanisms. The reason of neurotoxicity may be that the neurons are rich in lipids, and polymyxin sulfate can combine with cell membrane lipids. Polymyxin sulfate binds to the presynaptic binding site at the neuromuscular junction, inhibiting the release of acetylcholine into the synapse, thus causing adverse reactions[39]. Similar to nephrotoxicity, polymyxin-induced neurotoxicity is concentration dependent. It mainly manifests as motor and sensory function disorders, ataxia, and motor neuron injury. Severe neurotoxicity can cause epileptic seizures, coma, and death. Serious complications often cause patients to become disabled for life, and thus needs critical consideration. Because the incidence of neurotoxicity is low and the onset is relatively mild, no specific treatment is provided in clinical practice, and symptoms can disappear by reducing the dose or stopping the medication.

Sepsis, septic shock, and high SOFA scores could significantly affect the results. The differences between the current research and previous trial results may be due to different doses and study populations. This review describes different

Table 1 Comparison of white blood cell, procalcitonin, C-reactive protein levels in both group patients

Group	White blood cell (× 10^9/L)	Procalcitonin (μg/L)	C-reactive protein (mg/L)
Control Group (n = 26)			
Before treatment	8.72 ± 2.36	2.58 ± 1.23	59.62 ± 25.03
After treatment	8.53 ± 1.52[a]	3.86 ± 0.22[a]	39.42 ± 12.87[a]
Treatment Group (n = 28)			
Before treatment	10.42 ± 2.87	2.22 ± 0.67	57.66 ± 22.46
After treatment	6.25 ± 2.72[a,b]	0.54 ± 0.11[a,b]	29.54 ± 13.43[a,b]

[a]P < 0.05, compared with before treatment.
[b]P < 0.05, compared with after treatment of control group.

Table 2 Comparison of total bilirubin, alanine transaminase, aspartate aminotransferase, creatinine, and glomerular filtration rate in both groups

Group	TBIL (μmol/L)	ALT (U/L)	AST (U/L)	Cr (μmol/L)	GFR (mL/min)
Control group (n = 26)					
Before treatment	43.4 ± 20.97[a]	42.35 ± 4.55[a]	40.29 ± 9.16	78.54 ± 15.67	97.28 ± 23.06
After treatment	23.43 ± 5.28	35.96 ± 3.66	39.88 ± 8.54	85.46 ± 12.67	102.87 ± 30.24
Treatment group (n = 28)					
Before treatment	38.92 ± 5.04	46.75 ± 7.43	43.11 ± 7.28	77.89 ± 15.38	92.45 ± 20.33
After treatment	38.26 ± 9.16	41.13 ± 8.75	42.54 ± 10.01	72.34 ± 16,43	98.29 ± 18.98

[a]P < 0.05, compared with before treatment.
TBIL: Total bilirubin; ALT: Alanine transaminase; AST: Aspartate aminotransferase; Cr: Creatinine; GFR: Glomerular filtration rate.

Table 3 Logistic regression analysis of predictive factors related to good clinical outcomes in 105 pneumonia

Variable	OR	95%CI	P value
Sulfate colistin treatment	2.93	1.03-5.88	0.027
SOFA score	0.88	0.79-0.96	0.005
Septic shock	0.42	0.17-0.88	0.021

SOFA: Sequential organ failure assessment; OR: Odds ratio.

clinical situations and proposes suggestions for improving the efficacy. Intravenous administration is the most commonly used route for administering medication to patients with sepsis and other infections. Existing research suggests that the amount of polymyxin B used for intravenous and non-intravenous administration is relatively small, and that there are many types of pathogens.

Polymyxin class of drugs (MDR) show strong antibacterial activity against *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, and other Gram-negative bacteria and have become the "last line of defense" for the treatment of MDR Gram-negative bacteria in foreign clinics. However, its pharmacokinetics, pharmacodynamics, and toxicology are not yet fully understood; therefore, there are certain limitations on its clinical application. This article reviews the progress made by domestic and foreign scholars in the pharmacokinetics and other aspects of polymyxin class of drugs in recent years. Optimization of the medication plan; selection of the best dosage, method of administration, and interval of medication; and improvement in the efficacy and safety of medication warrant a large number of randomized controlled trials.

CONCLUSION

This study shows that compared to the conventional intravenous administration of polymyxin sulfate, nebulized administration of polymyxin sulfate along with intravenous administration does not provide better efficacy and bactericidal effect in patients with pneumonia caused by Gram-negative bacilli in the clinical setting. However, by controlling continuous bacterial contamination of the respiratory tract from tracheal intubation (reduction of inoculum), it may provide more beneficial clinical results. Although there are no such issues with non-specific infections, such as bronchitis and emphysema, intravenous injection of polymyxin sulfate combined with nebulization may also be used for other diseases. The study suggests a novel administration approach for clinical application and helps develop feasible treatment plans that are safer and more acceptable to patients.

FOOTNOTES

Author contributions: Xu HC and Cui Y conceptualized the research project, wrote the paper and checked for scientific accuracy; Wang XY and Wu HB collected data and checked the manuscript for scientific accuracy; Li W and Wang D collected data, performed statistical analyses and checked the manuscript for scientific accuracy; Lin N, Lin L and Zhang YH collected data, performed statistical analyses and checked the manuscript for scientific accuracy.

Institutional review board statement: The study was approved by the Ethics Committee of the People's Liberation Army Northern Theater General Hospital (No: Y2024-016).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: There are no conflicts of interest for any of the authors of this study.

Data sharing statement: All the authors report no relevant conflicts of interest for this article.

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: Hai-Chang Xu 0009-0009-4504-0106; Yan Cui 0009-0007-7871-4854.

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

REFERENCES

1 **Chen Y**, Mu XL. [Clinical Retrospective Study on the Treatment of ICU Patients with Pulmonary Acinetobacter Baumannii Infection by Polymyxin E]. *Kongjun Yike Daxue Xuebao* 2022; **7**: 871-874, 878
2 **Cai CL**, Wang T, Tang C, Qian WD. [Study on the Resistance of Escherichia Coli Mutated by Low Energy Nitrogen Ion Implantation to Polymyxin B]. *Xian Gongye Daxue Xuebao* 2022; **42**: 217-222
3 **Wang MJ**, Xu JQ, Song WF, Liu XL. [The Effect of Polymyxin B on Autophagy of Rat Hepatic Stellate Cells Induced by Lipopolysaccharide]. *Zhongguo Yiyao Kexue* 2022; **12**: 35-38
4 **Deng T**. [Study on the Role of Rhodomycin in Restoring the Sensitivity of Drug-resistant Gram-negative Bacteria to Polymyxin and Tigecycline]. M.Sc. Thesis, Yangzhou University, 2022 [DOI: 10.27441/d.cnki.gyzdu.2022.002404]
5 **Bian MY**, Zhang Q. [Clinical Analysis of Polymyxin B Sulfate in the Treatment of Hospital-acquired Pneumonia Caused by Multidrug-resistant Gram-negative Bacteria]. *Shiyong Yaowu Yu Linchunag* 2022; **25**: 243-246
6 **Miguela-Villoldo P**, Moreno MA, Rodríguez-Lázaro D, Gallardo A, Hernández M, Serrano T, Sáez JL, de Frutos C, Agüero M, Quesada A, Domínguez L, Ugarte-Ruiz M. Longitudinal study of the mcr-1 gene prevalence in Spanish food-producing pigs from 1998 to 2021 and its relationship with the use of polymyxins. *Porcine Health Manag* 2022; **8**: 12 [PMID: 35300732 DOI: 10.1186/s40813-022-00255-0]
7 **de Carvalho FRT**, Telles JP, Tuon FFB, Rabello Filho R, Caruso P, Correa TD. Antimicrobial Stewardship Programs: A Review of Strategies to Avoid Polymyxins and Carbapenems Misuse in Low Middle-Income Countries. *Antibiotics (Basel)* 2022; **11** [PMID: 35326841 DOI: 10.3390/antibiotics11030378]
8 **Ramaloko WT**, Osei Sekyere J. Phylogenomics, epigenomics, virulome and mobilome of Gram-negative bacteria co-resistant to carbapenems and polymyxins: a One Health systematic review and meta-analyses. *Environ Microbiol* 2022; **24**: 1518-1542 [PMID: 35129271 DOI: 10.1111/1462-2920.15930]

9 **Martin-Loeches I**, Leone M, Einav S. Antibiotic Stewardship: Dead Bugs do not Mutate. *J Transl Int Med* 2022; **10**: 290-293 [PMID: 36860631 DOI: 10.2478/jtim-2022-0059]

10 **Silva KED**, Rossato L, Leite AF, Simionatto S. Overview of polymyxin resistance in Enterobacteriaceae. *Rev Soc Bras Med Trop* 2022; **55**: e0349 [PMID: 35239902 DOI: 10.1590/0037-8682-0349-2021]

11 **Han CL**, Wei HX. [Clinical Efficacy Analysis of Tigecycline Combined with Polymyxin in the Treatment of Patients with Pulmonary Infection Caused by Multidrug-resistant Bacteria]. *Zhongguo Zhiye Yaoshi* 2021; **18**: 90-94

12 **Queiroz PA**, Meneguello JE, Silva BR, Caleffi-Ferracioli KR, Scodro RB, Cardoso RF, Marchiosi R, Siqueira VL. Proteomic profiling of Klebsiella pneumoniae carbapenemase (KPC)-producer Klebsiella pneumoniae after induced polymyxin resistance. *Future Microbiol* 2021; **16**: 1195-1207 [PMID: 34590903 DOI: 10.2217/fmb-2021-0005]

13 **Rodríguez-Santiago J**, Cornejo-Juárez P, Silva-Sánchez J, Garza-Ramos U. Polymyxin resistance in Enterobacterales: overview and epidemiology in the Americas. *Int J Antimicrob Agents* 2021; **58**: 106426 [PMID: 34419579 DOI: 10.1016/j.ijantimicag.2021.106426]

14 **Zhang FS**, Ma FY. [Clinical Study on the Treatment of Ventilator-associated Pneumonia Infected by Acinetobacter Baumannii with Polymyxin B Sulfate and Sulbactam Sodium]. *Zhongguo Xiandai Yaowu Yingyong* 2021; **15**: 124-127 [DOI: 10.14164/j.cnki.cn11-5581/r.2021.13.045]

15 **Li YJ**, Wang HT, Ma XP, Teng W, Zhou JJ. [Efficacy Observation of Polymyxin B Combined with Cefoperazone Sodium Sulbactam Sodium and Tigecycline in the Treatment of Multidrug-resistant Acinetobacter Baumannii Pneumonia]. *Zhongwen Keji Ziliao Mulu (Zhongcaoyao Fence)* 2021; **44**: 376-380

16 **Zhang X**, Qu F, Jia W, Huang B, Shan B, Yu H, Tang Y, Chen L, Du H. Polymyxin resistance in carbapenem-resistant Enterobacteriaceae isolates from patients without polymyxin exposure: a multicentre study in China. *Int J Antimicrob Agents* 2021; **57**: 106262 [PMID: 33347990 DOI: 10.1016/j.ijantimicag.2020.106262]

17 **Wu Y**, Zhang J. Standardized inhalation capability assessment: A key to optimal inhaler selection for inhalation therapy. *J Transl Int Med* 2023; **11**: 26-29 [PMID: 37223614 DOI: 10.2478/jtim-2022-0073]

18 **Periasamy H**, Gnanamani A. Polymyxins resistance among Gram-negative pathogens in India. *Lancet Infect Dis* 2020; **20**: 1362-1363 [PMID: 33186513 DOI: 10.1016/S1473-3099(20)30855-0]

19 **Perez LRR**, Carniel E, Narvaez GA, Dias CG. Evaluation of a polymyxin drop test for polymyxin resistance detection among non-fermentative gram-negative rods and enterobacterales resistant to carbapenems. *APMIS* 2021; **129**: 138-142 [PMID: 33164263 DOI: 10.1111/apm.13096]

20 **Dhaouadi S**, Soufi L, Hamza A, Fedida D, Zied C, Awadhi E, Mtibaa M, Hassen B, Cherif A, Torres C, Abbassi MS, Landolsi RB. Co-occurrence of mcr-1 mediated colistin resistance and β-lactamase-encoding genes in multidrug-resistant Escherichia coli from broiler chickens with colibacillosis in Tunisia. *J Glob Antimicrob Resist* 2020; **22**: 538-545 [PMID: 32251867 DOI: 10.1016/j.jgar.2020.03.017]

21 **Zhang K**, Liang JP, Zhong XZ. [Efficacy and Safety of Polymyxin B in the Treatment of Ventilator-associated Pneumonia Caused by Multidrug-resistant Bacteria]. *Yixue Daobao* 2020; **38**: 432-435 [DOI: 10.3870/j.issn.1004-0781.2020.01.00222]

22 **Sartori L**, Sellera FP, Moura Q, Cardoso B, Fontana H, Côrtes LA, Cerdeira L, Lincopan N. Genomic features of a polymyxin-resistant Klebsiella pneumoniae ST491 isolate co-harbouring bla (CTX-M-8) and qnrE1 genes from a hospitalised cat in São Paulo, Brazil. *J Glob Antimicrob Resist* 2020; **21**: 186-187 [PMID: 32224265 DOI: 10.1016/j.jgar.2020.03.006]

23 **Shoaib M**, Hussain A, Satti L, Hussain W, Zaman G, Hanif F. Evaluation of rapid polymyxin Nordmann Poirel test for detection of polymyxin resistance in clinical isolates of Enterobacteriaceae. *Eur J Clin Microbiol Infect Dis* 2020; **39**: 2195-2198 [PMID: 32529457 DOI: 10.1007/s10096-020-03942-4]

24 **Doi Y**, van Duin D. Polymyxin Resistance in Klebsiella pneumoniae: Complexity at Every Level. *Clin Infect Dis* 2020; **70**: 2092-2094 [PMID: 31513703 DOI: 10.1093/cid/ciz627]

25 **Liu AM**. [Clinical Distribution and Drug Sensitivity Analysis of 96 Strains of Multidrug-resistant Acinetobacter Baumannii]. *Zhongxiyi Jiehe Huli* 2020; **7**: 172-174

26 **Xu YH**, Zhang SH, Liu H. [Study on the In vitro Antibacterial Activity of Polymyxin B Combined with Drugs Against Carbapenem-resistant Klebsiella Pneumoniae Pneumonia]. *Zhongguo Xiaoduxue Zazhi* 2020; **37**: 260-262 [DOI: 10.11726/j.issn.1001-7658.2020.04.007]

27 **Wang WL**, Ding WQ, Huang JD, Chen LX, Yu F. [Observation of the Effect of Meropenem Combined with Polymyxin B Sulfate on Patients with Pan-drug-resistant Acinetobacter Baumannii Bacteremia and its Impact on PCT and CRP]. *Quanke Yixue Linchuang Yu Jiaoyu* 2020; **18**: 212-214 [DOI: 10.13558/j.cnki.issn1672-3686.2020.003.006]

28 **Filioussis G**, Kachrimanidou M, Christodoulopoulos G, Kyritsi M, Hadjichristodoulou C, Adamopoulou M, Tzivara A, Kritas SK, Grinberg A. Short communication: Bovine mastitis caused by a multidrug-resistant, mcr-1-positive (colistin-resistant), extended-spectrum β-lactamase-producing Escherichia coli clone on a Greek dairy farm. *J Dairy Sci* 2020; **103**: 852-857 [PMID: 31733863 DOI: 10.3168/jds.2019-17320]

29 **Hassen B**, Abbassi MS, Ruiz-Ripa L, Mama OM, Hassen A, Torres C, Hammami S. High prevalence of mcr-1 encoding colistin resistance and first identification of bla (CTX-M-55) in ESBL/CMY-2-producing Escherichia coli isolated from chicken faeces and retail meat in Tunisia. *Int J Food Microbiol* 2020; **318**: 108478 [PMID: 31855787 DOI: 10.1016/j.ijfoodmicro.2019.108478]

30 **Huang C**, Xiao YH. [Clinical Application and Dilemma of Polymyxin]. *Yixue Daobao* 2020; **39**: 10-16 [DOI: 10.3870/j.issn.1004-0781.2020.01.002]

31 **Huang M**, Lv QP, Hu SS. [Analysis of the Distribution and Drug Resistance of Major Pathogens in the Comprehensive ICU]. *Zhihui Jiankang* 2019; **5**: 30-32 [DOI: 10.19335/j.cnki.2096-1219.2019.36.015]

32 **Gazel D**, Tatman Otkun M, Akçalı A. In vitro activity of methylene blue and eosin methylene blue agar on colistin-resistant A. baumannii: an experimental study. *J Med Microbiol* 2019; **68**: 1607-1613 [PMID: 31535963 DOI: 10.1099/jmm.0.001078]

33 **Boluki E**, Moradi M, Azar PS, Fekrazad R, Pourhajibagher M, Bahador A. The effect of antimicrobial photodynamic therapy against virulence genes expression in colistin-resistance Acinetobacter baumannii. *Laser Ther* 2019; **28**: 27-33 [PMID: 31190695 DOI: 10.5978/islsm.28_19-OR-03]

34 **Moon SH**, Kaufmann Y, Huang E. Paenipeptin Analogues Potentiate Clarithromycin and Rifampin against mcr-1-Mediated Polymyxin-Resistant Escherichia coli In Vivo. *Antimicrob Agents Chemother* 2020; **64** [PMID: 32015033 DOI: 10.1128/AAC.02045-19]

35 **Moffatt JH**, Harper M, Boyce JD. Mechanisms of Polymyxin Resistance. *Adv Exp Med Biol* 2019; **1145**: 55-71 [PMID: 31364071 DOI: 10.1007/978-3-030-16373-0_5]

36 **Scott A**, Pottenger S, Timofte D, Moore M, Wright L, Kukavica-Ibrulj I, Jeukens J, Levesque RC, Freschi L, Pinchbeck GL, Schmidt VM, McEwan N, Radford AD, Fothergill JL. Reservoirs of resistance: polymyxin resistance in veterinary-associated companion animal isolates of Pseudomonas aeruginosa. *Vet Rec* 2019; **185**: 206 [PMID: 31239295 DOI: 10.1136/vr.105075]

37 **Sobur A**, Haque ZF, Sabuj AA, Ievy S, Rahman AT, El Zowalaty ME, Rahman T. Molecular detection of multidrug and colistin-resistant Escherichia coli isolated from house flies in various environmental settings. *Future Microbiol* 2019; **14**: 847-858 [PMID: 31373221 DOI: 10.2217/fmb-2019-0053]

38 **Zhao CY**, Wang YD, Li XY, Ma LY, Yang ST. [Clinical Characteristics and Prevention and Control Measures of Carbapenem-resistant Enterobacteriaceae]. *Zhongguo Chuanranbing Zazhi* 2019; **37**: 321-326 [DOI: 10.3760/cma.j.issn.1000-6680.2019.06.001]

39 **Qian MR**. [New Progress in the Study of the Mechanism of Action of Polymyxin B]. *Gansu Yixue* 2019; **38**: 397-399

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2182-2193

DOI: 10.12998/wjcc.v12.i13.2182

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Establishment and evaluation of a prognostic model for patients with unresectable gastric cancer liver metastases

Zheng-Yao Chang, Wen-Xing Gao, Yue Zhang, Wen Zhao, Di Wu, Lin Chen

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: Toyoshima O, Japan

Received: February 1, 2024
Peer-review started: February 1, 2024
First decision: February 28, 2024
Revised: March 8, 2024
Accepted: March 28, 2024
Article in press: March 28, 2024
Published online: May 6, 2024

Zheng-Yao Chang, Wen-Xing Gao, Di Wu, Lin Chen, Department of General Surgery, The First Medical Center of Chinese PLA General Hospital, Beijing 100853, China

Yue Zhang, Department of Endocrinology, The First Medical Center of Chinese PLA General Hospital, Beijing 100853, China

Wen Zhao, School of Medicine, Nankai University, Tianjin 300071, China

Corresponding author: Lin Chen, MD, PhD, Chief, Chief Doctor, Professor, Surgeon, Department of General Surgery, The First Medical Center of Chinese PLA General Hospital, No. 28 Fuxing Road, Haidian District, Beijing 100853, China. chenlinbj@sina.com

Abstract

BACKGROUND

Liver metastases (LM) is the primary factor contributing to unfavorable outcomes in patients diagnosed with gastric cancer (GC). The objective of this study is to analyze significant prognostic risk factors for patients with GCLM and develop a reliable nomogram model that can accurately predict individualized prognosis, thereby enhancing the ability to evaluate patient outcomes.

AIM

To analyze prognostic risk factors for GCLM and develop a reliable nomogram model to accurately predict individualized prognosis, thereby enhancing patient outcome assessment.

METHODS

Retrospective analysis was conducted on clinical data pertaining to GCLM (type III), admitted to the Department of General Surgery across multiple centers of the Chinese PLA General Hospital from January 2010 to January 2018. The dataset was divided into a development cohort and validation cohort in a ratio of 2:1. In the development cohort, we utilized univariate and multivariate Cox regression analyses to identify independent risk factors associated with overall survival in GCLM patients. Subsequently, we established a prediction model based on these findings and evaluated its performance using receiver operator characteristic curve analysis, calibration curves, and clinical decision curves. A nomogram was created to visually represent the prediction model, which was then externally validated using the validation cohort.

RESULTS
A total of 372 patients were included in this study, comprising 248 individuals in the development cohort and 124 individuals in the validation cohort. Based on Cox analysis results, our final prediction model incorporated five independent risk factors including albumin levels, primary tumor size, presence of extrahepatic metastases, surgical treatment status, and chemotherapy administration. The 1-, 3-, and 5-years Area Under the Curve values in the development cohort are 0.753, 0.859, and 0.909, respectively; whereas in the validation cohort, they are observed to be 0.772, 0.848, and 0.923. Furthermore, the calibration curves demonstrated excellent consistency between observed values and actual values. Finally, the decision curve analysis curve indicated substantial net clinical benefit.

CONCLUSION
Our study identified significant prognostic risk factors for GCLM and developed a reliable nomogram model, demonstrating promising predictive accuracy and potential clinical benefit in evaluating patient outcomes.

Key Words: Gastric cancer; Liver metastases; Nomogram; Prognostic model; Survival analysis

Core Tip: This study identifies pivotal prognostic factors and introduces a nomogram model for predicting individualized prognosis in gastric cancer liver metastases (GCLM). The developed model, supported by comprehensive validation, showcases substantial potential for improving patient outcome evaluation. Notably, the incorporation of five independent risk factors demonstrates promising predictive accuracy, paving the way for enhanced clinical decision-making in managing GCLM patients, ultimately offering valuable insights for personalized treatment strategies.

Citation: Chang ZY, Gao WX, Zhang Y, Zhao W, Wu D, Chen L. Establishment and evaluation of a prognostic model for patients with unresectable gastric cancer liver metastases. *World J Clin Cases* 2024; 12(13): 2182-2193
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2182.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2182

INTRODUCTION

Among all malignant tumor types, gastric cancer (GC) has the highest morbidity and fatality rates. It is one of the most frequent malignant tumors in the world[1]. With the development of treatment technology, the prognosis of patients with GC continues to improve. However, the 5-year overall survival rate (OS) of GC is only about 5%-20%[2]. Therefore, many studies have focused on exploring and analyzing the factors affecting the prognosis of GC patients, such as tumor size and distant metastases. Liver is the most common distant metastases organ. The incidence of GC with liver metastases (GCLM) is 5%-34%[3], which is the main cause of poor prognosis of GC patients[4]. Although the comprehensive treatment technology has made some progress, the prognosis of GCLM is still not ideal[5]. Therefore, effective individualized treatment and comprehensive prognosis evaluation for GCLM patients are of great significance for the implementation of clinical strategies.

Based on a large number of clinical data, nomogram prediction models are widely used to evaluate the prognosis of patients with various types of cancer by combining multiple independent prognostic evaluation factors and quantifying individual survival risk[6-8]. Previous studies have explored the clinical prognostic factors of GCLM patients, but due to the small case size and incomplete research content, the analysis of the prognosis of patients is limited.

Due to the great differences in pathological types, clinical manifestations, tumor size and clinical stage among different types of GCLM patients, the prediction of disease prognosis and the selection of diagnosis and treatment methods are still controversial in clinical practice. Chinese type for GCLM (C-GCLM)[9] is a new clinical classification standard proposed by Chinese experts, which has a high reference value for clinical diagnosis and treatment decisions. This study focused on patients with C-GCLM type III, namely unresectable patients, and developed a prediction model to improve the ability to evaluate the individualized prognosis of patients.

MATERIALS AND METHODS

Study population

A total of 761 individuals diagnosed with GCLM were selected for this study from January 2010 to January 2018 at multiple centers within the Chinese PLA General Hospital's General Surgery Department. Following the exclusion of participants who were lost during follow-up, GCLM Type I and Type II, or lacking essential clinical data, a final cohort of 372 patients was included (Figure 1). The Ethics Committee of the Chinese PLA General Hospital approved this study

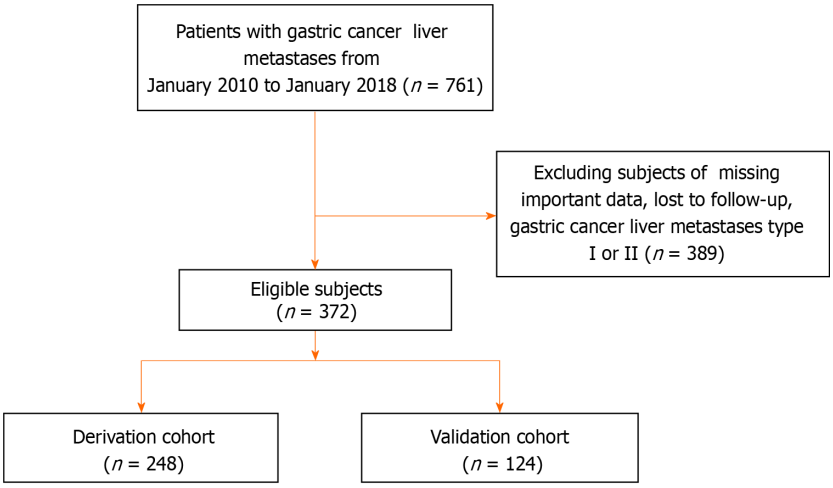

Figure 1 Flow chart of study.

(S2023-724-02), and all participant information was anonymized prior to analysis.

Data collection

Obtaining demographic information and clinical data from electronic medical record systems, Age, gender, height, weight, drinking habits, tumor size, tumor location, metastases size, metastases location, aspartate aminotransferase, alanine aminotransferase, hemoglobin, albumin, γ-glutamyl transferase, chemotherapy, surgery, *etc.* All the above data were collected and reviewed by uniformly trained professionals.

Definition

The classification of GCLM was formulated by the consensus of Chinese experts[9], and the specific classification criteria were as follows: Type I: (1) The invasion depth of the primary tumor of GC was ≤ T4a, and the lymph node metastases was within the D2 dissection range (Bulky N2 was not included); Bulky N2-presence of at least one lymph node ≥ 3 cm in diameter or at least three adjacent lymph nodes ≥ 1.5 cm in diameter along the hepatic, celiac, or splenic arteries; and (2) 1-3 LM; the maximum diameter of the metastatic lesions was ≤ 4 cm or they were confined to one lobe of the liver and did not involve important blood vessels or bile ducts. Type II: (1) The invasion depth of the primary tumor was T4b, or Bulky N2, or Bulky No. 16a2, b1-abdominal aortic lymph nodes; and (2) the number and size of LM were beyond the scope of Type I, but surgical techniques for removal are possible. Type III: (1) Primary GC significantly invaded adjacent tissues or organs; regional lymph nodes such as mesenteric or paraaortic lymph nodes were fixed, fused, or unresectable and confirmed by imaging studies or biopsy; and (2) LM were divided into type III a, bilobar multiple diffuse metastases without extrahepatic metastases, and type III b, LM with one or more extrahepatic organs with or without peritoneal metastases. The difference between the date of GCLM diagnosis and the date of death or the final follow-up was known as overall survival.

Statistical analysis

There were two cohorts created: One for derivation and the other for validation, with a 2:1 ratio. Utilizing chi-square analyses, categorical variables were compared and are shown as percentages (%). Continuous variable data were presented as the median and interquartile range (25^{th}, 75^{th}). Mann-Whitney *U* test was applied for comparing differences between groups for continuous variables. The 20 clinical factors underwent univariate Cox regression analysis to evaluate their individual associations with the outcome. Subsequently, significant prognostic variables ($P < 0.05$) related to GCLM were incorporated into multivariate Cox regression to identify independent risk factors for predicting patient prognosis. A nomogram was created to visualize the model and calculate 1-, 3-, and 5-years overall survival rates. The predictive accuracy of the prediction model was evaluated using receiver operating characteristic (ROC) curves in both development and validation cohorts. Calibration curves were employed to assess agreement between predicted results and actual outcomes, while Hosmer-Lemeshow statistics determined goodness-of-fit for the model. Survival curves for each major variable were generated using Cox hazard models. *P* values with two sides less than 0.05 were considered statistically significant. Software versions 22.0 and 4.0 of SPSS and R were used for all statistical analyses.

RESULTS

Baseline characteristics of the study participants

This study analyzed 372 individuals diagnosed with GCLM, with an average age of 60 years. The group consisted of 306 males and 66 females. Table 1 displays the patients' fundamental characteristics. 96 (25.8%) patients underwent surgery, 72 (19.4%) patients had concurrent extrahepatic metastases, and 60 (16.1%) patients received chemotherapy. All

Table 1 Demographic and clinical characteristics of the derivation and validation cohorts, *n* (%)/median (25th, 75th)

Variables	Derivation cohort	Validation cohort	*P* value
n	248	124	
Age (yr)	60.0 (52-67)	60.0 (53-67)	0.198
Sex			0.427
Men	204 (82.3)	102 (82.3)	0.219
Women	44 (17.7)	22 (17.7)	0.274
BMI, kg/m^2	23.6 (21.1-25.7)	23.6 (20.9-25.8)	0.295
Albumin, g/L	36.2 (33.5-40.0)	36.4 (33.6-40.3)	0.187
Hemoglobin, g/L	117.0 (95-135.3)	117.0 (95-135)	0.109
CEA, ng/mL	9.7 (2.5-59.3)	9.6 (2.4-59)	0.159
AFP, μg/L	3.5 (2.2-8.2)	3.4 (2.2-8.)	0.213
ALT, U/L	18.6 (11.8-35.2)	18.7 (11.9-35.4)	0.308
AST, U/L	22.8 (15.4-47.9)	22.7 (15.4-47.7)	0.103
GGT, U/L	22.5 (10.3-46.2)	22.4 (10.3-46.0)	0.235
TG, mmol/L	1.1 (0.9-1.4)	1.1 (0.9-1.4)	0.122
TC, mmol/L	4.2 (3.5-4.8)	4.2 (3.4-4.8)	0.169
Drinking habit			0.155
Yes	91 (36.8)	46 (37)	
No	157 (63.2)	78 (63)	
Primary tumor size, cm	3.4 (2.4-5)	3.4 (2.5-5)	0.213
Surgery			0.409
Yes	64 (25.9)	32 (25.8)	
No	184 (74.1)	92 (74.2)	
Extrahepatic metastases			0.504
Yes	48 (19.4)	24 (19.4)	
No	200 (80.6)	100 (80.6)	
Chemotherapy			0.306
Yes	40 (16.1)	20 (16.1)	
No	208 (83.9)	104 (83.9)	
Primary site			0.186
Proximal	60 (24.2)	30 (24.2)	
Gastric body	75 (30.3)	37 (29.8)	
Distal	101 (40.7)	51 (41.1)	
Multiple or whole stomach/anastomosis	12 (4.8)	6 (4.8)	
Metastases size (max)	3.3 (2.2-5.7)	3.3 (2.2-5.6)	0.279
Metastases site			0.127
Left liver	24 (9.6)	12 (9.6)	
Right liver	39 (15.7)	19 (15.3)	
Whole liver	182 (73.4)	91 (73.4)	
Hilar	2 (0.9)	1 (0.9)	
Other	1 (0.4)	1 (0.8)	

Data expressed as median (25^{th}, 75^{th}) for skewed variables and percentage (%) for categorical variables. BMI: Body mass index; CEA: Carcinoembryonic antigen; AFP: Alpha-fetoprotein; TC: Total cholesterol; TG: Triglyceride; AST: Aspartate transferase; GGT: Gamma-glutamyl transferase; ALT: Alanine aminotransferase.

participants were assigned randomly to the development group (n = 248) and the validation group (n = 124), as a ratio of 2:1, prior to further analysis. According to the results, there were no appreciable variations based on gender, age, tumor site, primary tumor dimensions, surgical procedures, radiotherapy or chemotherapy between the modeling and validation groups (all P > 0.05).

Construction of nomogram

In the development cohort, a total of 20 clinical factors were included in univariate Cox regression analysis, 6 significant risk factors (all P < 0.05) for OS in GCLM patients were screened: Body mass index, albumin levels, primary tumor size, presence of extrahepatic metastases, surgical intervention, and chemotherapy, respectively. Age and sex are important clinical factors for this study. Although they did not show statistical significance in the univariate Cox regression, we still included them in the multivariate Cox regression for analysis. Finally, 8 clinical factors were included in multivariate Cox regression analysis. Multivariate Cox regression analysis revealed that albumin [P = 0.016, hazard ratio (HR) 95%CI: 0.95 0.91-0.99], primary tumor size (P = 0.031, HR 95%CI: 1.12 1.05-1.25), surgical intervention (P = 0.005, HR 95%CI: 0.38 0.19-0.70), presence of extrahepatic metastases (P = 0.004, HR 95%CI: 2.20 1.30-3.64) and administration of chemotherapy (P = 0.010, HR 95%CI: 0.45, 0.24-0.85) were identified as independent prognostic factors for patients diagnosed with GCLM (Table 2). Based on the above results, a nomogram was drawn using 5 variables. By utilizing the respective scale associated with every risk factor on the nomogram, we derived individual scores for each factor and obtained a cumulative score by summing them up. By further comparing the percentage at the bottom, the predictive value of the 1-, 3-, and 5-years OS of C-GCLM type III patients could be obtained (Figure 2).

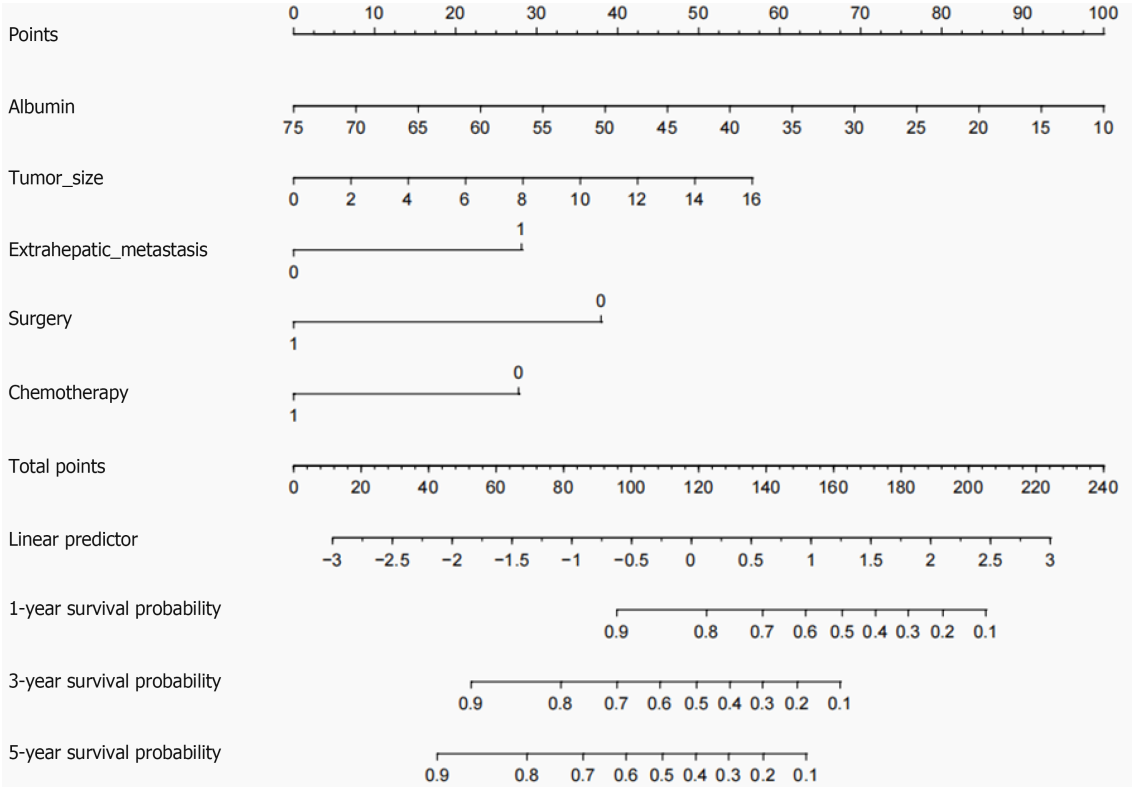

Figure 2 A nomogram model for predicting 1-, 3- and 5-yr overall survival in patients with Chinese type for gastric cancer liver metastases type III.

Assessment of nomogram

The nomogram in the development cohort correctly predicted overall survival after 1-, 3-, and 5-years, with area under the curve values of 0.753, 0.859, and 0.909, respectively, according to the ROC curve. In the validation cohort, the values of 0.772, 0.848, and 0.923 were observed, all exceeding the threshold of 0.7 (Figure 3), suggesting a favorable predictive capacity of the nomogram. Patient overall survival rates from the development and validation cohorts were used to create the calibration curve at 1, 3, and 5 years. The findings indicated a strong concordance between the OS predicted by the nomogram model and the actual observation, as evidenced by the close alignment of their prediction curve with the 45°

Table 2 Cox regression analysis of factors for outcome in the derivation cohort

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (yr)	0.96 (0.75-1.23)	0.108	0.84 (0.69-1.02)	0.074
Sex, *n* (%)			0.96 (0.82-1.11)	0.557
Men	Reference			
Women	0.89 (0.76-1.05)	0.286		
BMI, kg/m^2	0.97 (0.96-0.99)	0.045	1.19 (0.87,1.64)	0.158
Albumin, g/L	0.64 (0.44-0.95)	0.016	0.95 (0.91, 0.99)	0.016
Hemoglobin, g/L	1.02 (0.98-1.06)	0.361		
CEA, ng/ml	0.98 (0.92-1.04)	0.170		
AFP, μg/L	0.46 (0.10-2.05)	0.251		
ALT, U/L	0.91 (0.83-1.01)	0.224		
AST, U/L	1.01 (0.43-2.33)	0.668		
GGT, U/L	0.99 (0.94-1.06)	0.145		
TG, mmol/L	0.76 (0.47-1.25)	0.130		
TC, mmol/L	0.88 (0.41-1.88)	0.254		
Drinking habit				
Yes	Reference			
No	1.19 (0.49-2.88)	0.638		
Primary tumor size, cm	1.49 (1.03-2.16)	0.009	1.12 (1.05-1.25)	0.031
Surgery				
Yes	0.49 (0.33-0.73)	0.001	0.38 (0.19-0.70)	0.005
No	Reference		Reference	
Extrahepatic metastases				
Yes	2.12 (1.35-3.34)	0.001	2.20 (1.30-3.64)	0.004
No	Reference		Reference	
Chemotherapy				
Yes	0.66 (0.48-0.90)	0.006	0.45 (0.24-0.85)	0.010
No	Reference		Reference	
Primary site				
Proximal	Reference			
Gastric body	1.48 (0.51-3.25)	0.213		
Distal	1.07 (0.89-1.30)	0.320		
Multiple or whole stomach/anastomosis	1.00 (0.57-1.74)	0.971		
Metastases size(max)	0.93 (0.48-1.84)	0.119		
Metastases site				
Left liver	Reference			
Right liver	1.31 (0.72-2.38)	0.192		
Whole liver	0.65 (0.30-1.38)	0.183		
Hilar	0.55 (0.18-1.65)	0.610		
Other	1.56 (0.67-3.62)	0.214		

BMI: Body mass index; CEA: Carcinoembryonic antigen; AFP: Alpha-fetoprotein; TC: Total cholesterol; TG: Triglyceride; AST: Aspartate transferase; GGT: Gamma-glutamyl transferase; ALT: Alanine aminotransferase; HR: Hazard ratio.

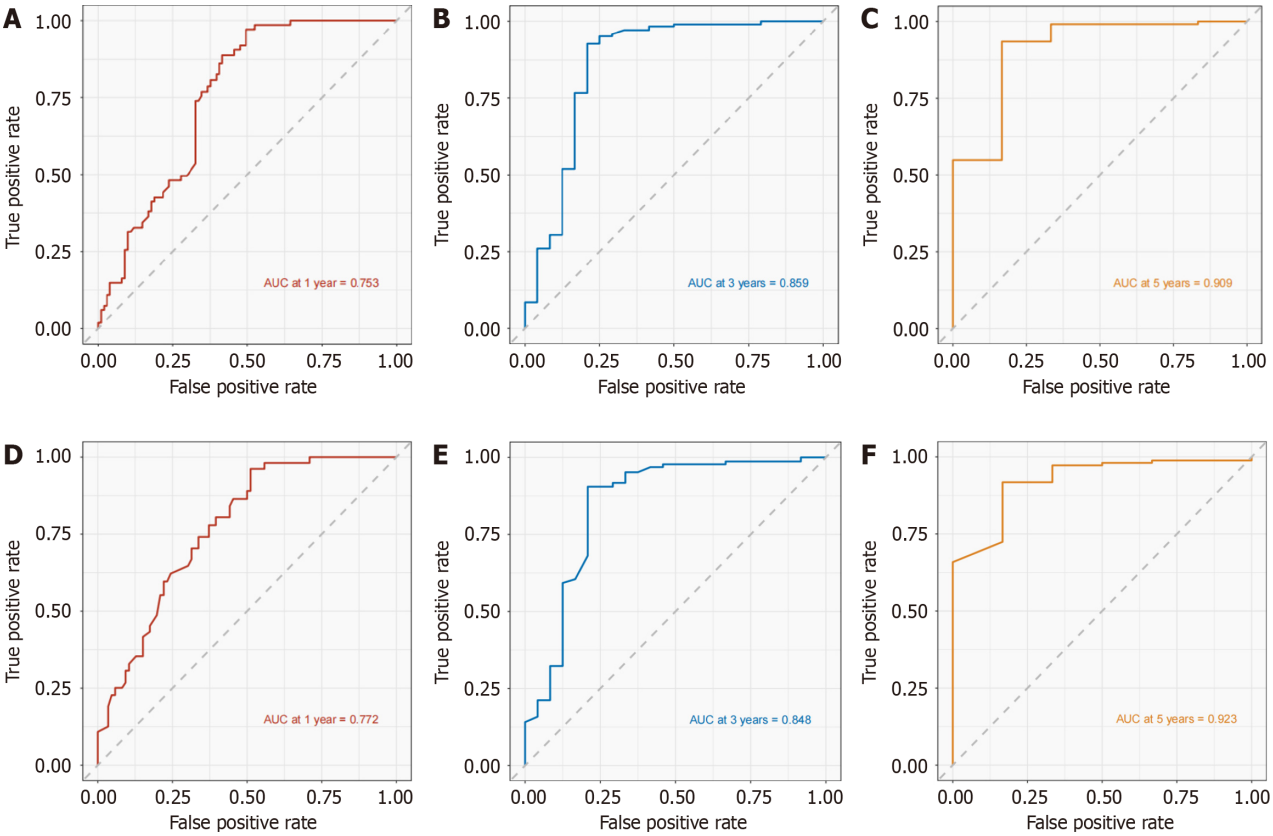

Figure 3 Area under the receiver operating curve for development cohort and validation cohort. A-C: Area under the receiver operating curve (AUC) of 1-, 3-, and 5-yr prognostic models for Chinese type for gastric cancer liver metastases (C-GCLM) type III patients in the developed cohort; D-F: AUC of the 1-, 3-, and 5-yr prognostic models of C-GCLM type III patients in the validation cohort.

diagonal. This indicated that the constructed model had good discrimination ability and accuracy (Figure 4). Decision curve analysis was conducted in both the development and validation cohorts, revealing favorable net benefits for 1-, 3-, and 5-year overall survival rates. These findings indicate that the predictive model holds certain clinical value when it comes to forecasting OS in patients with unresectable GCLM (Figure 5).

Kaplan-Meier survival curve analysis

The impact of each individual factor on overall survival was further examined. Patients in the low-risk group had a significantly higher OS than those in the high-risk group, according to the Kaplan-Meier curve survival analysis ($P < 0.05$) (Figure 6).

DISCUSSION

In this study, a cohort of 372 individuals diagnosed with C-GCLM type III were assigned to two groups in a random manner, maintaining a ratio of 2:1. The development group was utilized to assess the correlation between potential factors that may pose risks and outcomes related to survival, as well as build a prognostic model. On the other hand, the validation group served to confirm the effectiveness of the developed model in predicting future events. Independent prognostic factors influencing the overall survival rate of patients with GCLM were identified through multivariate Cox regression analysis, including albumin levels, size of the primary tumor, presence of extrahepatic metastases, utilization of surgical treatment and administration of chemotherapy. Additionally, a nomogram model was developed to assess the survival rates at 1-, 3-, and 5-year intervals for patients with C-GCLM type III. The findings demonstrated that the proposed model exhibited satisfactory prognostic discrimination ability and survival prediction capability, indicating its potential in facilitating clinical decision-making.

GC is a highly invasive cancer, and LM is the most common distant metastases mode[10], and the prognosis is poor. Multidisciplinary comprehensive treatment has become the main treatment mode of GCLM. However, the prognosis and treatment effect of patients with unresectable GCLM are still controversial. Therefore, it is essential to construct a reliable,

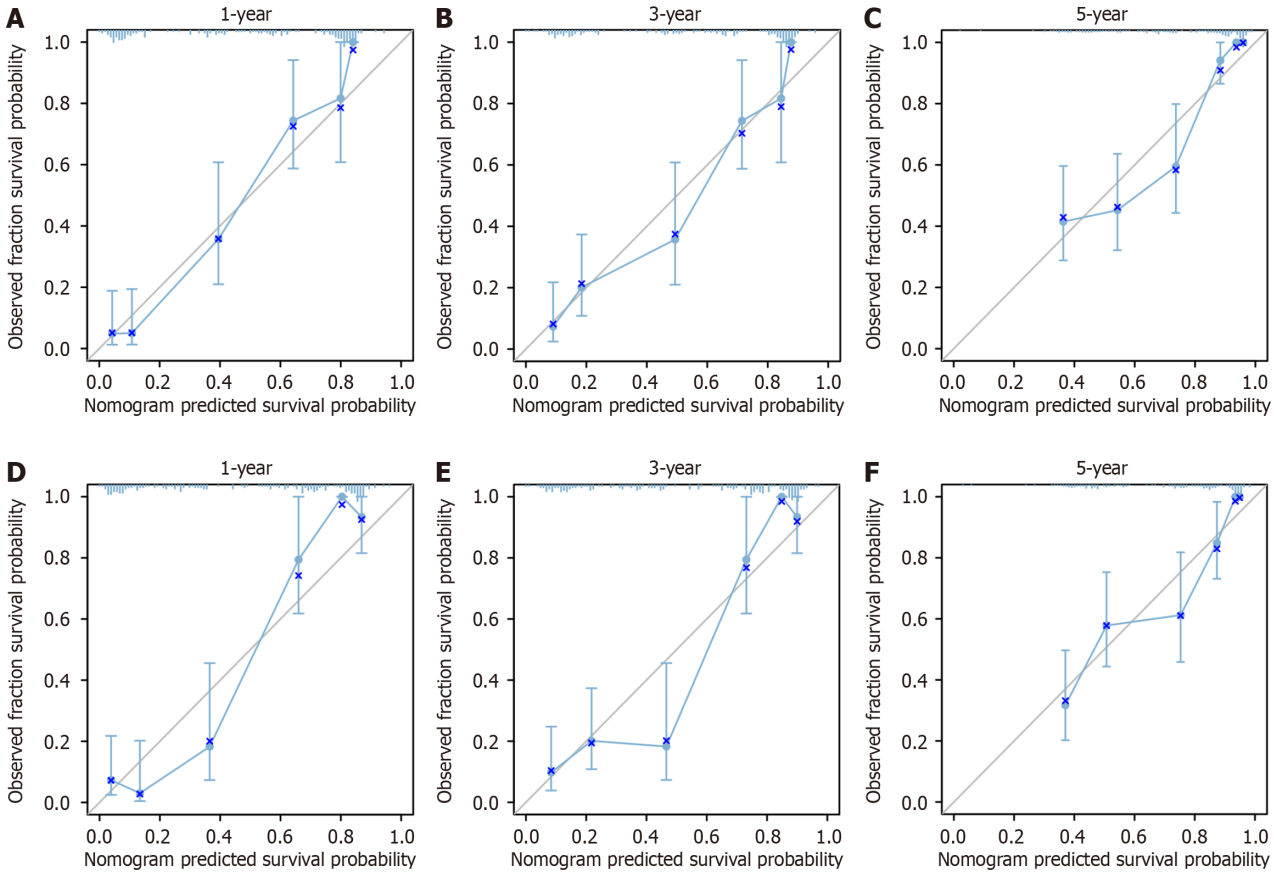

Figure 4 Calibration curves for development cohort andvalidation cohort. A-C: Calibration curves of 1-, 3-, and 5-yr prognostic models for Chinese type for gastric cancer liver metastases (C-GCLM) type III patients in the development cohort; D-F: Validate the calibration curve of the 1-, 3-, and 5-yr prognostic models for C-GCLM type III patients in the validation cohort.

efficient and easy to generalize prognostic model to improve the survival rate of GCLM patients. Most of the previous studies that proposed survival prediction models for GC have limited samples, limited predictors, or difficult to obtain evaluation indicators, which greatly limits the clinical application of these models. Chau *et al*[11] established a four-factor prognostic model including performance status, LM, peritoneal metastases and alkaline phosphatase level. A meta study involving 1304 GCLM patients found that surgical resection of GCLM had better 5-year overall survival and 10-year overall survival than medical control alone[12]. In addition, Ma *et al*[13] developed and verified a nomogram prognostic scoring model including 9 variables, and simplified metastatic or recurrent GC into low, medium and high risk subgroups according to the survival rate to evaluate the prognosis. However, the applicability or reliability of these models in GCLM patients are limited. This study attempts to construct a clinical prediction model with good prediction ability and convenience, so that clinicians can make appropriate treatment according to individualized prediction and achieve better prognosis of patients.

The influence of the independent risk factors included in this study on the prognosis of patients with GCLM has also been confirmed in other studies. Nationwide retrospective studies from the United Kingdom have shown that gastrectomy and hepatectomy for GCLM may confer a survival advantage for selected patients[14]. A systematic review showed that the median OS of patients who underwent gastrectomy combined with liver resection was significantly longer than that of patients who received palliative care (23.7 *vs* 7.6 months)[15]. Similar to the findings of our investigation, surgical intervention demonstrates a beneficial impact on patient prognosis. This could be attributed to the presence of primary lesions, which potentially stimulate para-cancerous tissues surrounding metastatic lesions to create a tumor microenvironment that facilitates the infiltration, spread, and proliferation of cancer cells[16]. Albumin is often used as an indicator of clinical nutritional status, and low albumin is an indication of cachexia, which is usually associated with poor prognosis of cancer patients[17,18]. A cohort study involving 147 patients with metastatic GC found that the score of hemoglobin, albumin, lymphocyte and platelet composition had good prognostic value in advanced GC [19]. In the prediction model of recurrent or metastatic GC established by Ma *et al*[13], albumin is also a risk factor affecting the prognosis[13]. Tumor size directly affects the survival of GC patients[20-22]. In this study, we found that tumor size was an independent prognostic factor in patients with unresectable LM from GC and was inversely associated with OS in our model. Chemotherapy is one of the main treatment methods for patients with GCLM. With the wide application of new chemotherapeutic drugs in recent years, preoperative neoadjuvant chemotherapy has been increasingly used in advanced or metastatic GC, which provides support for reducing postoperative recurrence and prolonging survival time for patients with multiple GCLM. A Japanese study showed that chemotherapy can be applied to patients who underwent R2 resection of LM (macroscopic residual tumor after resection), and the general condition

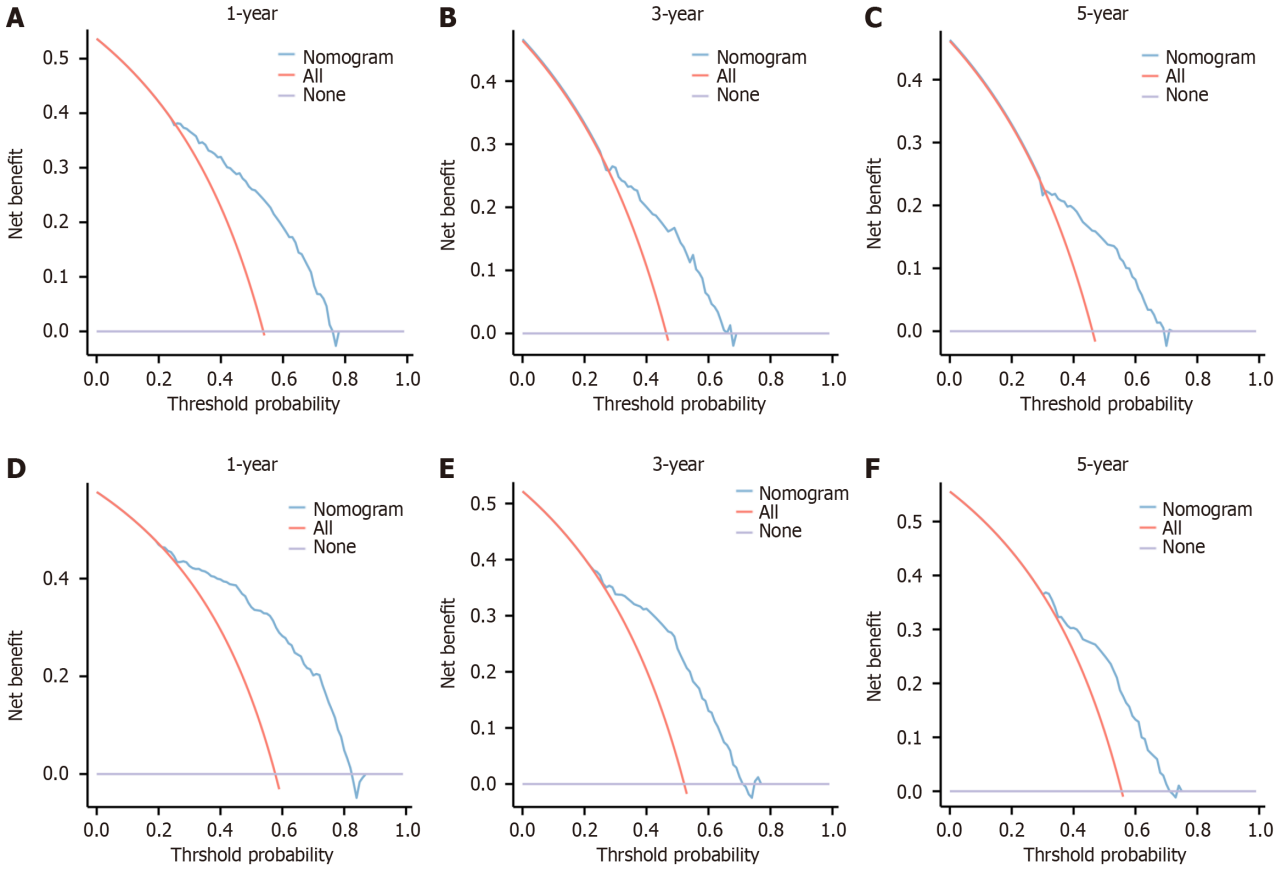

Figure 5 Decision analysis curves for development cohort and validation cohort. A-C: Decision analysis curves (DAC) of 1-, 3-, and 5-yr prognostic models for Chinese type for gastric cancer liver metastases (C-GCLM) type III patients in the development cohort; D-F: DAC of 1-, 3- and 5-yr prognostic models for C-GCLM type III patients in the validation cohort.

and major organ function of these patients should be ensured before receiving chemotherapy[23]. For GCLM patients who cannot undergo radical resection at the time of initial diagnosis, preoperative chemotherapy can reduce the stage of the primary tumor, so as to obtain a high R0 resection rate (R0 resection refers to the absence of cancer cells at the surgical margin under the microscope)[24]. The metastases of GCLM outside the liver indicates that the patient has entered a more advanced stage of the tumor, suggesting a worse prognosis. GCLM is usually multifocal, and can be accompanied by extrahepatic metastases (peritoneum, lymph node, *etc*.). Ueda *et al*[25] showed that peritoneal metastases and lymph node metastases were independent risk and prognostic factors of GCLM. The outcomes of advanced GC patients with distant metastases were poor, with lung, bone, and brain metastases being 4 months, 3 months, 4 months, and 3 months, respectively[26]. This study found that the survival time of patients with extrahepatic metastases was significantly reduced, and simultaneous hepatectomy can be attempted in GCLM patients without extrahepatic metastases.

At present, with the promotion of multidisciplinary treatment mode, GCLM has gradually changed from a single-discipline treatment mode to a multidisciplinary treatment mode[9]. In addition to surgery, the treatment of unresectable GC also includes chemotherapy, immunosuppressant, molecular targeted drugs and so on[27]. In the process of treatment, we should correctly evaluate the patient's condition and take the patient as the center. According to the individual differences of patients, we should study and formulate an individualized treatment plan of "one person, one policy", so as to improve the quality of life of patients and prolong the survival time of patients as far as possible.

The strength of this study is that it is the first prediction model for OS in patients with GCLM type III, which has multi-center and large sample data, and has been internally and externally validated, reflecting good performance. However, it has the following limitations: (1) As a retrospective cohort study, selection bias is inevitable; (2) the data came from Chinese patients, and there may be limitations in generalization to other countries and ethnic groups; (3) with the in-depth study of tumor biological behavior and invasion mechanism, a variety of new tumor treatment methods have emerged, such as immunotherapy, targeted drugs and targeted gene therapy, and have achieved good results. However, the collection of relevant data in this study was not complete, which may cause certain bias; and (4) *Helicobacter pylori (H. pylori)* infection is prevalent in most cases of GC, but our analysis concentrated on factors directly impacting the prognosis of patients with GCLM, aiming to provide a targeted and detailed investigation in this specific context. Therefore, the relationship with *H. pylori* was not included in our study.

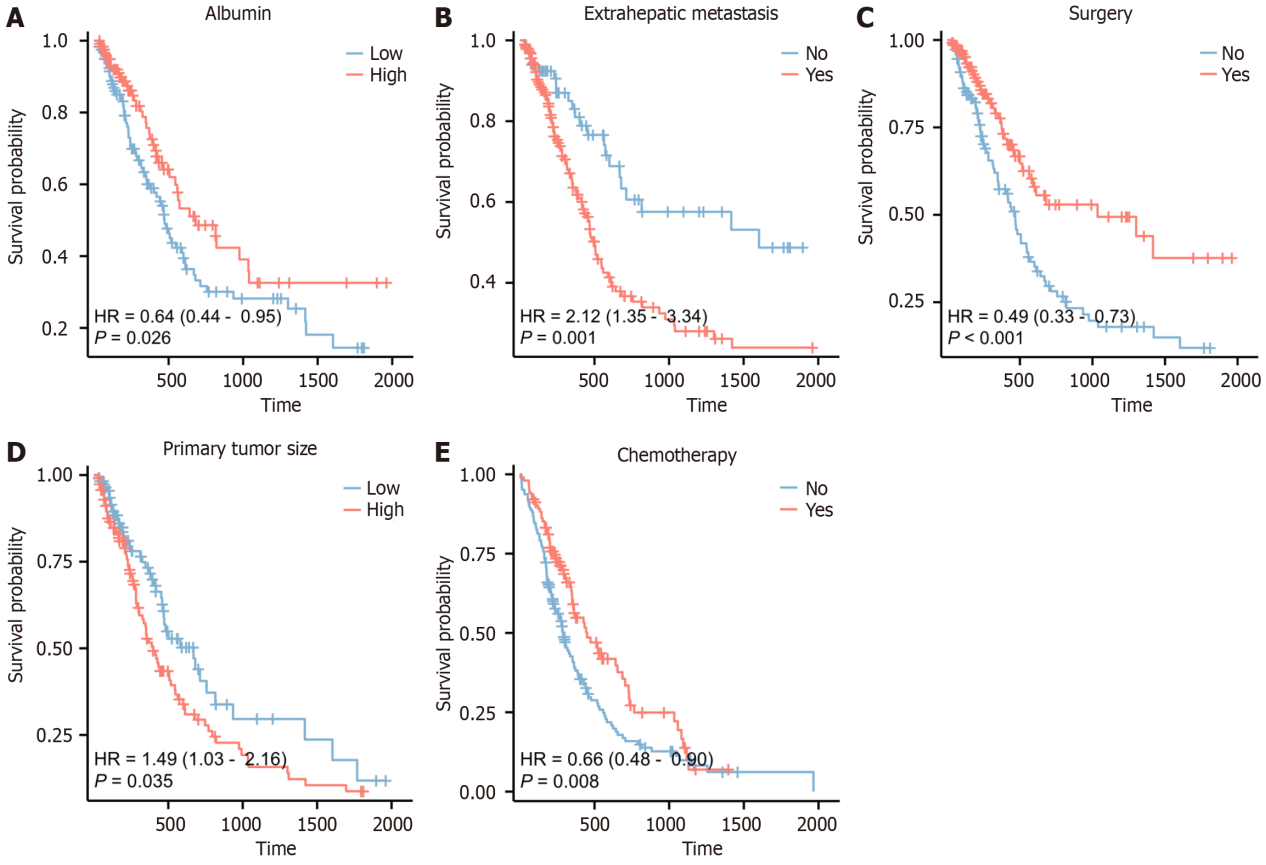

Figure 6 Kaplan-Meier survival curves for each predictor. A: Albumin; B: Extrahepatic metastases; C: Surgery; D: Tumor size; E: Chemotherapy.

CONCLUSION

In conclusion, it is significant for clinicians to conduct precision medicine and individualized medicine by evaluating the prognosis of patients with unresectable GCLM and constructing the corresponding prognostic model. The nomogram model developed in this study offers a convenient, accurate, and user-friendly tool for clinicians to predict and evaluate the prognosis of GCLM patients.

FOOTNOTES

Co-first authors: Zheng-Yao Chang and Wen-Xin Gao.

Co-corresponding authors: Di Wu and Lin Chen.

Author contributions: Chang ZY and Gao WX contributed to the research design and manuscript writing; Zhang Y and Zhao W contributed to the data collection and analysis; Wu D and Chen L overall supervise the study. All authors have read and approve the submitted version.

Institutional review board statement: The study was reviewed and approved for publication by the Ethics Committee of the Chinese PLA General Hospital.

Informed consent statement: The study was reviewed by the Ethics Committee of the General Hospital of the Chinese People's Liberation Army to review and waive informed consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for 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: Zheng-Yao Chang 0000-0003-4136-3003; Di Wu 0000-0003-1620-2224; Lin Chen 0000-0001-6245-8509.

S-Editor: Liu H
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 **Thrift AP**, El-Serag HB. Burden of Gastric Cancer. *Clin Gastroenterol Hepatol* 2020; **18**: 534-542 [PMID: 31362118 DOI: 10.1016/j.cgh.2019.07.045]
3 **Sano T**, Coit DG, Kim HH, Roviello F, Kassab P, Wittekind C, Yamamoto Y, Ohashi Y. Proposal of a new stage grouping of gastric cancer for TNM classification: International Gastric Cancer Association staging project. *Gastric Cancer* 2017; **20**: 217-225 [PMID: 26897166 DOI: 10.1007/s10120-016-0601-9]
4 **Kerkar SP**, Kemp CD, Avital I. Liver resections in metastatic gastric cancer. *HPB (Oxford)* 2010; **12**: 589-596 [PMID: 20961366 DOI: 10.1111/j.1477-2574.2010.00224.x]
5 **Li Q**, Li H, Jiang H, Feng Y, Cui Y, Wang Y, Ji Y, Yu Y, Li W, Xu C, Yu S, Zhuang R, Liu T. Predictive factors of trastuzumab-based chemotherapy in HER2 positive advanced gastric cancer: a single-center prospective observational study. *Clin Transl Oncol* 2018; **20**: 695-702 [PMID: 29168107 DOI: 10.1007/s12094-017-1772-5]
6 **Chen T**, Xu L, Ye L, Qiu H, Hu Y, Liu H, Zhou Z, Li G, Yu J. A new nomogram for recurrence-free survival prediction of gastrointestinal stromal tumors: Comparison with current risk classification methods. *Eur J Surg Oncol* 2019; **45**: 1109-1114 [PMID: 30594406 DOI: 10.1016/j.ejso.2018.12.014]
7 **Bakhti SZ**, Latifi-Navid S, Safaralizadeh R. Helicobacter pylori-related risk predictors of gastric cancer: The latest models, challenges, and future prospects. *Cancer Med* 2020; **9**: 4808-4822 [PMID: 32363738 DOI: 10.1002/cam4.3068]
8 **Valentini V**, van Stiphout RG, Lammering G, Gambacorta MA, Barba MC, Bebenek M, Bonnetain F, Bosset JF, Bujko K, Cionini L, Gerard JP, Rödel C, Sainato A, Sauer R, Minsky BD, Collette L, Lambin P. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. *J Clin Oncol* 2011; **29**: 3163-3172 [PMID: 21747092 DOI: 10.1200/JCO.2010.33.1595]
9 **Zhang K**, Chen L. Chinese consensus on the diagnosis and treatment of gastric cancer with liver metastases. *Ther Adv Med Oncol* 2020; **12**: 1758835920904803 [PMID: 32127925 DOI: 10.1177/1758835920904803]
10 **Sekiguchi M**, Oda I, Matsuda T, Saito Y. Epidemiological Trends and Future Perspectives of Gastric Cancer in Eastern Asia. *Digestion* 2022; **103**: 22-28 [PMID: 34515086 DOI: 10.1159/000518483]
11 **Chau I**, Norman AR, Cunningham D, Waters JS, Oates J, Ross PJ. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from three multicenter, randomized, controlled trials using individual patient data. *J Clin Oncol* 2004; **22**: 2395-2403 [PMID: 15197201 DOI: 10.1200/JCO.2004.08.154]
12 **Montagnani F**, Crivelli F, Aprile G, Vivaldi C, Pecora I, De Vivo R, Clerico MA, Fornaro L. Long-term survival after liver metastasectomy in gastric cancer: Systematic review and meta-analysis of prognostic factors. *Cancer Treat Rev* 2018; **69**: 11-20 [PMID: 29860024 DOI: 10.1016/j.ctrv.2018.05.010]
13 **Ma T**, Wu Z, Zhang X, Xu H, Feng Y, Zhang C, Xie M, Yang Y, Zhang Y, Feng C, Sun G. Development and validation of a prognostic scoring model for mortality risk stratification in patients with recurrent or metastatic gastric carcinoma. *BMC Cancer* 2021; **21**: 1326 [PMID: 34895168 DOI: 10.1186/s12885-021-09079-7]
14 **Markar SR**, Mackenzie H, Mikhail S, Mughal M, Preston SR, Maynard ND, Faiz O, Hanna GB. Surgical resection of hepatic metastases from gastric cancer: outcomes from national series in England. *Gastric Cancer* 2017; **20**: 379-386 [PMID: 26939792 DOI: 10.1007/s10120-016-0604-6]
15 **Liao YY**, Peng NF, Long D, Yu PC, Zhang S, Zhong JH, Li LQ. Hepatectomy for liver metastases from gastric cancer: a systematic review. *BMC Surg* 2017; **17**: 14 [PMID: 28193210 DOI: 10.1186/s12893-017-0215-0]
16 **van der Wal GE**, Gouw AS, Kamps JA, Moorlag HE, Bulthuis ML, Molema G, de Jong KP. Angiogenesis in synchronous and metachronous colorectal liver metastases: the liver as a permissive soil. *Ann Surg* 2012; **255**: 86-94 [PMID: 22156924 DOI: 10.1097/SLA.0b013e318238346a]
17 **Gupta D**, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. *Nutr J* 2010; **9**: 69 [PMID: 21176210 DOI: 10.1186/1475-2891-9-69]
18 **Crumley AB**, Stuart RC, McKernan M, McMillan DC. Is hypoalbuminemia an independent prognostic factor in patients with gastric cancer? *World J Surg* 2010; **34**: 2393-2398 [PMID: 20602101 DOI: 10.1007/s00268-010-0641-y]
19 **Duzkopru Y**, Kocanoglu A, Dogan O, Sahinli H, Cilbir E, Altinbas M. Hemoglobin, albumin, lymphocyte, and platelet score as a predictor of prognosis in metastatic gastric cancer. *World J Gastrointest Oncol* 2023; **15**: 1626-1635 [PMID: 37746652 DOI: 10.4251/wjgo.v15.i9.1626]
20 **Wang HM**, Huang CM, Zheng CH, Li P, Xie JW, Wang JB, Lin JX, Lu J. Tumor size as a prognostic factor in patients with advanced gastric cancer in the lower third of the stomach. *World J Gastroenterol* 2012; **18**: 5470-5475 [PMID: 23082065 DOI: 10.3748/wjg.v18.i38.5470]
21 **Park JM**, Ryu WS, Kim JH, Park SS, Kim SJ, Kim CS, Mok YJ. Prognostic factors for advanced gastric cancer: stage-stratified analysis of patients who underwent curative resection. *Cancer Res Treat* 2006; **38**: 13-18 [PMID: 19771253 DOI: 10.4143/crt.2006.38.1.13]

22 **Zu H**, Wang F, Ma Y, Xue Y. Stage-stratified analysis of prognostic significance of tumor size in patients with gastric cancer. *PLoS One* 2013; **8**: e54502 [PMID: 23382906 DOI: 10.1371/journal.pone.0054502]

23 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* 2021; **24**: 1-21 [PMID: 32060757 DOI: 10.1007/s10120-020-01042-y]

24 **Yu P**, Zhang Y, Ye Z, Chen X, Huang L, Du Y, Cheng X. Treatment of Synchronous Liver Metastases from Gastric Cancer: A Single-Center Study. *Cancer Manag Res* 2020; **12**: 7905-7911 [PMID: 32904676 DOI: 10.2147/CMAR.S261353]

25 **Ueda K**, Iwahashi M, Nakamori M, Nakamura M, Naka T, Ishida K, Ojima T, Yamaue H. Analysis of the prognostic factors and evaluation of surgical treatment for synchronous liver metastases from gastric cancer. *Langenbecks Arch Surg* 2009; **394**: 647-653 [PMID: 18343941 DOI: 10.1007/s00423-008-0311-9]

26 **Qiu MZ**, Shi SM, Chen ZH, Yu HE, Sheng H, Jin Y, Wang DS, Wang FH, Li YH, Xie D, Zhou ZW, Yang DJ, Xu RH. Frequency and clinicopathological features of metastasis to liver, lung, bone, and brain from gastric cancer: A SEER-based study. *Cancer Med* 2018; **7**: 3662-3672 [PMID: 29984918 DOI: 10.1002/cam4.1661]

27 **Guan WL**, He Y, Xu RH. Gastric cancer treatment: recent progress and future perspectives. *J Hematol Oncol* 2023; **16**: 57 [PMID: 37245017 DOI: 10.1186/s13045-023-01451-3]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2194-2200

DOI: 10.12998/wjcc.v12.i13.2194

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Therapeutic effect of Wendan Decoction combined with mosapride on gastroesophageal reflux disease after esophageal cancer surgery

Yu-Jing Zhang, Shen-Ping 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): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Roviello G, Italy

Received: January 25, 2024
Peer-review started: January 25, 2024
First decision: February 8, 2024
Revised: February 9, 2024
Accepted: March 27, 2024
Article in press: March 27, 2024
Published online: May 6, 2024

Yu-Jing Zhang, Shen-Ping Wu, Department of Oncology, Beijing Integrated Traditional Chinese and Western Medicine Hospital, Beijing 100039, China

Corresponding author: Yu-Jing Zhang, MM, Attending Doctor, Department of Oncology, Beijing Integrated Traditional Chinese and Western Medicine Hospital, No. 3 East Street, Yongding Road, Haidian District, Beijing 100039, China. tzvz674@163.com

Abstract

BACKGROUND

Gastroesophageal reflux disease (GERD) is a common complication of esophageal cancer surgery that can affect quality of life and increase the risk of esophageal stricture and anastomotic leakage. Wendan Decoction (WDD) is a traditional Chinese herbal formula used to treat various gastrointestinal disorders, such as gastritis, functional dyspepsia, and irritable bowel syndrome. Mosapride, a prokinetic agent, functions as a selective 5-hydroxytryptamine 4 agonist, enhancing gastrointestinal motility.

AIM

To evaluate the therapeutic effects of WDD combined with mosapride on GERD after esophageal cancer surgery.

METHODS

Eighty patients with GERD were randomly divided into treatment (receiving WDD combined with mosapride) and control (receiving mosapride alone) groups. The treatment was conducted from January 2021 to January 2023. The primary outcome was improved GERD symptoms as measured using the reflux disease questionnaire (RDQ). The secondary outcomes were improved esophageal motility (measured using esophageal manometry), gastric emptying (measured using gastric scintigraphy), and quality of life [measured *via* the Short Form-36 (SF-36) Health Survey].

RESULTS

The treatment group showed a notably reduced RDQ score and improved esophageal motility parameters, such as lower esophageal sphincter pressure, peristaltic amplitude, and peristaltic velocity compared to the control group. The treatment group showed significantly higher gastric emptying rates and SF-36 scores (in both physical and mental domains) compared to the control group. No serious adverse effects were observed in either group.

CONCLUSION
WDD combined with mosapride is an effective and safe therapy for GERD after esophageal cancer surgery. It can improve GERD symptoms, esophageal motility, gastric emptying, and the quality of life of patients. Further studies with larger sample sizes and longer follow-up periods are required to confirm these findings.

Key Words: Gastroesophageal reflux disease; Esophageal cancer surgery; Wendan Decoction; Mosapride; Treatment effects; Gastroesophageal reflux disease symptoms

Core Tip: This study suggests that combining Wendan Decoction with mosapride is an effective and safe therapy for managing gastroesophageal reflux disease (GERD) after esophageal cancer surgery. It improves GERD symptoms, esophageal motility, gastric emptying, and the quality of life of patients. Larger studies with longer follow-up periods are needed to further validate these findings.

Citation: Zhang YJ, Wu SP. Therapeutic effect of Wendan Decoction combined with mosapride on gastroesophageal reflux disease after esophageal cancer surgery. *World J Clin Cases* 2024; 12(13): 2194-2200
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2194.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2194

INTRODUCTION

Esophageal cancer is a common malignant tumor of the digestive tract with high incidence and mortality rates worldwide, seriously affecting the quality of life and prognosis of patients[1]. The treatment of esophageal cancer includes surgery, radiotherapy, and chemotherapy, among which surgery is one of the most effective radical methods[2]. However, the postoperative complication rate of esophageal cancer is high, with gastroesophageal reflux disease (GERD) being the most common. GERD refers to a series of symptoms and complications, such as heartburn, acid regurgitation, retrosternal pain, dysphagia, esophagitis, esophageal ulcer, esophageal stricture, hiatal hernia, caused by the reflux of gastric contents into the esophagus[3,4]. GERD not only affects the quality of life of patients but also increases the risk of anastomotic leakage and stricture and may even lead to the recurrence and metastasis of esophageal cancer.

Currently, drugs for treating GERD mainly include proton pump inhibitors (PPI), H2 receptor antagonists (H2RA), and prokinetic agents[5]. Prokinetic agents can enhance the motility of the gastrointestinal tract, accelerate gastric emptying, and reduce the stimulation of gastric contents in the esophagus. Mosapride is a selective 5-hydroxytryptamine 4 (5-HT4) receptor agonist that can increase the intracellular calcium ion concentration in gastrointestinal smooth muscle cells by stimulating 5-HT4 receptors, thereby enhancing peristalsis and tension in the gastrointestinal tract. Mosapride has been widely used in the treatment of various digestive system diseases, such as functional dyspepsia and constipation, and some clinical studies have shown that mosapride has a therapeutic effect on GERD after esophageal cancer surgery[6].

Wendan Decoction (WDD) is a traditional Chinese herbal formula composed of five herbs: *Poria cocos*, *Citrus reticulata*, *Pinellia ternata*, *Zingiber officinale*, and *Aurantium fructus*[7]. It warms the middle, regulates qi, resolves phlegm, and opens the orifices. WDD is mainly used to treat neurological and psychiatric diseases caused by cold spleen-stomach deficiency, qi stagnation, and phlegm obstruction, such as coma, epilepsy, convulsion[8]. In recent years, WDD has been used to treat various digestive system diseases, such as chronic gastritis, functional dyspepsia, and irritable bowel syndrome[7]. WDD can improve the digestive and absorptive function of the gastrointestinal tract by warming the spleen and stomach, regulating qi flow, dissolving sticky food retention, thereby relieving indigestion and reflux symptoms. This study aimed to evaluate the therapeutic effect of WDD combined with mosapride on GERD after esophageal cancer surgery.

MATERIALS AND METHODS

Study design and approval

This experiment was conducted at the Beijing Integrated Traditional Chinese and Western Medicine Hospital in China. The research protocol was approved by the hospital ethics committee, and all patients provided written informed consent before participating in the study.

Inclusion and exclusion criteria

This study included patients: (1) Who underwent esophagectomy for esophageal cancer with anastomosis of the stomach and cervical esophagus; (2) who developed GERD symptoms, such as heartburn, acid regurgitation, retrosternal pain, or dysphagia, within 6 months after surgery; (3) with a reflux disease questionnaire (RDQ) score of > 12 points; (4) aged between 18 and 75 years; and (5) with no contraindications to WDD or mosapride. The exclusion criteria were as follows:

(1) patients with severe complications after surgery, such as anastomotic leakage, bleeding, infection, or fistula; (2) patients with other gastrointestinal diseases, such as peptic ulcer, gastric cancer, or inflammatory bowel disease; (3) patients with severe diseases, such as liver cirrhosis, renal failure, or cardiovascular disease; (4) pregnant or lactating females; (5) individuals allergic to WDD or mosapride; and (6) patients taking drugs that could affect the gastrointestinal motility or acid secretion, such as PPI, H2RA, anticholinergics, opioids.

Randomization and intervention

Eligible patients were randomly assigned to either the treatment or control group using a computer-generated random number table. The allocation ratio was set at 1:1. The treatment group received WDD in combination with mosapride, whereas the control group received mosapride alone. The treatment was conducted from January 2021 to January 2023. The dosage and administration of WDD and mosapride were as follows: WDD was prepared by decocting 15 g *Poria cocos*, 10 g *Citrus reticulata*, 9 g *Pinellia ternata*, 6 g *Zingiber officinale*, and 6 g *Aurantium fructus* in 300 mL water for 30 min. The decoction was divided into two doses and administered orally twice daily before breakfast and dinner. Mosapride was administered orally at a dose of 5 mg three times daily before each meal. Patient compliance was monitored by counting the remaining pills and decoction bags at each follow-up visit.

Outcome measures

The primary outcome was improvement in GERD symptoms, as measured with the RDQ. The RDQ is a self-administered questionnaire consisting of 12 items covering four domains: Heartburn, regurgitation, chest pain, and dysphagia. Each item is rated on a six-point Likert scale ranging from 0 (no symptoms) to 5 (very severe symptoms). The total score ranges from 0 to 60 points, with higher scores indicating more severe symptoms. The RDQ was administered at baseline and every 6 months during the follow-up period.

The secondary outcomes were improvement in esophageal motility function, measured using esophageal manometry; gastric emptying function, measured using gastric scintigraphy; and quality of life, as measured with the Short Form-36 (SF-36) Health Survey. Esophageal manometry measures the pressure and coordination of the esophageal muscles during swallowing. It can provide information on lower esophageal sphincter pressure (LESP), peristaltic amplitude (PA), and peristaltic velocity (PV). It can provide information on the gastric emptying half-life (GEHT), the time required for half of a test meal to leave the stomach. The SF-36 is a self-administered questionnaire that assesses eight domains of health-related quality of life: Physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Each domain was scored from 0 to 100 points, with higher scores indicating a better quality of life. Esophageal manometry, gastric scintigraphy, and the SF-36 Health Survey were performed at baseline and at the end of the follow-up period.

Sample size calculation

The sample size was calculated based on the primary outcomes. According to previous studies[9], the mean RDQ score of patients with GERD after esophageal cancer surgery is approximately 25 points, with a standard deviation of approximately 10 points. Assuming a significance level of 0.05, power of 0.80, and mean difference of 5 points between the two groups, the required sample size was 34 patients per group. Considering a dropout rate of 20%, the final sample size was 40 patients per group.

Data analysis

Data were analyzed using SPSS 22.0. The baseline characteristics of the patients were compared using *t*- or chi-square test, as appropriate. Changes in the RDQ and SF-36 scores over time were analyzed using repeated-measures analysis of variance (ANOVA), with group, time, and group-by-time interactions as factors. Changes in esophageal manometry and gastric scintigraphy parameters from baseline to the end of the follow-up period were compared using the *t*- or Mann-Whitney *U* test, as appropriate. The significance level was set at $P < 0.05$.

RESULTS

Patient enrollment and characteristics

Eighty patients were enrolled in the study and were randomly and equally assigned to each group. The baseline patient characteristics are shown in Table 1. No significant differences were observed between the two groups in terms of age, sex, tumor stage, surgical approach, or RDQ score.

RDQ score over time

The changes in the RDQ scores over time are shown in Table 2. Repeated-measures ANOVA revealed a significant group-by-time interaction effect on the RDQ score ($F = 5.32$, $P < 0.01$), indicating that the treatment group had a greater improvement in GERD symptoms than the control group over time. *Post hoc* tests showed that the treatment group had a significantly lower RDQ score than the control group at each time point after baseline ($P < 0.05$).

Esophageal manometry and gastric emptying

The changes in esophageal manometry parameters from baseline to the end of the follow-up period are shown in Table 3. The *t*- or Mann-Whitney *U* test showed that the treatment group had significantly higher LESP, PA, and PV than the

Table 1 Baseline characteristics of patients

Variable	Treatment group (*n* = 40)	Control group (*n* = 40)	*P* value
Age (yr)	58.3 ± 9.2	57.6 ± 8.7	0.68
Sex (male/female)	28/12	26/14	0.67
Tumor stage (I/II/III)	10/18/12	12/16/12	0.81
Surgical approach (open/thoracoscopic)	22/18	24/16	0.69
RDQ score	25.4 ± 9.8	24.8 ± 10.2	0.76

RDQ: Reflux disease questionnaire.

Table 2 Changes in the reflux disease questionnaire score over time

Time	Treatment group (*n* = 40)	Control group (*n* = 40)	*P* value
Baseline	25.4 ± 9.8	24.8 ± 10.2	0.76
6 months	18.2 ± 8.6[a]	21.6 ± 9.4[a]	< 0.05
12 months	14.6 ± 7.8[a]	18.4 ± 8.2[a]	< 0.05
18 months	12.4 ± 7.2[a]	16.2 ± 7.6[a]	< 0.05
24 months	10.2 ± 6.4[a]	14.8 ± 7.4[a]	< 0.05

[a]*P* < 0.05, compared with baseline within each group.

Table 3 Changes in the esophageal manometry parameters from baseline to the end of the follow-up period

Variable	Treatment group (*n* = 40)	Control group (*n* = 40)	*P* value
LESP (mmHg)	Baseline: 11.2 ± 3.4	Baseline: 10.8 ± 3.6	< 0.01
	End: 15.6 ± 4.2[a]	End: 12.4 ± 3.8[a]	
PA (mmHg)	Baseline: 38.6 ± 11.2 End: 52.4 ± 12.6[a]	Baseline: 37.4 ± 10.8 End: 41.2 ± 11.4[a]	< 0.01
PV (cm/s)	Baseline: 2.8 ± 0.9 End: 3.6 ± 1.1[a]	Baseline: 2.7 ± 0.8 End: 2.9 ± 0.9[a]	< 0.01

[a]*P* < 0.05, compared with baseline within each group.
LESP: Lower esophageal sphincter pressure; PA: Peristaltic amplitude; PV: Peristaltic velocity.

control group at the end of the follow-up period ($P < 0.05$).

Changes in gastric emptying function

Changes in gastric emptying function from baseline to the end of the follow-up period are shown in Table 4. The *t*-test showed that the treatment group had a significantly lower GEHT than the control group at the end of the follow-up period ($P < 0.05$).

SF-36 score over time

Changes in SF-36 scores over time are shown in Table 5. The repeated measures ANOVA indicated a significant group-by-time interaction effect on both the physical and mental domains of the SF-36 score (F = 6.24, $P < 0.01$ for the physical domain; F = 4.56, $P < 0.01$ for the mental domain). This implies that, over time, the treatment group experienced a more substantial improvement in quality of life than the control group. *Post hoc* tests corroborated that at each subsequent time point, the treatment group registered a significantly higher SF-36 score than the control group in both the physical and mental domains.

Table 4 Changes in the gastric emptying function from baseline to the end of the follow-up period

Variable	Treatment group (*n* = 40)	Control group (*n* = 40)	*P* value
GEHT (min)	Baseline: 76.4 ± 18.6	Baseline: 75.6 ± 19.2	< 0.05
	End: 58.2 ± 15.4[a]	End: 68.4 ± 16.8[a]	

[a]*P* < 0.05, compared with baseline within each group.
GEHT: Gastric emptying half-life.

Table 5 Changes in the Short Form-36 score over time

Time	Treatment group (*n* = 40)	Control group (*n* = 40)	*P* value (physical/mental)
Physical domain	Baseline: 72.4 ± 15.6	Baseline: 71.6 ± 16.2	< 0.05
	End: 82.6 ± 14.2[a]	End: 76.4 ± 15.8[a]	
Mental domain	Baseline: 68.2 ± 13.4	Baseline: 67.4 ± 14.2	< 0.05
	End: 78.4 ± 12.6[a]	End: 72.2 ± 13.8[a]	

[a]*P* < 0.05, compared with baseline within each group.

DISCUSSION

This study assessed the therapeutic effect of WDD combined with mosapride on GERD post-esophageal cancer surgery, finding that the combination significantly improves GERD symptoms, esophageal motility function, gastric emptying function, and quality of life and is safe. These results are consistent with those of previous studies and provide innovative ideas and evidence for the integrated treatment of GERD after esophageal cancer surgery[10-14].

WDD is a traditional Chinese herbal formula, and its main mechanism of action may be related to the various aspects. First, WDD can warm the spleen and stomach, regulate qi flow, dissolve sticky food retention, and improve the digestive and absorptive functions of the gastrointestinal tract, thereby relieving indigestion and reflux symptoms. Second, WDD can reduce gastric acid secretion and increase mucus secretion by lowering stomach pH and increasing bicarbonate concentration, thus protecting the esophageal mucosa from stimulation and damage by gastric contents. Third, WDD inhibited inflammatory cytokines and oxidative stress, thereby reducing the inflammatory response and oxidative damage to the esophageal mucosa. Fourth, WDD can regulate the nervous and endocrine systems, improve the tension and coordination of the lower esophageal sphincter, and prevent the reflux of gastric contents[15-17].

Mosapride is a selective 5-HT4 receptor agonist, and its main mechanism of action may be related to the following. First, mosapride can increase the intracellular calcium ion concentration of gastrointestinal smooth muscle cells by stimulating 5-HT4 receptors, thereby enhancing the peristalsis and tension of the gastrointestinal tract. Second, mosapride can promote gastric emptying, thereby reducing the stimulation time and the degree of gastric content in the esophagus. Third, mosapride can increase lower esophageal sphincter pressure by stimulating 5-HT4 receptors on cholinergic neurons in the myenteric plexus, preventing the reflux of gastric contents. Fourth, mosapride can inhibit 5-HT3 receptors, reducing adverse reactions such as nausea and vomiting[18-20].

The therapeutic effect of WDD combined with mosapride on GERD after esophageal cancer surgery may be due to their synergistic effect, which can adjust the spleen-stomach function from the perspective of traditional Chinese medicine theory and improve gastrointestinal motility function from the perspective of Western medicine theory, thus comprehensively intervening in the occurrence and development of GERD[21,22]. The novelty of this study is that it is the first to apply WDD combined with mosapride to treat GERD after esophageal cancer surgery and to use multiple evaluation indicators for a comprehensive assessment, providing innovative data and insights for this field.

This study has some limitations, such as a small sample size, short follow-up duration, and lack of a placebo control group. Therefore, further large-scale, long-term follow-up, multicenter, double-blind, placebo-controlled clinical trials are needed to verify the results of this study and explore the mechanism and optimization scheme of WDD combined with mosapride for the treatment of GERD after esophageal cancer surgery.

CONCLUSION

This study evaluated the therapeutic effect of WDD combined with mosapride on GERD after esophageal cancer surgery and found that WDD combined with mosapride can significantly improve GERD symptoms, esophageal motility function, gastric emptying function, and quality of life, and has good safety. These results provide new ideas and evidence for the integrated treatment of GERD after esophageal cancer surgery and new data and insights for this field. The novelty of this study is that it is the first to apply WDD combined with mosapride to treat GERD after esophageal

cancer surgery and to use multiple evaluation indicators for comprehensive assessment.

FOOTNOTES

Author contributions: Zhang YJ and Wu SP proposed the concept of this study; Wu SP participated in the data collection; Zhang YJ and Wu SP wrote the initial draft; Wu SP contributed to the formal analysis; Zhang YJ conducted guiding research, methodology, and visualization of the manuscript; Both authors participated in this study, validated it, and jointly reviewed and edited the manuscript.

Institutional review board statement: This study has been reviewed and approved by the Ethics Committee of Beijing Integrated Traditional Chinese and Western Medicine Hospital

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: We declare that there is no disclosure of any conflict of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Yu-Jing Zhang 0009-0001-9287-3225.

S-Editor: Che XX
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
2 **Lordick F**, Mariette C, Haustermans K, Obermannová R, Arnold D; ESMO Guidelines Committee. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; **27**: v50-v57 [PMID: 27664261 DOI: 10.1093/annonc/mdw329]
3 **Lagergren J**, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999; **340**: 825-831 [PMID: 10080844 DOI: 10.1056/NEJM199903183401101]
4 **Vakil N**, van Zanten SV, Kahrilas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; **101**: 1900-1920; quiz 1943 [PMID: 16928254 DOI: 10.1111/j.1572-0241.2006.00630.x]
5 **Katz PO**, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; **108**: 308-328; quiz 329 [PMID: 23419381 DOI: 10.1038/ajg.2012.444]
6 **Tack J**, Camilleri M. New developments in the treatment of gastroparesis and functional dyspepsia. *Curr Opin Pharmacol* 2018; **43**: 111-117 [PMID: 30245474 DOI: 10.1016/j.coph.2018.08.015]
7 **Ling W**, Huang Y, Xu JH, Li Y, Huang YM, Ling HB, Sui Y, Zhao HL. Consistent Efficacy of Wendan Decoction for the Treatment of Digestive Reflux Disorders. *Am J Chin Med* 2015; **43**: 893-913 [PMID: 26243580 DOI: 10.1142/S0192415X15500524]
8 **Xu JH**, Huang YM, Ling W, Li Y, Wang M, Chen XY, Sui Y, Zhao HL. Wen Dan Decoction for hemorrhagic stroke and ischemic stroke. *Complement Ther Med* 2015; **23**: 298-308 [PMID: 25847568 DOI: 10.1016/j.ctim.2015.01.001]
9 **Wang Q**, Lu J, Sui Y, Fan J, Ren J, Wang Z, Chen X. Predicting reflux symptom recurrence: The impact of gastroesophageal junction indicators and body mass index among outpatients. *Exp Ther Med* 2023; **26**: 351 [PMID: 37324506 DOI: 10.3892/etm.2023.12050]
10 **Xu LY**, Yu BY, Cen LS. New treatment for gastroesophageal reflux disease: Traditional Chinese medicine Xiaochaihu decoction. *World J Gastroenterol* 2022; **28**: 1184-1186 [PMID: 35431502 DOI: 10.3748/wjg.v28.i11.1184]
11 **Lin W**, Huang G, Liu X, Lin H, Zhou H, Feng C, Wang T, Liang R. Efficacy and safety of traditional Chinese herbal formula combined with western medicine for gastroesophageal reflux disease: A protocol for systematic review and meta-analysis. *Medicine (Baltimore)* 2020; **99**: e22454 [PMID: 33031277 DOI: 10.1097/MD.0000000000022454]
12 **Fu Y**, Fan Y, Fan W, Lv Y, Ai S, Yu C. Efficacy and safety of traditional Chinese herbal formula combined with western medicine for uterine fibroid: A protocol for systematic review and meta-analysis. *Medicine (Baltimore)* 2020; **99**: e22039 [PMID: 32899062 DOI: 10.1097/MD.0000000000022039]
13 **Liu J**, Huang J, Zhang B, Yin X, Lv M, Liu Z, Wang F, Tang X. Treatment of the Gastroesophageal Reflux Disease with Chinese Herbal Medicine (BanxiaXiexin Decoction): Evidence from Meta-Analysis. *Evid Based Complement Alternat Med* 2022; **2022**: 1500660 [PMID: 35754695 DOI: 10.1155/2022/1500660]
14 **Zhao YH**, Liu ZI, Li LH, Jiang SH, Shi CH. Systematic review of randomized controlled trials of traditional Chinese medicine treatment of non-acute bronchial asthma complicated by gastroesophageal reflux. *J Tradit Chin Med* 2012; **32**: 12-18 [PMID: 22594096 DOI:

10.1016/s0254-6272(12)60025-9]
15 **Jin Q**, Li J, Chen GY, Wu ZY, Liu XY, Liu Y, Chen L, Wu XY, Zhao X, Song YH. Network and Experimental Pharmacology to Decode the Action of Wendan Decoction Against Generalized Anxiety Disorder. *Drug Des Devel Ther* 2022; **16**: 3297-3314 [PMID: 36193286 DOI: 10.2147/DDDT.S367871]
16 **Jia KK**, Ding H, Yu HW, Dong TJ, Pan Y, Kong LD. Huanglian-Wendan Decoction Inhibits NF-κB/NLRP3 Inflammasome Activation in Liver and Brain of Rats Exposed to Chronic Unpredictable Mild Stress. *Mediators Inflamm* 2018; **2018**: 3093516 [PMID: 29853787 DOI: 10.1155/2018/3093516]
17 **Lan TH**, Zhang LL, Wang YH, Wu HL, Xu DP. Systems Pharmacology Dissection of Traditional Chinese Medicine Wen-Dan Decoction for Treatment of Cardiovascular Diseases. *Evid Based Complement Alternat Med* 2018; **2018**: 5170854 [PMID: 29861771 DOI: 10.1155/2018/5170854]
18 **Liu Q**, Feng CC, Wang EM, Yan XJ, Chen SL. Efficacy of mosapride plus proton pump inhibitors for treatment of gastroesophageal reflux disease: a systematic review. *World J Gastroenterol* 2013; **19**: 9111-9118 [PMID: 24379638 DOI: 10.3748/wjg.v19.i47.9111]
19 **Sung KW**, Hahn SJ. Effect of mosapride on Kv4.3 potassium channels expressed in CHO cells. *Naunyn Schmiedebergs Arch Pharmacol* 2013; **386**: 905-916 [PMID: 23793103 DOI: 10.1007/s00210-013-0896-6]
20 **Kojima Y**, Fujii H, Katsui R, Nakajima Y, Takaki M. Enhancement of the intrinsic defecation reflex by mosapride, a 5-HT4 agonist, in chronically lumbosacral denervated guinea pigs. *J Smooth Muscle Res* 2006; **42**: 139-147 [PMID: 17159330 DOI: 10.1540/jsmr.42.139]
21 **Teschke R**, Wolff A, Frenzel C, Eickhoff A, Schulze J. Herbal traditional Chinese medicine and its evidence base in gastrointestinal disorders. *World J Gastroenterol* 2015; **21**: 4466-4490 [PMID: 25914456 DOI: 10.3748/wjg.v21.i15.4466]
22 **Chen J**, Huang X, Li Y, Wu H, Qin S, Zheng H, Li J, Zhang H, Hu L, Huang S. Efficacy and safety of Chinese medicine combined with balloon dilatation vs. balloon dilatation alone for achalasia patients: a systematic review and meta-analysis. *Ann Transl Med* 2022; **10**: 275 [PMID: 35433949 DOI: 10.21037/atm-22-744]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2201-2209

DOI: 10.12998/wjcc.v12.i13.2201

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Clinical Trials Study

Yiwei Xiaoyu granules for treatment of chronic atrophic gastritis with deficiency syndrome of the spleen and stomach

Wan-Qun Chen, Qing-Feng Fan, Yuan-Jun He, Fei Li, Xin Wu, Yan-Ping Li, Xiao-Jun Yang

Specialty type: Gastroenterology and hepatology

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: Kirkik D, Turkey

Received: January 11, 2024
Revised: March 3, 2024
Accepted: April 1, 2024
Published online: May 6, 2024

Wan-Qun Chen, Qing-Feng Fan, Yuan-Jun He, Fei Li, Xin Wu, Yan-Ping Li, Xiao-Jun Yang, Department of Gastroenterology, Chongqing Hospital of Traditional Chinese Medicine, Chongqing 400000, China

Corresponding author: Xiao-Jun Yang, PhD, Doctor, Department of Gastroenterology, Chongqing Hospital of Traditional Chinese Medicine, No. 6 Panxi Seven Branch Road, Jiangbei District, Chongqing 400000, China. yxj20220606@163.com

Abstract

BACKGROUND

The Correa sequence, initiated by *Helicobacter pylori* (*H. pylori*), commonly progresses to gastric cancer through the stage of chronic atrophic gastritis (CAG). Although eradication of *H. pylori* only reduces the risk of gastric cancer, it does not eliminate the risk for neoplastic progression. Yiwei Xiaoyu granules (YWXY) are a commonly used composite preparation in Chinese clinics. However, the pursuit of excellence in clinical trials and the establishment of standardized animal experiments are still needed to contribute to full understanding and application of traditional Chinese medicine in the treatment of CAG.

AIM

To demonstrate the effectiveness of YWXY in patients with CAG and spleen-stomach deficiency syndrome (DSSS), by alleviating histological scores, improving response rates for pathological lesions, and achieving clinical efficacy in relieving DSSS symptoms.

METHODS

We designed a double-blind, randomized, controlled trial. The study enrolled seventy-two *H. pylori*-negative patients (mean age, 52.3 years; 38 men) who were randomly allocated to either the treatment group or control group in a 1:1 ratio, and treated with 15 g YWXY or 0.36 g Weifuchun (WFC) tablet combined with the respective dummy for 24 wk. The pre-randomization phase resulted in the exclusion of 72 patients: 50 participants did not meet the inclusion criteria, 12 participants declined to participate, and 10 participants were excluded for various other reasons. Seven visits were conducted during the study, and histopathological examination with target endoscopic biopsy of narrow-band imaging was requested before the first and seventh visits. We also evaluated endoscopic performance scores, total symptom scores, serum pepsinogen and gastrin-17.

RESULTS
Six patients did not complete the trial procedures. Treatment with YWXY improved the Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) stage, compared with WFC ($P < 0.05$). YWXY provided better relief from symptoms of DSSS and better improvement in serum gastric function, compared with WFC ($P < 0.05$).

CONCLUSION
YWXY compared with WFC significantly reduced the risk of mild or moderate atrophic disease, according to OLGIM stage, significantly relieved symptoms of DSSS, and improved serum gastric function.

Key Words: Chronic atrophic gastritis; Yiwei Xiaoyu granules; Randomized clinical trial; Weifuchun tablet; Traditional Chinese medicine; *Helicobacter pylori*

Core Tip: Despite the successful eradication of *Helicobacter pylori* (*H. pylori*), which has been shown to reduce the risk of gastric cancer (GC), patients with chronic atrophic gastritis (CAG) still remain susceptible to disease progression leading to GC. Our findings suggest that treatment with Yiwei Xiaoyu granules for CAG patients without *H. pylori* improved the stage of Operative Link on Gastric Intestinal Metaplasia Assessment, provided better clinical symptoms relief and better improvement in serum gastric function levels compared to Weifuchun tablet. However, the total sample size of this study is limited and prolong follow-up hasn't been carried out.

Citation: Chen WQ, Fan QF, He YJ, Li F, Wu X, Li YP, Yang XJ. Yiwei Xiaoyu granules for treatment of chronic atrophic gastritis with deficiency syndrome of the spleen and stomach. *World J Clin Cases* 2024; 12(13): 2201-2209
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2201.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2201

INTRODUCTION

The global burden of stomach cancer remains substantial, with it being ranked fifth in terms of incidence and fourth in terms of mortality worldwide[1]. Chronic atrophic gastritis (CAG) is one of the most common stages in the progression to gastric cancer for the Correa sequence caused by *Helicobacter pylori* (*H. pylori*)[2]. The latest research has already demonstrated that the eradication of *H. pylori* can reduce the risk of gastric cancer, although it cannot completely eliminate the risk of neoplastic progression. This progression is associated with the extent of genetic alterations and epigenetic modifications present at the time of *H. pylor*i eradication[3,4]. More therapeutic methods, but not only of *H. pylori* eradication, should be explored for CAG or gastric precancerous lesions.

Some traditional Chinese medicine (TCM) herbs that are effective for therapy of CAG have gradually gained global recognition, as for Moluodan's recommendation in the European Society of Gastrointestinal Endoscopy guideline update 2019[5,6]. However, because of the specific characteristics of TCM such as holistic theory and syndrome differentiation and treatment, the comprehensive comprehension and application of TCM for the treatment of CAG necessitates the conduction of rigorous clinical trials with high methodological quality and standardized animal experiments.

Our group has focused on the effects of TCM on CAG for > 20 years. Yiwei Xiaoyu granules (YWXY) are a commonly used composite preparation in Chinese clinics. YWXY have been shown to improve mucosal atrophy, intestinal metaplasia (IM) and dysplasia of CAG[7], and water reflux extraction technology and quality standards of YWXY have been optimized[8,9]. The mechanisms of inhibition of YWXY on spasmolytic polypeptide-expressing metaplasia lesions, atrophy and IM have been explored[10-12]. The widely used high-definition endoscopy with chromoendoscopy has improved the diagnostic accuracy for atrophy, IM and dysplasia[5]. *H. pylori* eradication has been recognized as the basic treatment for CAG[13]; and the present study was designed as a double-blinded, randomized controlled trial in order to substantiate the therapeutic efficacy of YWXY.

MATERIALS AND METHODS

Study design and patient selection

The study design employed in this research was a single-center, randomized, double-blind, controlled trial. We recruited patients with a previous endoscopic and histological diagnosis of CAG, with or without IM, from both outpatient and inpatient units of the Department of Gastroenterology at Chongqing Hospital of Traditional Chinese Medicine, in accordance with the Consensus on Chronic Gastritis in China[14].

Diagnostic criteria for TCM syndrome differentiation

The diagnosis and treatment of CAG is based on the consensus reached by integrating TCM and Western medicine in 2017[15], the diagnosis of DSSS was as follows: Primary symptoms and tongue manifestations were indispensable, and more than two secondary symptoms were needed, at the same time, pulse condition must be referred to as indications to assist in DSSS diagnosis.

Inclusion criteria

The study included patients exhibiting the following characteristics: Age 19-69 years; without *H. pylori* infection; and mild or moderate grade of atrophic border (C1–C3, O1) according to the Kimura–Takemoto classification[16]. Patients with TCM syndrome differentiation according to DSSS and with mild or moderate histological severity of atrophic changes were referred to the Operative Link on Gastritis Assessment (OLGA) and Updated Sydney System[17,18].

Exclusion criteria

The following patients were excluded: Patients with severe dysplasia and atrophy; suspected stomach or other cancers; patients who underwent gastric surgery; combination of gastric or duodenal ulceration; patients with severe systemic disease (cardiovascular, hepatic, blood, kidney or lung disease); administration of nonsteroidal anti-inflammatory drugs; pregnant or lactating women; or patients who refuses to undergo gastroscopic examination or give informed consent.

Withdrawal or dropout criteria

The criteria for withdrawal or dropout were as follows: Patients who no longer continued to use the study drugs or were receiving visits; patients who decided to withdraw on their own volition, after failing to be dissuaded by the investigator; or patients experiencing serious adverse events or complications.

Interventions and groups

Participants were randomized into the treatment group (TG) and control group (CG). Before the trial, YWXY and Weifuchun (WFC) tablets (Hangzhou Huqing Yutang Pharmaceutical Co. Ltd., China; batch No. Z20040003) were prepared, along with placebo granules of YWXY and placebo tablets of WFC. YWXY and the two placebos were made by the Pharmaceutical Department of Chongqing Hospital of Traditional Chinese Medicine. The TG received 15 g/package of YWXY (four times a day) and placebo tablets of WFC (three times a day) for 24 wk. The CG received 0.36 g WFC and placebo YWXY with the same frequency and duration as the TG.

Randomization and blinding

A random allocation sequence number of 72 patients was obtained by an independent researcher *via* SAS version 9.1.3 (SAS Institute, Cary, NC, United States). Sequentially numbered opaque sealed envelopes were used to store randomized numbers associated with specific drugs based on group assignments. Each envelope was assigned a unique number. When recruiting eligible patients, a researcher independently and randomly selected one envelope from a pool without knowledge of its code's meaning. Experimental conditions "1" and "2" were represented by chosen envelopes, where "1" indicated TG and "2" represented CG. The TG and CG groups were allocated to consecutive patients in a 1:1 ratio through random assignment.

Researchers and patients were blinded to the grouping. Because of the difference in formation and dosage between YWXY and WFC, placebo granules and placebo tablets were made identical to the two drugs in terms of color, odor and packaging. Otherwise, the tablets of WFC (0.36 g) were packaged into a sealed plastic bag, with the exact appearance of YWXY. The Pharmaceutical Department marked the medicine packages with "1" or "2" codes, corresponding to YWXY + placebo or WFC + placebo respectively. Patients were instructed to take 92 tablets of YWXY and 84 tablets of placebo, or 92 tablets of placebo and 84 tablets of WFC every 4 wk. An independent researcher, who did not participate in case observations or efficacy assessments, was responsible for drug distribution, storage and return.

Baseline visit

The recruitment was advertised at our hospital, targeting potential patients who had previously been diagnosed with a mild to moderate grade of CAG for the purpose of endoscopic and histological presentation. After signing informed consent, the patients were interviewed to collect demographic data, symptoms and signs, medical and treatment history, complications and drug combinations, as well as undergo physical examinations. In addition, vital signs and safety data were recorded.

Endoscopy and histopathological examination

All participants included were requested to perform endoscopy prior to treatment (visit 1) and 24 wk after treatment completion (visit 7), by experienced senior endoscopists using a high-resolution magnifying endoscope (GIF-290H; Olympus, Tokyo, Japan). According to the Kyoto global consensus[19], the following endoscopic characteristics were evaluated: atrophic change, severity of atrophy (open/closed, O/C), IM and its location, hyperplasia, regular arrangement of collecting venules, and diffuse redness.

Following the screening stage, targeted biopsy utilizing narrow-band imaging (NBI) was conducted in accordance with the updated Sydney System biopsy protocol[17]. Five biopsies of the suspicious places were confirmed in combination with NBI. The submucosa was injected with 0.2-0.3 mL of India ink solution (manufactured by the Pharmaceutical Department of Sir Run Run Shaw Hospital, Hangzhou, China) using an endoscopic needle (ENDO-FLEX GmbH,

NET2522-C4, Germany). Five biopsies were obtained from the stomach: two from the antrum, one from the incisura, one along the lesser curvature of the gastric body, and one along the greater curvature of the gastric body. Each biopsy specimen was sufficiently large to reach the lamina propria. The final visit was 24 wk after the termination of treatment, when all participants were required to undergo another endoscopy with five biopsies at the edges of the marked areas.

The biopsy specimen was retrieved, immersed in a 10% formalin solution, and subsequently dispatched to the Pathology Department of Chongqing Hospital. The histological diagnosis of the lesion and assessment of resection margin involvement were conducted in accordance with the Consensus on Chronic Gastritis in China (Shanghai, 2017) and the updated Sydney System[17]. Two independent senior histopathologists were called in to examine the biopsies. When disagreements arose, they stopped and re-examined the relevant biopsy until agreement was reached.

Treatment period

Seven clinical visits were scheduled, consisting of baseline visit (visit 1), follow-up visit every 4 wk for the consecutive six treatment periods (visits 2–6), and follow-up at 24 wk after completing the treatment (visit 7). Each visit allowed a window of 3 d. For each treatment visit, the patient was required to return the plastic outer packaging and was interviewed to document adherence and to ask about adverse events. The severity and frequency of symptoms were evaluated at each treatment visit[20].

Outcomes and measurements

The main aim was to assess the effectiveness of YWXY in alleviating histological scores, response rates for pathological lesions, and rate of disappearance of atrophy or IM. The atrophy, chronic inflammatory cell infiltration, and IM were assessed using a four-tiered scale (0-3) based on the visual analog scale of the Houston-updated Sydney system. The secondary objectives were to evaluate the efficacy of YWXY in alleviating the total symptom score, the change in the score of the endoscopic findings, and the shift in the serum pepsinogen test between the two groups after treatment. The total symptom scores were evaluated with reference to the TCM symptom evaluation table of gastrointestinal diseases[21]. The 32 most common symptoms were assessed using a four-tiered scale (0, 3, 5, and 7), with the efficacy score calculated as the difference between the total number of syndrome points before and after treatment divided by the total number of syndrome points before treatment multiplied by 100%.

Safety and adverse event reporting

After enrollment and the day following completion of the intervention period, all participants underwent a comprehensive range of tests including electrocardiography, complete blood cell count, assessment of renal function (serum uric acid, serum creatinine, and blood urea nitrogen), evaluation of liver function (alanine transaminase, aspartate transaminase, and total bilirubin), and routine stool examination. Any details pertaining to adverse events such as occurrence time, severity, duration, measures taken for mitigation or resolution, and outcomes were meticulously recorded in a Clinical Research Form. Based on the severity of adverse events observed, the investigators made informed decisions regarding suspension or withdrawal of patients from the trial.

Ethical considerations

The study design, reporting, and informed consent procedures were conducted in accordance with the recommendations of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol received approval from the Ethics Review Board of Chongqing Hospital of Traditional Chinese Medicine (No. 2019-ky-24), and was registered on the Chinese clinical trial registry website (http://www.chictr.org.cn/index.aspx, ChiCTR1900026455).

Data management

The responsibility of data management was entrusted to an independent data safety and monitoring committee, comprising statisticians and gastroenterologists, who operated independently from the sponsor's and competing interests. Prior to commencing the trial, all investigators underwent a comprehensive 2-h training session to ensure their proficiency in overseeing the entire trial process. Patient data was securely stored in a password-protected Excel file.

Statistical analysis

The data were analyzed using SPSS 22.0 (IBM Corp., Armonk, NY, United States), with a significance level set at $P < 0.05$. The baseline data between groups were compared using either Student's *t*-test or chi-square test. Efficacy primary outcomes were analyzed based on the intention-to-treat principle, utilizing both the intent-to-treat (ITT) and per-protocol (PP) populations. The missing data were managed using the last-observation-carried-forward approach. Continuous variables were presented as mean ± SD or median, with *t*-tests used for normally distributed variables and paired *t*-tests conducted to assess significant differences before and after treatment. The Wilcoxon signed-rank test was employed to analyze non-normally distributed data.

RESULTS

Patients were recruited from December 1, 2019 to November 30, 2021. The follow-up period ended on July 31, 2022. The study enrolled a total of 72 patients. The CORSORT graph of patient recruitment and analysis is shown in Figure 1. Two patients were discharged for self-induced causes such as long travel and taken other drugs of the same type. In the CG,

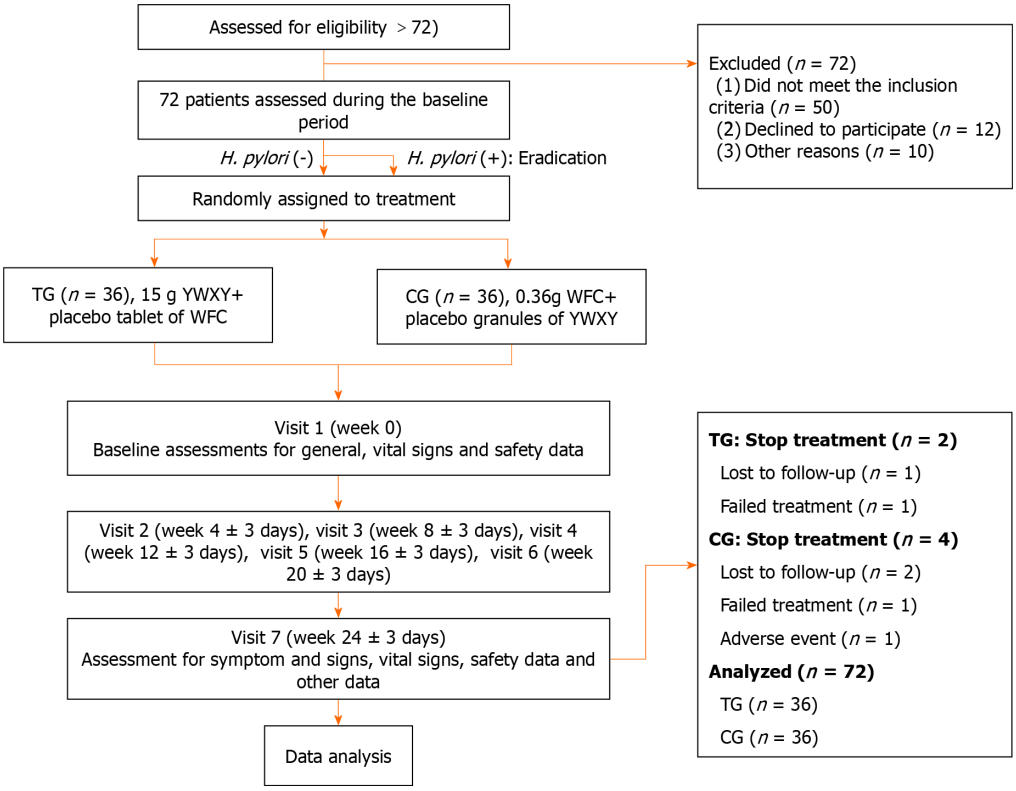

Figure 1 CONSORT diagram of patients' recruitment and analysis. CG: Control group; TG: Treatment group; YWXY: Yiwei Xiaoyu granules; WFC: Weifuchun tablets.

two patients were withdrawn for self-induced causes, two were lost to follow-up, and one had an adverse reaction of mild liver enzyme elevation. The clinical characteristics are presented in Table 1. There were no significant differences observed in terms of sex, age, Kimura-Takemoto staging, OLGA stage, and OLGIM stage between the two groups prior to treatment ($P > 0.05$). The symptom scores of DSSS were compared, and no significant differences were observed in the six typical symptoms between the two groups.

After 6 months of treatment, we examined by gastroscopy whether there was any change in atrophy between the two groups. Extent of atrophy according to Kimura–Takemoto classification showed no change (Table 2). Two patients showed regression in the TG compared with five in the CG, using ITT and PP statistical analysis, and there was no significant difference between the TG and CG.

OLGA classification improved in most patients in both groups ($P > 0.05$). OLGIM stage showed regression in 16 patients in the TG, but only six in the CG. Patients with YWXY had better results for OLGIM stage improvement than those with WFC ($P < 0.05$).

Among the six specific symptoms of DSSS, patients in the TG had better relief than those in the CG for epigastric pain, limb weakness and stomach chill afraid of cold. The efficacy scores for patients in the TG were better than those in the CG ($P < 0.05$) (Table 3). We evaluated the effect of YWXY and WFC on serum gastric function in patients with CAG, and we published this part[22]. Exclusively in a Chinese journal, the results showed that YWXY significantly improved the serum gastric function level in patients with CAG.

DISCUSSION

In China, approximately 24.5% of the population is estimated to be diagnosed with CAG according to a nationwide multicenter cross-sectional study[23]. However, faced with such a large number of patients with CAG, there were only limited therapeutic strategies with anti-*H. pylori* treatment and endoscopic monitoring worldwide[5,24]. The risk of gastric cancer, however, only decreases by less than 50% after undergoing H. pylori eradication therapy[25].

YWXY have been widely used to treat CAG in China for > 20 years, which are a compound preparation formulated by Professor Yan-Ping Li of our team. According to the principles of TCM, the spleen governs the processes of transformation and transportation, as well as the elevation of pure substances; whereas, the stomach is responsible for receiving and maturing ingested food and fluids. In other words, the spleen regulates upward movements while the stomach controls downward movements. If there is a deficiency in the spleen and stomach, it can lead to impaired digestion and manifest as symptoms such as abdominal distention or pain, diarrhea, or appetite disorders. YWXY is a Chinese formula, whose primary therapeutic effect is to benefit the spleen and stomach, and the secondary therapeutic effect is to remotivate Qi or invigorate circulation of the blood. That is why YWXY had a better effect on the relief of

Table 1 Clinical characteristics of patients before treatment

Characteristics	TG	CG	*P* value
Age at enrollment (yr)			0.38
≤ 45	6	11	
46–55	11	9	
≥ 55	19	16	
Age, year (mean ± SD)	54.61 ± 10.20	50.06 ± 11.27	0.08
Sex			0.64
Female	18	16	
Male	18	20	
Kimura–Takemoto classification			0.80
C1	4	4	
C2	18	19	
C3	13	13	
O1	1	0	
OLGA stage			0.39
0	0	0	
I	14	20	
II	14	8	
III	6	5	
IV	2	3	
OLGIM stage			0.63
0	13	17	
I	15	13	
II	7	6	
III	1	0	
IV	0	0	
Symptom scores of DSSS (mean ± SD)			
Abdominal bloating	3.58 ± 0.30	3.42 ± 0.36	0.72
Epigastric pain	2.5 ± 0.39	2.81 ± 0.34	0.55
Loose stools	2.42 ± 0.34	1.83 ± 0.34	0.23
Fatigue	2.14 ± 0.33	2.36 ± 0.38	0.66
Feel weakness of limps	2.36 ± 0.34	3.75 ± 0.30	0.39
Stomach cold	3.25 ± 0.35	3.33 ± 0.34	0.86
Total symptomatic scores	61.5 ± 3.55	57.67 ± 3.98	0.47

CG: Control group; TG: Treatment group; OLGA: Operative Link on Gastritis Assessment; OLGIM: Operative Link on Gastric Intestinal Metaplasia Assessment; DSSS: Deficiency syndrome of the spleen-stomach.

characteristic symptoms of DSSS ($P < 0.05$).

The effects of the two drugs were evaluated in this study using both invasive and noninvasive serological tests. The elimination of *H. pylori* was a notable aspect of our study, aimed at mitigating its persistent impact on the gastric mucosa. Eradication of *H. pylori* or *H. pylori* negativity was required before enrollment because *H. pylori* infection could have influenced the gastric mucosa and its histology, as well as associated dyspeptic symptoms[19]. Another feature is a consistent team of skilled endoscopists and a standardized biopsy protocol, particularly with endoscopists, histopathologists, investigators and patients blinded to the evaluation. Also, the primary outcome was assessed by combination of serum pepsinogen levels and OLGA/OLGIM stage[26,27].

Table 2 Change in extent of atrophy and Operative Link on Gastritis Assessment/Operative Link on Gastric Intestinal Metaplasia Assessment classification

	TG (n = 36)			CG (n = 36)			P value
	Regression	No change	Progression	Regression	No change	Progression	
Kimura–Takemoto classification	2	32	2	5	30	1	0.43
OLGA stage	29	5	2	26	7	2	0.79
OLGIM stage	16	18	2	6	27	3	0.04

CG: Control group; TG: Treatment group; OLGA: Operative Link on Gastritis Assessment; OLGIM: Operative Link on Gastric Intestinal Metaplasia Assessment.

Table 3 Clinical efficacy/effectiveness of treatment for symptom relief of deficiency syndrome of the spleen-stomach

	TG	CG	P value
Symptom scores of DSSS (mean ± SD)			
Abdominal bloating	1.83 ± 0.25	2.47 ± 0.30	0.11
Epigastric pain	1.56 ± 0.27	2.33 ± 0.26	0.04
Loose stools	1.17 ± 0.25	1.81 ± 0.31	0.11
Fatigue	1.17 ± 0.25	1.86 ± 0.32	0.09
Limb weakness	1.25 ± 0.25	2.22 ± 0.28	0.01
Stomach chill afraid of cold	1.58 ± 0.25	2.39 ± 0.27	0.03
Symptomatic relief (n)			0.11
Cure	0	0	
Obvious effect	5	2	
Effective	26	22	
Ineffective	5	12	

CG: Control group; TG: Treatment group; DSSS: Deficiency syndrome of the spleen-stomach.

The OLGIM system is derived from the OLGA system, both of which are utilized for the classification and grading of atrophy and IM severity and distribution. In particular, as some evidence has shown[28], guided biopsies by virtual chromoendoscopy can upgrade OLGA and OLGIM stages, and can be used in combination with target biopsies, as in this study. IM is claimed to be the most reliable marker of risk for gastric cancer[29]. Our results show that YWXY improved the OLGIM stage more than WFC ($P < 0.05$), which is consistent with our previous animal experiments.

We selected WFC as the positive control medication due to its well-established status as a Chinese herbal preparation, comprising Panax ginseng (HS: 131 g), Citrus aurantium (ZQ: 250 g), and Isodon amethystoides (XCC: 2500 g) as documented in the Chinese Pharmacopoeia, 2020 edition. The inclusion of WFC in this pharmacopoeia highlights its efficacy in tonifying spleen Qi, promoting blood circulation, and facilitating detoxification. Moreover, WFC has been extensively utilized for numerous years in China for the treatment of GPL[30].

There were some limitations to our study. First, the 24-wk study period was difficult for many patients to endure, so the dropout rate was high throughout the study. Second, although eradication of *H. pylori* was a prerequisite for enrollment, the enduring impact of *H. pylori* on the gastric mucosa cannot be disregarded. For instance, research has demonstrated that even one year after *H. pylori* eradication, gastric microbes continue to contribute to the progression of gastric carcinogenesis[31], since *H. pylori* was negative in the included patients, we did not analyze the length of time between *H. pylori* eradication and inclusion. Twenty-four weeks of treatment was not sufficient and future follow-up at 2 and 5 years after treatment should be carried out. Finally, the sample size may have limited the results.

CONCLUSION

Our randomized study suggests that YWXYs, compared with WFC, significantly reduce the risk of mild or moderate atrophic disease, according to OLGA/OLGIM stage, clearly relieves symptoms of DSSS, and improves serum gastric

function levels.

FOOTNOTES

Co-corresponding authors: Yan-Ping Li and Xiao-Jun Yang.

Author contributions: The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them; Yang XJ and Li YP contributed equally to this work; Yang XJ, Li YP and Chen WQ conceptualized and designed the research; Fan QF, He YJ, Li F and Wu X screened patients and acquired clinical data; Fan QF and He YJ collected gastric specimen and performed laboratory analysis; Yang XJ and Li YP performed Data analysis; Chen WQ wrote the paper. All the authors have read and approved the final manuscript. Chen WQ proposed, designed and conducted serum function analysis, performed data analysis and prepared the first draft of the manuscript. Both Yang XJ and Li YP have played important and indispensable roles in the experimental design, data interpretation and manuscript preparation as the co-corresponding authors. Yang XJ applied for and obtained the funds for this research project. Yang XJ conceptualized, designed, and supervised the whole process of the project. Yang XJ searched the literature, revised and submitted the early version of the manuscript with the focus on the preventive effect of Yiwei Xiaoyu granules on chronic atrophic gastritis. Li YP was instrumental and responsible for data re-analysis and re-interpretation, figure plotting, comprehensive literature search, preparation and submission of the current version of the manuscript with a new focus on a double-blind, randomized, controlled trial. This collaboration between Yang XJ and Li YP is crucial for the publication of this manuscript and other manuscripts still in preparation.

Supported by the National Natural Science Foundation of China, No. 81904175; Chongqing Health Planning Commission Project, No. ZY201802063, No. 2019ZY013111, and No. 2022QNXM061; Chongqing Performance Incentive Project, No. jxyn2021-1-1; and Chongqing Technology Innovation and Application Development Special Key Project, No. CSTB2022TIAD-KPX0187.

Institutional review board statement: The protocol received approval from the Ethics Review Board of Chongqing Hospital of Traditional Chinese Medicine (No. 2019-ky-24).

Clinical trial registration statement: This study was registered on the Chinese clinical trial registry website (http://www.chictr.org.cn/index.aspx, ChiCTR1900026455).

Informed consent statement: All study participants provided informed written consent prior to study.

Conflict-of-interest statement: There was no conflict of interest associated with this work.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at [yxj20220606@163.com].

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

Country/Territory of origin: China

ORCID number: Wan-Qun Chen 0000-0002-1126-2968; Yan-Ping Li 0000-0002-4983-014X; Xiao-Jun Yang 0000-0003-3768-8649.

S-Editor: Liu JH
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 **Correa P**, Houghton J. Carcinogenesis of Helicobacter pylori. *Gastroenterology* 2007; **133**: 659-672 [PMID: 17681184 DOI: 10.1053/j.gastro.2007.06.026]

3 **Rugge M**, Meggio A, Pravadelli C, Barbareschi M, Fassan M, Gentilini M, Zorzi M, Pretis G, Graham DY, Genta RM. Gastritis staging in the endoscopic follow-up for the secondary prevention of gastric cancer: a 5-year prospective study of 1755 patients. *Gut* 2019; **68**: 11-17 [PMID: 29306868 DOI: 10.1136/gutjnl-2017-314600]

4 **Choi IJ**, Kook MC, Kim YI, Cho SJ, Lee JY, Kim CG, Park B, Nam BH. Helicobacter pylori Therapy for the Prevention of Metachronous Gastric Cancer. *N Engl J Med* 2018; **378**: 1085-1095 [PMID: 29562147 DOI: 10.1056/NEJMoa1708423]

5 **Pimentel-Nunes P**, Libânio D, Marcos-Pinto R, Areia M, Leja M, Esposito G, Garrido M, Kikuste I, Megraud F, Matysiak-Budnik T,

Annibale B, Dumonceau JM, Barros R, Fléjou JF, Carneiro F, van Hooft JE, Kuipers EJ, Dinis-Ribeiro M. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. *Endoscopy* 2019; **51**: 365-388 [PMID: 30841008 DOI: 10.1055/a-0859-1883]

6 **Liu S**, Su ZQ, Liu XY, Fan QY, Gao J, Ma XJ, Wang T. Literature Study on Current Status of Traditional Chinese Medicine for Chronic Atrophic Gastritis Based on PubMed and Web of Science Databases. *Zhongguo Shiyan Fangjixue Zazhi* 2021; **27**: 149-158

7 **Wu LJ**, Xie HM, Tian FL, Li YP, Zhang CY. 30 cases of chronic atrophic gastritis treatment with Yiwei Xiaoyu granules. *Zhongguo Zhongxiyi Jiehe Xiaohua Zazhi* 2007; **15**: 57-58

8 **Liu X**, Xu C, Leng J, Guo XH, Tian FL. Optimization of the water extraction process of Yiwei Xiaoyu Granules by orthogonal test. *Zhonghua Zhongyiyao Zazhi* 2018; **33**: 1605-1607

9 **Liu X**, Xu C, Wu WH, Guo XH, Sun Q, Tian FL. Study on Quality Standard of Yiwei Xiaoyu Granules. *Zhonghua Zhongyiyao Xinxi Zazhi* 2018; **25**: 77-80

10 **Chen WQ**, Tian FL, Zhang JW, Yang XJ, Li YP. Preventive and inhibitive effects of Yiwei Xiaoyu granules on the development and progression of spasmolytic polypeptide-expressing metaplasia lesions. *World J Gastrointest Oncol* 2021; **13**: 1741-1754 [PMID: 34853647 DOI: 10.4251/wjgo.v13.i11.1741]

11 **Tian FL**, Li YP, Yang XJ, Liu Y, Chen WQ. Improvement effect of Yiwei Xiaoyu granules on gastric mucosa intestinal metaplasia of rats. *Chongqing Yixue* 2018; **47**: 6

12 **Yang XJ**, Tian FL, Liu Y, Li YP. Effects of yiwei xiaoyu granules on intestinal metaplasia of gastric mucosa and the related inflammatory mediators in the rats. *Shijie Zhongxiyi Jiehe Zazhi* 2019; **14**: 5

13 **Mera RM**, Bravo LE, Camargo MC, Bravo JC, Delgado AG, Romero-Gallo J, Yepez MC, Realpe JL, Schneider BG, Morgan DR, Peek RM Jr, Correa P, Wilson KT, Piazuelo MB. Dynamics of Helicobacter pylori infection as a determinant of progression of gastric precancerous lesions: 16-year follow-up of an eradication trial. *Gut* 2018; **67**: 1239-1246 [PMID: 28647684 DOI: 10.1136/gutjnl-2016-311685]

14 **Fang JY**, Du YQ, Liu WZ, Ren JL, Li YQ, Chen XY, Lv NH, Chen YX, Lv B; Chinese Society of Gastroenterology, Chinese Medical Association. Chinese consensus on chronic gastritis (2017, Shanghai). *J Dig Dis* 2018; **19**: 182-203 [PMID: 29573173 DOI: 10.1111/1751-2980.12593]

15 **Li JX**, Chen J, Lv B, Wang YG; Chinese Association of Integrated Traditional and Western Medicine digestive diseases professional committee. Consensus of chronic atrophic gastritis on integrated TCM and Western medicine diagnosis and treatment (in 2017). *Zhongguo Zhongxiyi Jiehe Xiaohua Zazhi* 2018; **26**: 121-131

16 **Kimura K**, Takemoto T. An Endoscopic Recognition of the Atrophic Border and its Significance in Chronic Gastritis. *Endoscopy* 1969; **1**: 87-97 [DOI: 10.1055/s-0028-1098086]

17 **Dixon MF**, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol* 1996; **20**: 1161-1181 [PMID: 8827022 DOI: 10.1097/00000478-199610000-00001]

18 **Rugge M**, Meggio A, Pennelli G, Piscioli F, Giacomelli L, De Pretis G, Graham DY. Gastritis staging in clinical practice: the OLGA staging system. *Gut* 2007; **56**: 631-636 [PMID: 17142647 DOI: 10.1136/gut.2006.106666]

19 **Sugano K**, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, Haruma K, Asaka M, Uemura N, Malfertheiner P; faculty members of Kyoto Global Consensus Conference. Kyoto global consensus report on Helicobacter pylori gastritis. *Gut* 2015; **64**: 1353-1367 [PMID: 26187502 DOI: 10.1136/gutjnl-2015-309252]

20 **Wang P**, Tang XD, Liu BY, Zi MJ. [Development of a patient-reported outcome instrument for chronic gastrointestinal diseases: item selection]. *Zhong Xi Yi Jie He Xue Bao* 2012; **10**: 1092-1098 [PMID: 23073192 DOI: 10.3736/jcim20121005]

21 Digestive Diseases Professional Committee of Chinese Association of Integrated Traditional and Western Medicine. Evaluation table of TCM symptoms of gastrointestinal diseases (2010, Suzhou). *Zhongguo Zhongxiyi Jiehe Xiaohua Zazhi* 2011; **19**: 66-68

22 **Chen WQ**, Fan QF, Li F, He YJ, Wu X, Tang ZR, Luo Y, Li YP, Yang XJ. The effect of Yiwei Xiaoyu Granules on serum gastric function in chronic atrophic gastritis. *Xiandai Yiyao Weisheng* 2023; **39**: 21-25

23 **Cai Q**, Zhu C, Yuan Y, Feng Q, Feng Y, Hao Y, Li J, Zhang K, Ye G, Ye L, Lv N, Zhang S, Liu C, Li M, Liu Q, Li R, Pan J, Yang X, Zhu X, Li Y, Lao B, Ling A, Chen H, Li X, Xu P, Zhou J, Liu B, Du Z, Du Y, Li Z; Gastrointestinal Early Cancer Prevention & Treatment Alliance of China (GECA). Development and validation of a prediction rule for estimating gastric cancer risk in the Chinese high-risk population: a nationwide multicentre study. *Gut* 2019; **68**: 1576-1587 [PMID: 30926654 DOI: 10.1136/gutjnl-2018-317556]

24 **Chinese Association of Integrative Medicine**; Chinese Medical Doctor Association; National Clinical Research Center for Chinese Medicine Cardiology; Cardiovascular Disease Working Group; Encephalopathy Disease Working Group; China Center for Evidence-Based Chinese Medicine, Chen KJ. Chinese Expert Consensus on Clinical Application of Oral Ginkgo biloba Preparations (2020). *Chin J Integr Med* 2021; **27**: 163-169 [PMID: 33420582 DOI: 10.1007/s11655-021-3289-6]

25 **Lee YC**, Chiang TH, Chou CK, Tu YK, Liao WC, Wu MS, Graham DY. Association Between Helicobacter pylori Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis. *Gastroenterology* 2016; **150**: 1113-1124.e5 [PMID: 26836587 DOI: 10.1053/j.gastro.2016.01.028]

26 **Ogutmen Koc D**, Bektas S. Serum pepsinogen levels and OLGA/OLGIM staging in the assessment of atrophic gastritis types. *Postgrad Med J* 2022; **98**: 441-445 [PMID: 33380437 DOI: 10.1136/postgradmedj-2020-139183]

27 **Unc OD**. [Obituary. Dr. Nicole Botezatu (18.09.1942-19.02.2014)]. *Chirurgia (Bucur)* 2014; **109**: 280-281 [PMID: 24830076]

28 **Bornschein J**, Rugge M. Bright future for endoscopy: the new frontier of gastric cancer secondary prevention. *Gut* 2020; **69**: 1723-1724 [PMID: 32532892 DOI: 10.1136/gutjnl-2020-321570]

29 **Dinis-Ribeiro M**, Kuipers EJ. How to Manage a Patient With Gastric Intestinal Metaplasia: An International Perspective. *Gastroenterology* 2020; **158**: 1534-1537 [PMID: 31926996 DOI: 10.1053/j.gastro.2020.01.008]

30 **Jin Y**, Tian T, Ma Y, Xu H, Du Y. Simultaneous determination of ginsenoside Rb1, naringin, ginsenoside Rb2 and oridonin in rat plasma by LC-MS/MS and its application to a pharmacokinetic study after oral administration of Weifuchun tablet. *J Chromatogr B Analyt Technol Biomed Life Sci* 2015; **1000**: 112-119 [PMID: 26222904 DOI: 10.1016/j.jchromb.2015.06.027]

31 **Sung JJY**, Coker OO, Chu E, Szeto CH, Luk STY, Lau HCH, Yu J. Gastric microbes associated with gastric inflammation, atrophy and intestinal metaplasia 1 year after Helicobacter pylori eradication. *Gut* 2020; **69**: 1572-1580 [PMID: 31974133 DOI: 10.1136/gutjnl-2019-319826]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2210-2217

DOI: 10.12998/wjcc.v12.i13.2210

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Relationship between clinical belonging, professional identity, and nursing information ability among nursing interns: Model construction

Gai Zhang, Shao-Juan Huang, Shu-Fang Li

Specialty type: Nursing

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: Alizadeh S, Iran

Received: August 29, 2023
Peer-review started: August 29, 2023
First decision: November 16, 2023
Revised: December 23, 2023
Accepted: March 25, 2024
Article in press: March 25, 2024
Published online: May 6, 2024

Gai Zhang, Shao-Juan Huang, Shu-Fang Li, Department of Nursing, Foshan Hospital of Traditional Chinese Medicine, Foshan 528000, Guangdong Province, China

Corresponding author: Shao-Juan Huang, MM, Chief Nurse, Department of Nursing, Foshan Hospital of Traditional Chinese Medicine, No. 6 Qinren Road, Chancheng District, Foshan 528000, Guangdong Province, China. 812264806@qq.com

Abstract

BACKGROUND

Clinical belonging refers to the feeling that clinical medical staff feel recognized and accepted by others or groups. The level of clinical belonging of nursing interns affects students' learning motivation and confidence, which in turn affects their clinical practice behavior.

AIM

To explore the effects of professional identity and nursing information ability on clinical belonging among nursing interns and establish a relationship model for these factors.

METHODS

The researchers used the convenience sampling method to select 682 nursing interns from China. The survey was conducted using a general information questionnaire, clinical sense of belonging scale, nursing information ability self-assessment scale, and a nursing student professional identity questionnaire. The mediating effect of nursing information ability between their professional identity and clinical sense of belonging was analyzed using SPSS 21.0 and the path analysis in structural equation modeling.

RESULTS

The total scores of clinical belonging, professional identity, and nursing information ability of nursing interns were (104.29 ± 13.11) points, (57.89 ± 7.16) points, and (70.29 ± 6.20) points, respectively. Nursing information ability had a direct effect on the clinical sense of belonging (effect value = 0.46, $P < 0.05$). Occupational identity had a direct effect (effect value = 0.52, $P < 0.05$) and an indirect effect (effect value = 0.21, $P < 0.05$) on clinical belonging.

CONCLUSION
Nursing administrators in nursing colleges and hospitals should take effective measures to improve the professional identity and nursing information ability of nursing interns, as well as the clinical sense of belonging among nursing interns.

Key Words: Belongingness; Nursing; Education; Undergraduate; Information literacy; Models

Core Tip: Nursing administrators in nursing colleges and hospitals should take effective measures to improve the professional identity and nursing information ability of nursing interns, as well as the clinical sense of belonging among nursing interns.

Citation: Zhang G, Huang SJ, Li SF. Relationship between clinical belonging, professional identity, and nursing information ability among nursing interns: Model construction. *World J Clin Cases* 2024; 12(13): 2210-2217
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2210.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2210

INTRODUCTION

Clinical belonging refers to the feeling that clinical medical staff feel recognized and accepted by others or groups[1]. The level of clinical belonging in nursing interns affects students' learning motivation and confidence, which in turn affects their clinical practice behavior[2]. Professional identity refers to individuals' identification with their professional roles, affirmation of their own professional ability, and positive evaluation of their professional value[3]. Previous studies have shown that occupational identity has a positive effect on clinical belonging, but the mechanism remains unclear[4]. Nursing information competence refers to comprehensive abilities in terms of knowledge, skills, and attitudes shown in various nursing information activities[5]. Studies have shown that good nursing information ability is conducive to the enhancement of nurses' professional sense of accomplishment and affects their clinical sense of belonging[6]. In this study, we aimed to explore the relationship among nursing interns' clinical sense of belonging, professional identity, and nursing information ability to provide a basis for improving nursing interns' clinical sense of belonging.

MATERIALS AND METHODS

Research participants

From October 2023 to March 2024, 682 nursing interns were selected as research participants in China. Inclusion criteria were: ≥ 4 clinical departments in rotation and duration of clinical practice ≥ 5 months. Exclusion criteria were nurses who terminated their internship early for various reasons. This study has been reviewed by the Ethics Committee of Foshan Traditional Chinese Medicine Hospital.

Data and methods

A general data questionnaire was designed by the researcher, to collect information on age, sex, educational background. Before the investigation, the research purpose was explained to the participants, consent was obtained, and informed consent forms were signed.

Clinical sense of belonging: We used a clinical belongingness scale to evaluate the level of clinical belonging in nursing interns which was developed by Levett-Jones *et al*[7]. The Chinese version was revised by Tian *et al*[8] and has good reliability and validity, Cronbach's α coefficient was 0.920, and the retest reliability was 0.872. The scale contains 34 items in three dimensions, including self-esteem, communication, and effectiveness. A 5-point Likert scale was adopted, with the total score ranging from 34 to 170 points. The higher the score, the higher the level of clinical belonging.

Nursing information ability self-rating scale: This scale was used to assess the nursing information competence level of nurses. The Chinese version was translated and revised by Yu *et al*[9]. The scale includes five dimensions (28 items): Basic computer knowledge and skills, clinical information role, application ability of computer skills, nursing information attitude, and wireless device skills. A five-level scale was used, and higher total scores indicated stronger nursing information ability. The scale's Cronbach's α coefficient was 0.931 and the retest reliability was 0.881.

Nursing students' professional identity questionnaire: This tool was used to evaluate the professional identity level of nursing interns[10]. The questionnaire includes 17 items in five dimensions: occupational self-concept, retention benefit and turnover risk, social comparison and self-reflection, autonomy of career choice, and social persuasion. The total score ranges from 17 to 85 points. The higher the score, the higher the sense of professional identity. Cronbach's α coefficient of

this questionnaire in this study was 0.858 with a half reliability of 0.850.

Methods of data collection: A cross-sectional study design was adopted. After obtaining the consent of the nursing department in each hospital, questionnaires were distributed through WeChat and Wenxing to collect data. All questionnaires were completed independently and anonymously by nursing interns. Unified guidelines were adopted to introduce research objectives and methods in detail. Each WeChat was set to answer the questionnaire only once, and the questionnaire could be submitted only after all items had been completed. At the end of the survey, the data were checked by two people, and questionnaires that did not meet the quality requirements were eliminated. A total of 690 questionnaires were collected in this study, of which 682 were valid, with an effective rate of 98.84%.

Ethical consideration

This study has been reviewed by the Ethics Committee of Foshan Traditional Chinese Medicine Hospital. Before conducting the study, the researcher explained the main purpose of the study to the participants who provided written informed consent.

Statistical analysis

Epidata 3.1 was used for data entry and IBM SPSS 21.0 and Amos 17.0 were used for statistical analysis. The general data are described by adoption rate and percentage. Mean and standard deviation were used to describe the relationship between clinical belonging, occupational identity, and nursing information ability. Pearson correlation analysis was used to explore the correlation between nursing information ability, professional identity, and clinical sense of belonging. The mediating effect of nursing information ability on occupational identity and clinical belonging was analyzed using the path of structural equation model. The test level was 0.05.

RESULTS

General information

A total of 682 nursing interns, aged (20.00 ± 1.23) years, were enrolled, including 78 male (11.43%) and 604 female (88.57%) nurses. There were 204 junior college students (29.91%), 413 undergraduates (60.56%), and 65 postgraduate students or above (9.53%); 34 students (4.99%) had experience as class leaders.

Nursing interns' clinical sense of belonging, professional identity, and nursing information ability

Tables 1 and 2 show the scores for clinical sense of belonging, professional identity, and nursing information ability among nursing interns (n = 682).

Correlation between nursing interns' clinical sense of belonging, professional identity, and nursing information ability

Pearson correlation analysis showed that the total score for nursing information ability was positively correlated with the total score for clinical sense of belonging. The total score for professional identity was positively correlated with the total score for clinical belonging, as shown in Table 3.

Relationship model between clinical belonging, professional identity, and nursing information ability among nursing interns

A hypothesis model was established with clinical belonging as the dependent variable, nursing information ability as the independent variable, and professional identity as the mediating variable. The structural equation model was applied to test the hypothesis. The data parameters were required to conform to a multivariate normal distribution. Considering that most of the data in this study had a non-normal distribution, the bootstrap method was used to correct the hypothesis. According to statistics, the relationship and path among variables are shown in Figure 1. In this study, the fit index was 0.984, the adjusted fit index was 0.977, the relative fit index was 0.906, the value-added fit index was 0.990, the comparative fit index was 0.990, the mean square and square root of residuals was 0.012, and the asymptotic residual mean square and square root was 0.014. All fitting indices were within the acceptable range, indicating that the model fit well; see Table 4 and Figure 1 for details.

DISCUSSION

Current situation regarding clinical belonging, professional identity, and nursing information ability among nursing interns

Results of the analysis: The results of this study showed that the total score for clinical sense of belonging among nursing students during their internship was 104.29 ± 13.11 points, and the entries were all 3.06 ± 0.38 points, which was slightly lower than the results of an investigation among undergraduate nursing students by Tian *et al*[11]. Our study showed that nursing interns had the lowest average score on the communication dimension, which was consistent with research results from China[12]. The participants in this study were hospital interns in Guangdong Province, most of whom were

Table 1 Scores for clinical sense of belonging, professional identity, and nursing information ability among nursing interns (*n* = 682)

Dimension	Number of entries	Dimension score	Entry average score
Total clinical belonging score	34	104.20 ± 13.11	3.06 ± 0.38
Self-esteem	15	47.04 ± 7.44	3.13 ± 0.49
Communication	11	31.73± 4.65	2.88 ± 0.42
Efficacy	8	25.52 ± 4.58	3.19 ± 0.57
Total score for professional identity	17	57.89 ± 7.16	3.40 ± 0.42
Occupational self-concept	6	20.71 ± 3.54	3.452 ± 0.59
Social persuasion	2	8.33 ± 1.20	4.16 ± 0.59
Autonomy in career choice	2	6.23 ± 1.87	3.11 ± 0.93
Benefits of retention and turnover risk	4	13.43 ± 2.75	3.36 ± 0.68
Social comparison and self-reflection	3	9.18 ± 2.30	3.06 ± 0.77
Total score for nursing information ability	28	70.29 ± 6.20	2.93 ± 0.26
Basic computer knowledge and skills	11	35.40 ± 4.34	3.21 ± 0.39
Clinical information roles	5	11.13 ± 2.50	2.23 ± 0.50
Applied computer skills	4	11.90 ± 2.51	2.97 ± 0.62
Wireless device skills	4	11.86 ± 2.52	2.96 ± 0.63
Nursing information attitudes	4	12.07 ± 2.65	3.02 ± 0.66

Table 2 Comparison of scores for clinical belonging, professional identity, and nursing information ability of nursing interns with different demographic characteristics

Item	Sex		Age (yr)		Education			Class leader experience	
	Male	Female	< 20	20-30	Junior college	Undergraduate	Graduate and above	Yes	No
Total clinical belonging score	103.02 ± 10.21	105.04 ± 11.39	103.17 ± 11.42	104.06 ± 12.10	101.16 ± 12.25	103.62 ± 12.06	105.38 ± 11.30	103.20 ± 12.04[a]	89.79 ± 9.60[a]
Total score for professional identity	55.02 ± 7.08	60.02 ± 4.72	57.90 ± 5.18	59.13 ± 4.86	58.70 ± 2.16	57.68 ± 3.15	58.89 ± 4.25	59.30 ± 5.14	57.22 ± 4.08
Nursing information ability	80.25 ± 9.32[a]	74.30 ± 8.14[a]	76.28 ± 5.26	77.05 ± 4.12	71.36 ± 6.15[a]	75.07 ± 5.16[a]	80.12 ± 4.17[a]	77.95 ± 5.33	78.02 ± 4.38

[a]$P < 0.01$.

from Hubei, Hunan, Jiangxi, and other places. There were certain language differences among them, which may have caused communication barriers. In addition, clinical work is demanding; clinical instructors should ensure the safety of clinical work based on education as their communication time with interns may be insufficient. In addition, as can be seen from Table 2, interns with different degrees have different levels of clinical belonging, which suggests that nursing management should strengthen teaching management, such as holding regular intern seminars, to understand the problems of interns at different levels to solve and assist them in these issues. Clinical educators should spend more time communicating with interns and taking the initiative to lead interns to integrate into the department and enhance their clinical sense of belonging[13].

Analysis regarding the status quo of professional identity among nursing students during internship: The results of this study showed that the total score for professional identity among 682 nursing interns was 57.89 ± 7.16, which was a medium-high level, consistent with the results of Xing *et al*[14]. This is related to the emphasis among nursing educators on cultivating professional attitudes, as well as society's recognition of the role of nursing staff in the field of health. Attitudes among the public regarding nurses are constantly improving[15], which increases nursing students' sense of professional identity. The highest score in all dimensions of professional identity among nursing students during the internship was for social persuasion (4.16 ± 0.59), which indirectly proves the role of public opinion and example gui-

Table 3 Correlation between clinical sense of belonging, professional identity, and nursing information ability among nursing interns

	Total clinical belonging score	Total professional identity score	Total score for nursing information competence
Total clinical belonging score	1.000	-	-
Total professional identity score	0.585[a]	1.000	-
Nursing information ability score	0.457[a]	0.382[a]	1.000

[a]$P < 0.01$.

Table 4 Effects of professional identity and nursing information ability on clinical belonging in nursing interns

Independent variable	Dependent variable	Direct effects	Indirect effects	Total effect
Professional identity	Clinical sense of belonging	0.52	0.21	0.73
Nursing information capability	Clinical sense of belonging	0.46	-	0.46

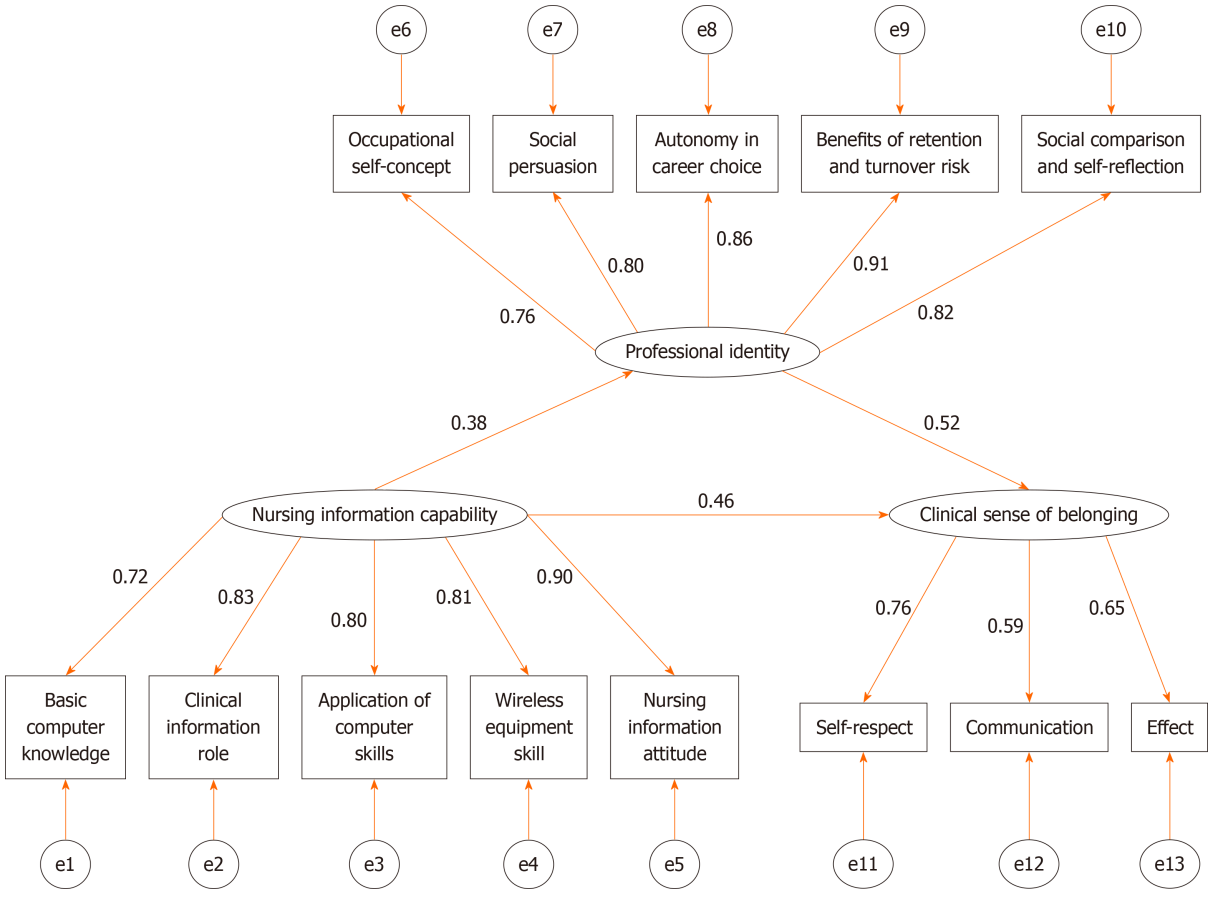

Figure 1 Structural equation model of clinical belonging, professional identity, and nursing information ability among nursing interns.

dance in improving professional identity among nursing students. The dimension of the benefit of retention and resignation risk had the lowest score; the item "nursing work can enable me to display my personal ability and expertise" in this dimension had a lower score, which was consistent with the results of the domestic survey. Table 2 shows that the professional identity of male interns and non-class leaders was low, which indicates that the nursing work at the present stage cannot meet the needs of the development platform for nurses, especially male nurses. It is suggested that nursing managers reasonably employ nurses according to their personal abilities and specialties, to mobilize their work enthusiasm.

Analysis regarding the status quo of nursing information ability among interns: The results of this study showed that the total score for nursing information ability among nursing interns was 70.29 ± 6.20 points, and the average score was 2.93 ± 0.26 points; this was lower than the average level and slightly higher than the survey results of Li *et al*. This may be because the research participants in this study included master's students (9.53%) whose nursing information ability is higher than that of undergraduate students[16]. As shown in Table 2, the nursing information ability of male students was higher than that of female students, which may be related to the fact that male students are more interested in computers and other Internet-related content and are willing to learn related content, leading to a better ability to apply computer skills. The scores for basic computer knowledge and skills were highest, similar to those of new nurses in an investigation by Liu *et al*[17] and higher than those of nursing students in a study by Hu *et al*[18] This may be because nursing interns in this study were all juniors or above; the higher the grade, the more computer theory courses and clinical practice have been completed, leading to improvement in computer knowledge and skills. The score for the clinical information role was the lowest, indicating that nursing students' ability to acquire and process clinical nursing information after entering the clinic was insufficient. It is suggested that nursing schools cooperate with hospitals to increase the time contact with clinical practice before actual practice so that nursing students can have a full understanding of clinical work procedures and working systems to improve their nursing information ability.

Model construction of nursing interns' clinical sense of belonging, professional identity, and nursing information ability

Correlation analysis results: The results of this study showed that nursing information ability was positively correlated with clinical sense of belonging, that is, stronger nursing information ability leads to a stronger clinical sense of belonging. This is because, in clinical practice, stronger nursing information ability among nursing interns means they will be more likely to receive appreciation from clinical educators. Research shows that a teacher's praise can promote clinical sense of belonging in nursing interns[19]. As shown in Table 3, professional identity among nursing interns is positively correlated with clinical sense of belonging. Studies show that the level of professional identity determines the performance of nursing interns in clinical work. The higher the level of professional identity, the higher their enthusiasm and professional quality in clinical practice, and the better they can integrate into the role of clinical nurses, which affects their clinical sense of belonging[4]. Nong *et al*[20] showed that with stronger competency among clinical educators, the professional identity of nursing interns was improved. Therefore, hospital managers should attach greater importance to the cultivation of teaching ability among nursing educators and guide them to use encouraging teaching methods to improve professional identity among nursing students, enhance their clinical sense of belonging, and thus stabilize the nursing team.

Mediating effect of nursing information ability on professional identity and clinical sense of belonging: The results of this study showed that the professional identity of nursing interns could directly affect their clinical sense of belonging (effect value = 0.51) and could also influence clinical sense of belonging through the partial mediating effect of nursing information ability **(**effect value = 0.20**)**. These results showed that nursing information ability was a protective factor and an important way for professional identity to affect clinical sense of belonging, that is, clinical sense of belonging could enhance nursing interns' professional identity by improving their nursing information ability. This may be because clinical practice is an important factor affecting the improvement of nursing information ability; with better clinical practice, nursing information ability is improved[21]. Professional identity also has a positive regulating effect on clinical practice behavior[22]; therefore, professional identity can improve nursing information ability to further enhance nursing students' clinical sense of belonging.

Limitations

The research in this study mainly focused on hospitals in Guangdong, China, and cities outside Guangdong Province were not included, which has certain geographical limitations. At the same time, the research subjects were mainly tertiary hospitals and secondary hospitals and community hospitals were not included, which limits the universality of the research results. Therefore, this study will collaborate with multiple provinces and cities to conduct research on multicenter and multi-level hospitals, in order to provide a better theoretical basis regarding interventions for nursing interns.

CONCLUSION

In this study, we assessed the current situation of clinical belonging, professional identity, and nursing information ability among nursing interns and constructed a relationship model for these three factors, which confirmed the direct effect of professional identity and nursing information ability on clinical belonging and the indirect effect of professional identity on clinical belonging through nursing information ability. Our findings suggested that nursing colleges should set up courses related to professional identity and nursing information ability and increase the clinical practice time of nursing students before internship to improve the basis of nursing interns' professional identity and nursing information ability. In addition, it is suggested that hospitals establish a good management system for nursing teachers, ensure adequate communication between nursing teachers and nursing interns, and strive to create a good atmosphere for interns and promote their integration into clinical nursing work to improve their sense of clinical belonging.

FOOTNOTES

Co-corresponding authors: Gai Zhang and Shao-Juan Huang.

Author contributions: Zhang G, Huang SJ, and Li SF conceptualized and designed the research; Zhang G and Li SF screened the research topics and acquired clinical data; Zhang G performed data analysis; Zhang G, Li SF wrote the paper. All the authors have read and approved the final manuscript. Both Zhang G and Huang SJ have played important and essential roles in the experimental design, data interpretation and manuscript preparation as the co-corresponding authors. Zhang G applied for and obtained the funds for this research project. Huang SJ conceptualized, designed, and supervised the whole process of the project. She searched the literature, revised and submitted the early version of the manuscript and was responsible for data re-analysis and re-interpretation, figure plotting, comprehensive literature search, preparation and submission of the current version of the manuscript.

Institutional review board statement: This study has been reviewed by the Ethics Committee of Foshan Traditional Chinese Medicine Hospital.

Informed consent statement: Before conducting the study, the researcher explained the purpose of the study to the participants and obtained signed informed consent forms.

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

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: Gai Zhang 0000-0003-0583-7531; Shao-Juan Huang 0000-0002-9601-6984.

S-Editor: Liu JH
L-Editor: Webster JR
P-Editor: Xu ZH

REFERENCES

1 **Zhou LJ**, Ren XH. The influencing factors and countermeasures of weak sense of belonging among clinical internship nursing students Modern nursing. *Zhonghua Xiandai Huli Zazhi* 2008; **14**: 2 [DOI: 10.3760/cma.j.issn.1674-2907.2008.01.057]
2 **Liu F**, Gui TH, Zheng KF, Zheng SL, Xu F. The mediating effect of clinical sense of belonging among nursing interns between perceived academic support and stress. *Zhonghua Huli Jiaoyu* 2022; 019
3 **Cowin LS**, Johnson M, Craven RG, Marsh HW. Causal modeling of self-concept, job satisfaction, and retention of nurses. *Int J Nurs Stud* 2008; **45**: 1449-1459 [PMID: 18242611 DOI: 10.1016/j.ijnurstu.2007.10.009]
4 **Xu JL**, Zhang HM. A study on the correlation between occupational identity, clinical sense of belonging, and turnover intention among newly hired nurses. *Zhejiang Zhongyiyao Daxue* 2019
5 **Staggers N**, Gassert CA, Curran C. A Delphi study to determine informatics competencies for nurses at four levels of practice. *Nurs Res* 2002; **51**: 383-390 [PMID: 12464758 DOI: 10.1097/00006199-200211000-00006]
6 **Zhu WJ**, Chen XW. A survey and study on the nursing information ability of undergraduate nursing students. *Zhonghua Huli Jiaoyu* 2020; **17**: 5 [DOI: 10.3761/j.issn.1672-9234.2020.03.012]
7 **Levett-Jones T**, Lathlean J, Higgins I, McMillan M. Development and psychometric testing of the Belongingness Scale-Clinical Placement Experience: an international comparative study. *Collegian* 2009; **16**: 153-162 [PMID: 19831149 DOI: 10.1016/j.colegn.2009.04.004]
8 **Tian J**, Liu HX, Su T, Deng ZZ, Lin H, An R. The mediating effect of clinical sense of belonging on the relationship between self-esteem and self-efficacy of nursing undergraduate students. *J Nurs Sci* 2016; **31**: 83-85
9 **Yu ZJ**, Zhang Y, Zhang BB, Zhang HY, Wang RH, Li HJ, Zhao J, Du CC. Revision and reliability and validity evaluation of the nursing information ability self-assessment scale. *Chongqing Yixue* 2019; **48**: 4
10 **Hao YF**, Liu XH. Research on the self-education model to enhance the professional identity and self-efficacy of nursing students. *Dier Junyi Daxue* 2011
11 **Tian J**, Liu HX, Su T, Lin H, Deng ZZ. A Study on the Relationship between Clinical Belongingness and Resignation Intention of Undergraduate Intern Nursing Students. *Zhongguo Gaodeng Yixue Jiaoyu* 2017; 2
12 **Teng YF**, Yang H, Cao YP. The mediating effect of clinical sense of belonging among nursing interns on the understanding of social support and career decision-making self-efficacy. *Zhonghua Huli Jiaoyu* 2022; **19**: 1007-1011 [DOI: 10.3761/j.issn.1672-9234.2022.11.010]
13 **Jiang Y**, Zhang Q, Shang D, Zhang LN, Yuan SL, Li S. A Study on the Relationship between Clinical Belongingness and Clinical Practice Behavior of Undergraduate Intern Nursing Students. *Hushi Jinxiu Zazhi* 2017; **32**: 3 [DOI: 10.16821/j.cnki.hsjx.2017.10.030]
14 **Xing S**. A study on the professional identity and influencing factors of vocational nursing students in the later stage of internship. *Shandong*

Daxue 2016 [DOI: 10.7666/d.Y3156582]
15 **Hu YN**, Ge GQ, Zhang FP, Zou GH, Li LM. Investigation on the status quo of professional identity of nursing students in post internship period in Henan Province under the background of novel coronavirus pneumonia. *Huli Shijian Yu Yanjiu* 2022; **19**: 6
16 **Li X**, Li XH. () Analysis of the current situation and influencing factors of nursing information ability among undergraduate nursing students in Liaoning Province. *Jiefangjuan Huli Zazhi* 2022; **39**
17 **Liu D**. A study on the relationship model between the sense of professional benefits and transformation impact of new nurses, as well as nursing information ability. *Huli Guanli Zazhi* 2021; **21**: 5
18 **Hu SH**, Zhou YQ, Wang T, Hu X. Research on the Current Situation and Influencing Factors of Nursing Information Ability among Undergraduate Nursing Students in Anhui Province. *Bengbu Yixueyuan Xuebao* 2022; **47**: 1435-1440
19 **Nong QL**, Ge Y, Wei GY. A correlation study between the competency of clinical teaching teachers and the professional identity of intern nursing students. *Weisheng Zhiye Jiaoyu* 2022; **40**: 3
20 **Xu GR**, Qiu PP, Hu RF, Lin XY, Wang XY, Xu Q, Song JH. An analysis of the mediating effect of sense of belonging on the occupational benefits and clinical practice behavior of nursing students. *Zhongguo Gaodeng Yixue Jiaoyu* 2020; 2
21 **Li XY**, Gao RJ, Liang YJ. A study on the correlation between professional identity and clinical practice behavior of undergraduate nursing interns. *Zhongxiyi Jiehe Huli* 2019; **5**: 3 [DOI: 10.11997/nitcwm.201910049]
22 **Cha QH**, Zhu DY, Tian QJ, Ni XP, Su J. Construction of an evaluation index system for nursing information ability of newly hired nurses. *Zhongguo Huli Guanli* 2022 [DOI: 10.3969/j.issn.1008-9993.2016.10.006]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2218-2230

DOI: 10.12998/wjcc.v12.i13.2218

ISSN 2307-8960 (online)

META-ANALYSIS

Efficacy and safety of Yangxinshi tablet for chronic heart failure: A systematic review and meta-analysis

Sheng-Hua Lu, Yun-Feng Yu, Si-Si Dai, Ya-Qi Hu, Jian-He Liu

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: Ito S, Japan

Received: February 2, 2024
Revised: March 10, 2024
Accepted: March 29, 2024
Published online: May 6, 2024

Sheng-Hua Lu, Yun-Feng Yu, Si-Si Dai, Ya-Qi Hu, Jian-He Liu, The First Clinical College of Chinese Medicine, Hunan University of Chinese Medicine, Changsha 410007, Hunan Province, China

Sheng-Hua Lu, Jian-He Liu, Branch of National Clinical Research Center for Chinese Medicine Cardiology, The First Hospital of Hunan University of Chinese Medicine, Changsha 410007, Hunan Province, China

Corresponding author: Jian-He Liu, MD, PhD, Professor, The First Clinical College of Chinese Medicine, Hunan University of Chinese Medicine, No. 95 Shaoshan Middle Road, Yuhua District, Changsha 410007, Hunan Province, China. ljhtcm1@163.com

Abstract

BACKGROUND

The specific benefits of Yangxinshi tablet (YXST) in the treating chronic heart failure (CHF) remain uncertain.

AIM

To systematically evaluate the efficacy and safety of YXST in the treatment of CHF.

METHODS

Randomized controlled trials (RCTs) investigating YXST for CHF treatment were retrieved from eight public databases up to November 2023. Meta-analyses of the included clinical studies were conducted using Review Manager 5.3.

RESULTS

Twenty RCTs and 1845 patients were included. The meta-analysis results showed that the YXST combination group, compared to the conventional drug group, significantly increased the clinical efficacy rate by 23% [relative risk (RR) = 1.23, 95%CI: 1.17-1.29], $P < 0.00001$), left ventricular ejection fraction by 6.69% [mean difference (MD) = 6.69, 95%CI: 4.42-8.95, $P < 0.00001$] and 6-min walk test by 49.82 m (MD = 49.82, 95%C: 38.84-60.80, $P < 0.00001$), and reduced N-terminal pro-B-type natriuretic peptide by 1.03 ng/L [standardized MD (SMD) = -1.03, 95%CI: -1.32 to -0.74, $P < 0.00001$], brain natriuretic peptide by 80.95 ng/L (MD = -80.95, 95%CI: -143.31 to -18.59, $P = 0.01$), left ventricular end-diastolic diameter by 3.92 mm (MD = -3.92, 95%CI: -5.06 to -2.78, $P < 0.00001$), and left ventricular end-systolic diameter by 4.34 mm (MD = -4.34, 95%CI: -6.22 to -2.47, $P < 0.00001$). Regarding safety, neither group reported any serious adverse events during

treatment (RR = 0.54, 95%CI: 0.15-1.90, P = 0.33). In addition, Egger's test results indicated no significant publication bias (P = 0.557).

CONCLUSION

YXST effectively improves clinical symptoms and cardiac function in patients with CHF while maintaining a favorable safety profile, suggesting its potential as a therapeutic strategy for CHF.

Key Words: Yangxinshi tablet; Chronic heart failure; Cardiac function; Systematic evaluation; Meta-analysis

Core Tip: Chronic heart failure (CHF) represents a severe manifestation and late-stage complication of various heart diseases. This study aims to conduct a systematic evaluation of the efficacy and safety of Yangxinshi tablet (YXST) in the treating CHF through meta-analysis. The results indicate that YXST effectively improved clinical symptoms and cardiac function in patients with CHF while maintaining a favorable safety profile, suggesting its potential as a therapeutic strategy for CHF.

Citation: Lu SH, Yu YF, Dai SS, Hu YQ, Liu JH. Efficacy and safety of Yangxinshi tablet for chronic heart failure: A systematic review and meta-analysis. *World J Clin Cases* 2024; 12(13): 2218-2230
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2218.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2218

INTRODUCTION

Chronic heart failure (CHF) is a complex clinical syndrome characterized by ventricular systolic and/or diastolic dysfunction caused by abnormal alterations in heart structure or function. CHF is primarily characterized by weakness, dyspnea, and fluid retention resulting from impaired ventricular function and inadequate peripheral blood supply[1,2]. Moreover, CHF represents the end-stage of various heart diseases. The condition is a significant cause of reduced quality of life and an elevated risk of mortality in patients with cardiovascular conditions. This makes CHF a critical global public health concern[3,4]. Epidemiological data reveal that the global prevalence of CHF in adults ranges from 1% to 3% and that the incidence of CHF significantly increases with age. Studies indicate that, on average, patients with congestive HF experience a heightened risk of mortality, with a survival rate of less than 50% within the first year and a more pronounced decline within 5 years[5,6]. The incidence of CHF in China is 2.75/100000 person-years (287/100000 person-years in men and 261/100000 person-years in women). Additionally, approximately, three million new cases of HF are recorded each year[7,8]. The 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America Guidelines for the Management of Heart Failure recommend a baseline treatment strategy for CHF consisting of a quadruple regimen, including renin-angiotensin system inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors (SGLT2i)[2]. Although these drugs have demonstrated beneficial effects on overall mortality, rates of rehospitalization, progression of left ventricular insufficiency, and exercise tolerance in patients with CHF, achieving satisfactory efficacy remains a challenge in some patients. Furthermore, concerns have arisen regarding adverse events associated with long-term medication[9,10].

As research advances, an increasing number of researchers are recognizing the potential role of Chinese medicine in enhancing the prognosis of CHF[11,12]. The treatment of CHF with traditional Chinese medicine (TCM) involves multiple components, targets, and mechanisms[13]. The Yangxinshi tablet (YXST) is a kind of proprietary Chinese medicine composed of *Panax ginseng* C. A. Mey. (Renshen), *Astragalus membranaceus* (Fisch.) Bunge. (Huangqi), *Salvia miltiorrhiza* Bge. (Danshen), *Corydalis yanhusuo* W.T.Wang (Yanhusuo), *Crataegus pinnatifida* Bge (Shanzha), *Codonopsis pilosula* (Franch.) Nannf. (Dangshen), *Ganoderma lucidum* (Leyss. ex Fr.) Karst. (Lingzhi), *Pueraria lobata* (Willd.) Ohwi (Gegen), *Angelica sinensis* (Oliv) Diels (Danggui), *Epimedium grandiflorum* Morr (Yinyanghuo), *Rehmannia glutinosa* (Gaetn.) DC (Dihuang), *Coptis chinensis* Franch (Huanglian), and *Glycyrrhizae radix* et Rhizoma (Gancao)[14]. YXST benefits Qi, warms Yang, activates blood circulation and reduces blood stasis. Moreover, YXST has been widely used since its development to treat CHF, coronary heart disease, myocardial infarction, depression, and other diseases[14]. YXST was identified to inhibit myocardial fibrosis and resist ventricular remodeling by inhibiting cardiomyocyte apoptosis[15]. In patients with CHF, YXST improves cardiac function by modulating multiple metabolic pathways, including oxidative stress, energy metabolism, and fatty acid and amino acid metabolism[16]. In patients with CHF, YXST also relieves anxiety and depression and increases exercise tolerance, thereby improving quality of life[17]. This may serve as a potential treatment strategy for patients with CHF. However, owing to the lack of high-quality evidence, the specific benefits of YXST in patients with CHF remain unclear. This was a meta-analysis of randomized controlled trials (RCTs) that evaluated the efficacy of YXST for the treatment of CHF. This study aimed to provide evidence-based support for the clinical use of YXST.

MATERIALS AND METHODS

This meta-analysis is registered with International Prospective Register of Systematic Reviews under registration number CRD42024507360.

Search strategy

A comprehensive search was conducted in English and Chinese databases to identify all relevant clinical studies from the time of database inception to November 2023. The search was conducted using English and Chinese databases, including PubMed, Cochrane Library, Web of Science, EMBASE, China National Knowledge Infrastructure, Wanfang, VIP, and China Biomedical Literature Database. The search strategy used a combination of subject terms and free words. The subject terms used were YXST and CHF, and the free terms were supplemented by MeSH and the Cochrane Library. The search was independently conducted by authors Lu and Yu and any differences were resolved by discussion.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) The study was designed as a RCT; (2) the included participants were adults (≥ 18 years) who met the diagnostic criteria for CHF[18]; (3) the experimental group received YXST in combination with conventional treatment, whereas the control group received conventional treatment alone; and (4) the efficacy indicators included clinical efficacy rate, N-terminal pro-B-type natriuretic peptide (NT-proBNP), brain natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), 6-min walk test (6-MWT), and readmission rate. The clinical efficacy rate represented the proportion of patients with signs and symptoms of CHF in remission. The safety indicator was adverse events.

The exclusion criteria were as follows: (1) The same research results were repeatedly reported; and (2) unavailable data.

Literature screening, data collection, and risk of bias evaluation

Literature screening, data collection, and risk-of-bias evaluation were independently performed by Lu and Yu. First, two researchers independently screened the literature using NoteExpress 3.9.0 software. Second, the two researchers independently organized and filled in the basic characteristics and data statistics tables of the included studies. Furthermore, the two researchers independently assessed the risk of bias in each study with the help of the Cochrane tools. At each step, the two researchers ensured that the results were consistent. Any disagreements that arose during this period were discussed and resolved by both researchers involved.

Data analysis

RevMan 5.3 software was used to perform the meta-analysis. Dichotomous variables were expressed as relative risk (RR) and 95%CI, whereas continuous variables were expressed as mean difference (MD) or standardized MD (SMD) with a 95%CI. When I-squared statistic (I^2) was < 50%, a fixed-effects model was used to analyze the data. When I^2 was ≥ 50%, a sensitivity analysis was required if significant clinical or methodological heterogeneity existed. A random-effects model was used if no significant clinical or methodological heterogeneity was detected. Results were considered statistically significant at $P < 0.05$. Egger's test was used to assess publication bias, with $P > 0.1$ indicating no publication bias in the results.

RESULTS

Results of literature screening

A total of 287 articles were retrieved from eight public databases. In the literature screening process, 130 duplicate articles were excluded along with 137 articles that did not conform to the research theme. Finally, 20 articles were included in this study[19-38]. The literature screening process is illustrated in Figure 1.

Basic characteristics of the included literature

Twenty clinical trials and 1845 patients were included[19-38]. Of these, 935 patients were included in the YXST combination group and 910 patients were included in the conventional drug group. The publication years of the aforementioned clinical trials ranged from 2008 to 2023, and all experimental centers were located in China. Among the 20 clinical trials, 19 (95%) followed the 2023 Focused Update of the 2021 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and CHF, while one trial conducted by Fan *et al*[23] did not describe specific treatment plans. Two studies used a YXST dosage of 0.12 g/dose[28,31], while two studies used a YXST dosage of 0.24 g/dose[33, 34], and the remaining studies utilized a dosage of 0.18 g/dose[19-27,29,30,32,35-38]. The frequency of administration in all studies was three times/d. The duration of the studies ranged from 1 to 48 wk. The baseline information of all experimental and control groups included in the studies was comparable. The basic characteristics of the included studies are presented in Table 1.

Risk of bias assessment

The risk of bias associated with the randomized approach was unclear in nine studies. Additionally, the risk of bias due to allocation concealment and intervention blinding was unclear in 20 studies. The risk of bias for the remaining areas was low. The risk of bias assessment is displayed in Figure 2.

Table 1 Basic characteristics of included studies

Ref.	Sample size	Male (%)	Age (yr)	Disease duration (yr)	Intervention	Treatment duration (wk)	Left ventricular function	Type of CHF	Baseline cardiac disease
Bai and Li [19], 2023	44	54.5	62.8 ± 5.3	10.6 ± 2.2	Perindopril, metoprolol, trimetazidine, and YXST (0.18 g tid)	4			ICM
	44	52.3	62.0 ± 5.1	10.8 ± 2.4	Perindopril, metoprolol, and trimetazidine	4			
Bai[20], 2019	50	50.0	66.6 ± 10.4		Telmisartan, amlodipine, and YXST (0.18 g tid)	4			ICM
	50	52.0	66.5 ± 10.2		Telmisartan and amlodipine	4			
Cheng *et al*[21], 2019	48	54.2	71.2 ± 3.6		Levocarnitine and YXST (0.18 g tid)	1	Left ventricular diastolic dysfunction	HFpEF	
	48	52.1	71.9 ± 3.8		Levocarnitine	1			
Chen[22], 2019	20	70.0	64.0 ± 11.0		ACEI/ARB, MRA, diuretic, cardiotonic, and YXST (0.18 g tid)	4			
	20	85.0	63.0 ± 10.0		ACEI/ARB, MRA, diuretic, and cardiotonic	4			
Fan *et al* [23], 2020	63	52.4	66.0 ± 3.7		Optimizing drug therapy and YXST (0.18 g tid)	48			
	63	57.1	67.0 ± 3.6		Optimizing drug therapy	48			
Fu *et al* [26], 2014	64	65.6	65.0 ± 10.2	2.4 ± 1.2	ACEI, diuretic, cardiotonic, and YXST (0.18 g tid)	12			NICM
	62	64.5	64.0 ± 10.8	2.3 ± 1.4	ACEI, diuretic, and cardiotonic	12			
Gu *et al* [25], 2016	60	65.0	61.8 ± 11.8		Perindopril, metoprolol, spironolactone, furosemide, isosorbide mononitrate, aspirin, clopidogrel, atorvastatin, and YXST (0.18 g tid)	24			
	60	70.0	62.5 ± 15.3		Perindopril, metoprolol, spironolactone, furosemide, isosorbide mononitrate, aspirin, clopidogrel, and atorvastatin	24			
Gao and Zhang [24], 2021	39	51.3	62.54 ± 7.5		Benazepril, metoprolol, furosemide, digoxin, and YXST (0.18 g tid)	24			
	39	53.8	63.0 ± 6.8		Benazepril, metoprolol, furosemide, and digoxin	24			
Huang *et al*[27], 2009	63	58.7	59.8 ± 11.2	5.2 ± 4.3	ACEI, β-blocker, diuretic, vasodilator, and YXST (0.18 g tid)	4	Left ventricular diastolic dysfunction	HFmrEF, HFpEF	
	62	58.1	61.2 ± 13.4	5.0 ± 4.9	ACEI, β-blocker, diuretic, and vasodilator	4			
Li and Zhou [28], 2019	60	56.7	66.6 ± 12.5	5.7 ± 2.1	Bisoprolol and YXST (0.12 g tid)	24			ICM
	60	43.3	64.9 ± 12.3	5.7 ± 2.0	Bisoprolol	24			
Li[29], 2017	47	53.2	61.35 ± 8.7	9.3 ± 3.6	Diuretic, vasodilator, trimetazidine, statin, and YXST (0.18 g tid)	4			ICM
	47	51.2	61.58 ± 7.6	9.52 ± 2.9	Diuretic, vasodilator, trimetazidine, and statin	4			
Liu[30], 2022	33	48.5	58.4 ± 11.5	9.5 ± 3.1	ACEI/ARB, β-blocker, MRA, diuretic, and YXST (0.18 g tid)	12	Left ventricular diastolic dysfunction	HFpEF	

	32	43.8	57.1 ± 12.8	10.2 ± 3.7	ACEI/ARB, β-blocker, MRA, and diuretic	12			
Qian and Wei[31], 2012	56				ACEI, β-blocker, diuretic, vasodilator, cardiotonic, and YXST (0.12g tid)	12			NICM
	56				ACEI, β-blocker, diuretic, vasodilator, and vardiotonic	12			
Qu[32], 2008	89	61.8	52.0 ± 13.1		ACEI, β-blocker, diuretic, vasodilator, cardiotonic, and YXST (0.18g tid)	24			
	82	62.2	53.3 ± 18.3		ACEI, β-blocker, diuretic, vasodilator, and cardiotonic	24			
Sun *et al* [35], 2016	34	44.1	58.0 ± 13.1		ACEI, β-blocker, diuretic, and YXST (0.18g tid)	16			
	34	52.9	54.3 ± 15.3		ACEI, β-blocker, and diuretic	16			
Wang *et al*[33], 2011	34	64.7			Spironolactone, hydrochlorothiazide, nitroglycerin, dobutamine, and YXST (0.24 g tid)	2			
	26	69.2			Spironolactone, hydrochlorothiazide, nitroglycerin, and dobutamine	2			
Yuan[34], 2012	40	52.5	68.7 ± 10.2	3.2 ± 0.7	ACEI, β-blocker, diuretic, vasodilator, and YXST (0.24 g tid)	4	Left ventricular diastolic dysfunction	HFpEF	
	35	51.4	71.3 ± 13.1	2.9 ± 0.9	ACEI, β-blocker, diuretic, and vasodilator	4			
Zhang and Niu [36], 2017	34	52.9	55.7 ± 9.6	6.0 ± 3.3	Benazepril, metoprolol, losartan potassium, hydrochlorothiazide, and YXST (0.18 g tid)	8	Left ventricular diastolic dysfunction	HFmrEF, HFpEF	
	33	63.6	54.1 ± 9.6	6.1 ± 3.2	Benazepril, metoprolol, losartan potassium, and hydrochlorothiazide	8			
Zhang [37], 2018	30	60.0	63.8 ± 4.8		ACEI, β-blocker, MRA, and YXST (0.18 g tid)	12			
	30	56.7	62.6 ± 5.2		ACEI, β-blocker and MRA	12			
Zhang [38], 2022	27	48.1	65.2 ± 5.3	5.2 ± 1.0	ARNI/ARB, β-blocker, MRA, diuretic, vasodilator, cardiotonic, and YXST (0.18 g tid)	8		HFrEF	
	27	58.6	64.1 ± 6.0	5.1 ± 1.2	ARNI/ARB, β-blocker, MRA, diuretic, vasodilator, and cardiotonic	8			

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor II blocker neprilysin inhibitor; MRA: Mineralcorticoid receptor antagonist; YXST: Yangxinshi tablet; CHF: Chronic heart failure; HFpEF: Heart failure with preserved ejection fraction; HFmrEF: Heart failure with mid-range ejection fraction; HFrEF: Heart failure with reduced ejection fraction; ICM: Ischemic cardiomyopathy; NICM: Non-ischemic cardiomyopathy.

Clinical efficacy rate

The meta-analysis demonstrated that the YXST combination group had a significantly increased clinical efficacy rate by 23% compared to that of the conventional drug group (RR = 1.23, 95%CI: 1.17-1.29, $P < 0.00001$) (Figure 3).

NT-proBNP and BNP

Meta-analysis demonstrated that in comparison to the conventional drug group, the YXST combination group reduced NT-proBNP by 1.03 ng/L (SMD = -1.03, 95%CI: -1.32 to -0.74, $P < 0.00001$) and BNP by 80.95 ng/L (MD = -80.95, 95%CI: -143.31 to -18.59, $P = 0.01$) (Figure 4).

LVEF, LVEDD and LVESD

Meta-analysis demonstrated that the YXST combination group significantly increased LVEF by 6.69% (MD = 6.69, 95%CI: 4.42-8.95, $P < 0.00001$), reduced LVEDD by 3.92 mm (MD = -3.92, 95%CI: -5.06 to -2.78, $P < 0.00001$) and LVESD by 4.34

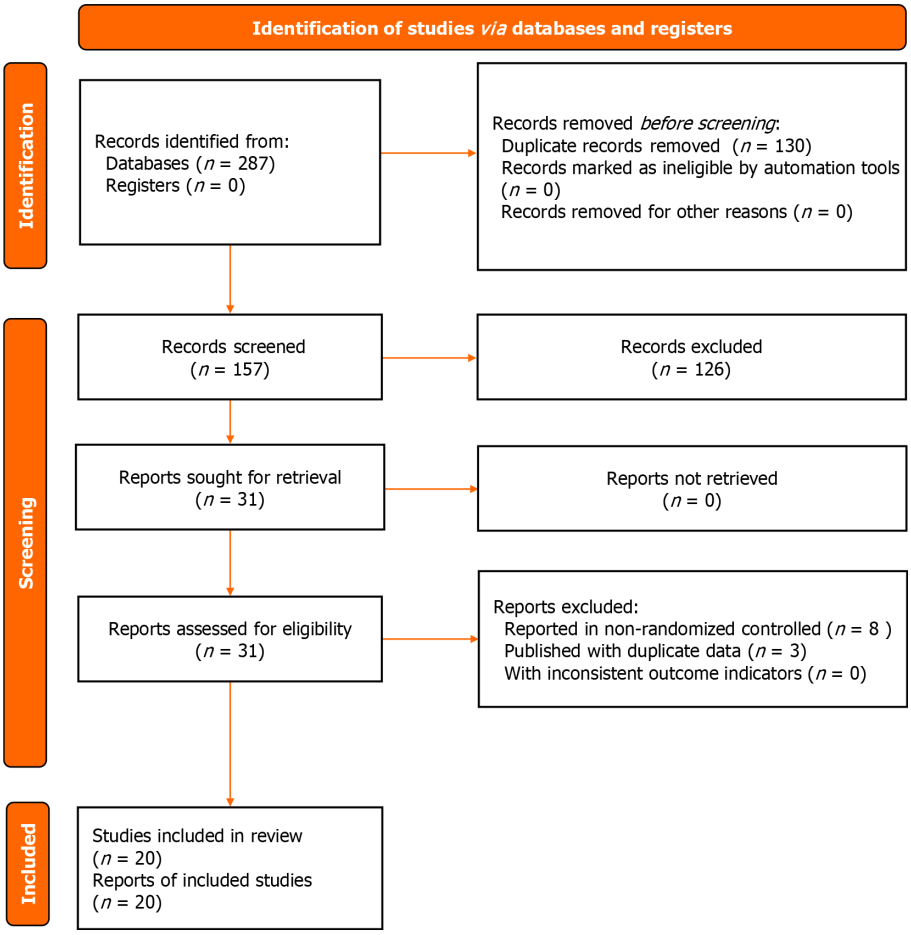

Figure 1 Literature screening flowchart.

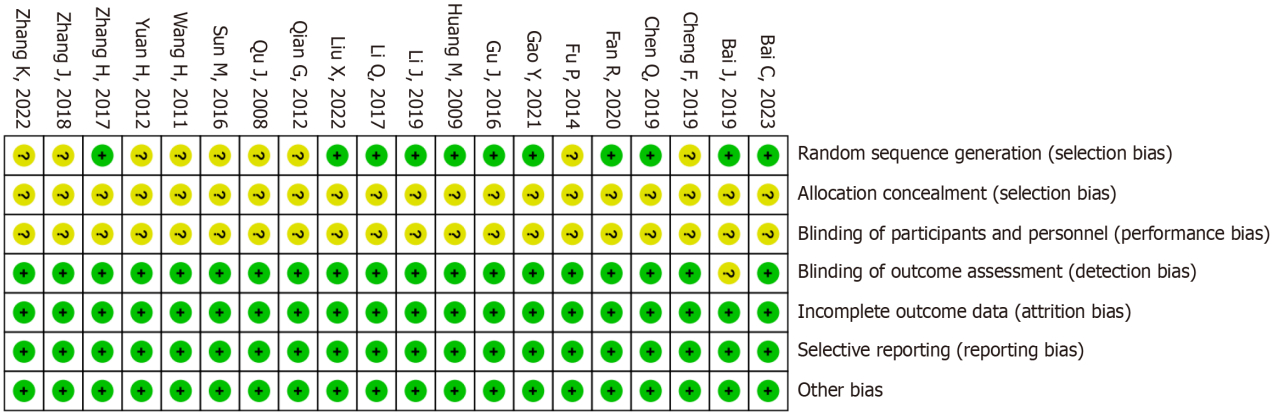

Figure 2 Risk of bias assessment of included studies.

mm (MD = -4.34, 95%CI: -6.22 to -2.47, $P < 0.00001$) compared to the conventional drug group (Figure 5).

6-MWT

Meta-analysis established that the YXST combination group significantly increased 6-MWT by 49.82 m compared to the conventional drug group (MD = 49.82, 95%CI: 38.84-60.80, $P < 0.00001$) (Figure 6).

Readmission rate

Thirteen patients in the YXST combination group and 27 in the conventional drug group were readmitted due to relapse during treatment. The readmission rate in the combined YXST group was significantly lower than that in the conventional drug group (RR = 0.48, 95%CI: 0.26-0.87, $P = 0.02$) (Figure 7).

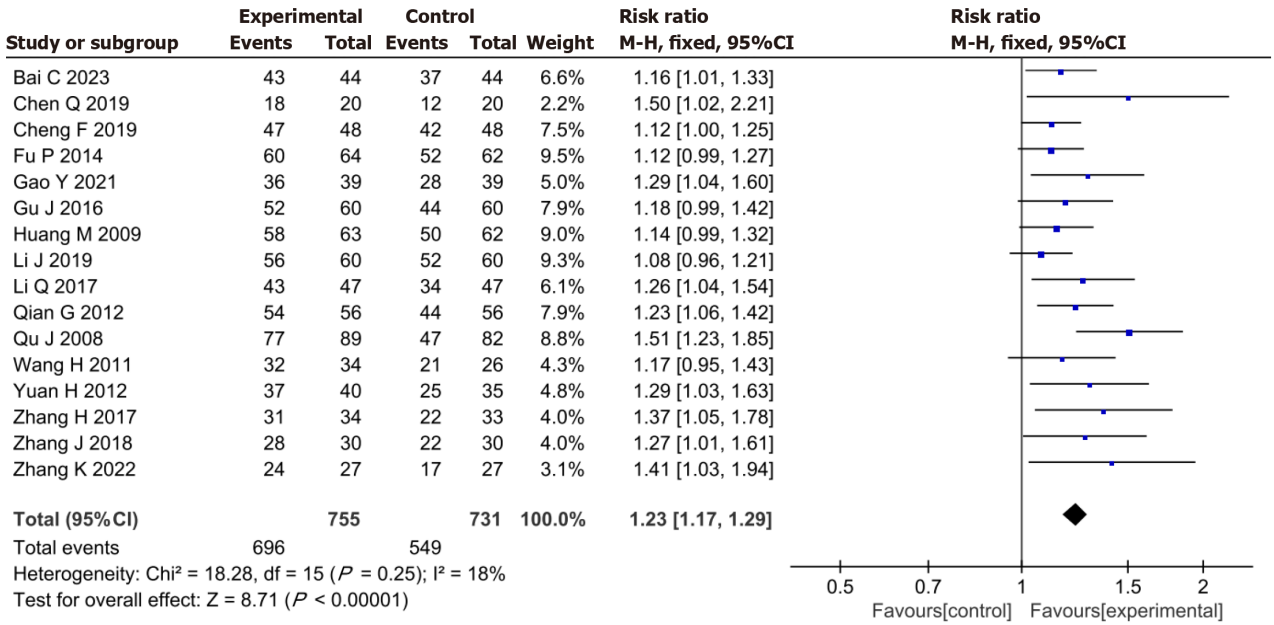

Figure 3 Meta-analysis results for the clinical efficacy rate.

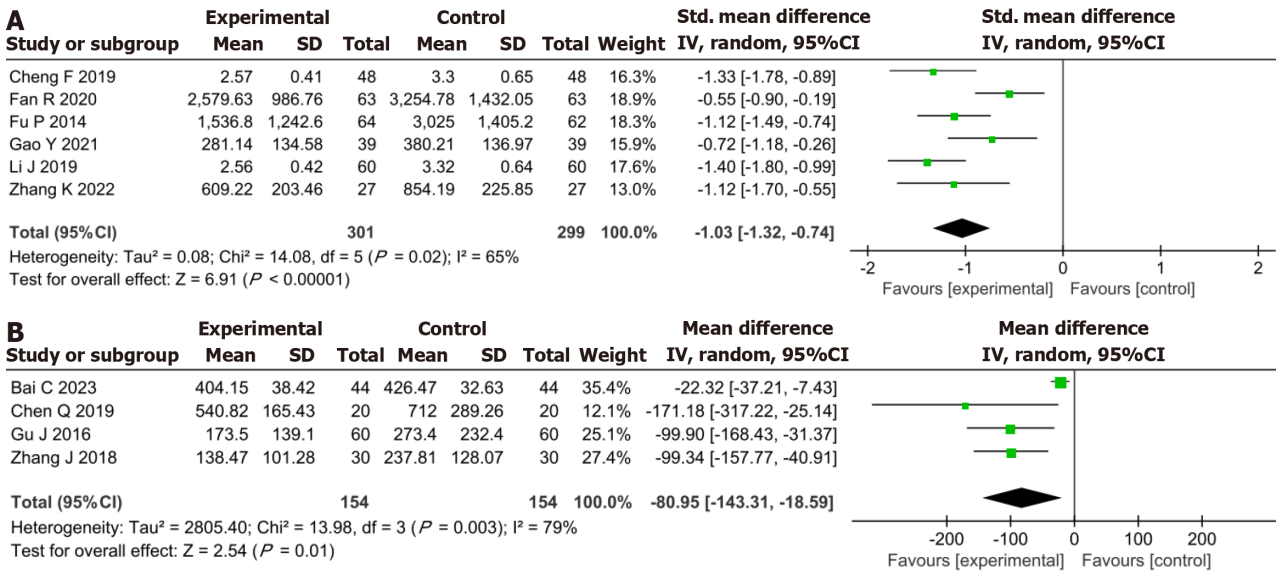

Figure 4 Meta-analysis results for N-terminal pro-B-type natriuretic peptide and brain natriuretic peptide. A: N-terminal pro-B-type natriuretic peptide; B: Brain natriuretic peptide.

Adverse events

Three patients in the YXST combination group experienced adverse events, including one case of nausea, one case of slightly dry mouth, and one case of itchy skin. Six adverse events occurred in the conventional drug group, including three cases of nausea, two cases of abdominal distension, and one case of slightly dry mouth. No significant difference was observed in adverse events between the YXST combination group and the conventional drug group (RR = 0.54, 95%CI: 0.15-1.90, P = 0.33) (Figure 8).

HF with preserved ejection fraction subgroup analysis

HF with preserved ejection fraction (HFpEF) subgroup analysis was employed to explore the clinical efficacy of YXST in the treatment of HFpEF. The results confirmed that, compared to the conventional drug group, the YXST combination group significantly improved the clinical effective rate by 19% (RR = 1.19, 95%CI: 1.06-1.33, P = 0.003), and increased the 6-MWT by 44.61 m (MD = 44.61, 95%CI: 17.58-71.65, P = 0.001). Additionally, the YXST combination group decreased the NT-proBNP by 0.73 ng/L (MD = -0.73, 95%CI: -0.95 to -0.51, P < 0.00001). As shown in Table 2.

Table 2 Meta-analysis results for efficacy endpoints of Yangxinshi tablet in treating heart failure with preserved ejection fraction

Outcome	Sample size (E/C)	I^2/%	MD/RR (95%CI)	*P* value
Clinical efficacy rate	88/83	37	1.19 (1.06-1.33)	0.003
NT-proBNP	48/48	0	-0.73 (-0.95 to -0.51)	< 0.00001
6-MWT	121/115	80	44.61 (17.58-71.65)	0.001

E: Experiment group; C: Control group; NT-proBNP: N-terminal pro-B-type natriuretic peptide; 6-MWT: 6-min walk test; MD: Mean difference; RR: Relative risk; I^2: I-squared statistic.

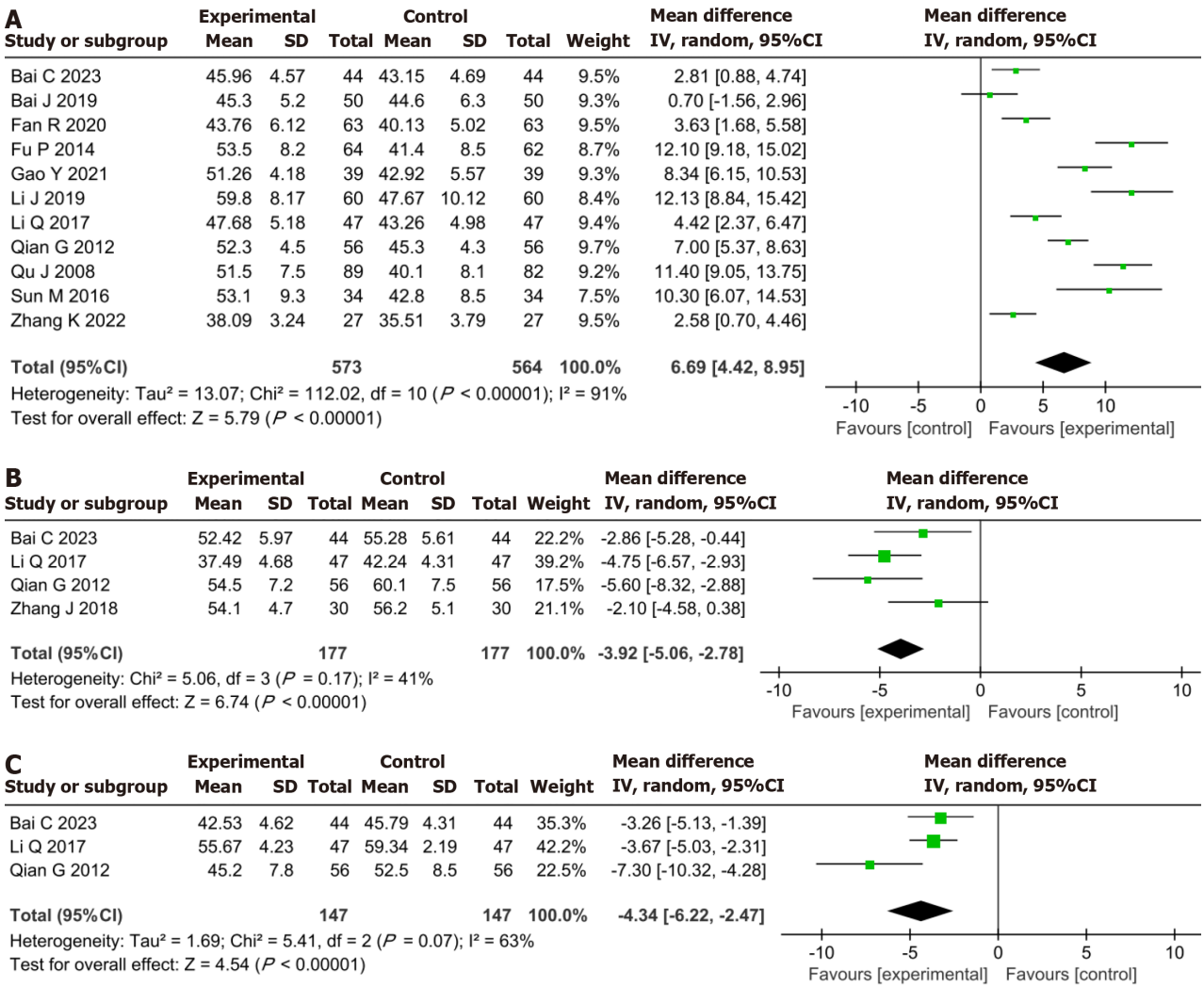

Figure 5 Meta-analysis results for cardiac function. A: Left ventricular ejection fraction; B: Left ventricular end-diastolic diameter; C: Left ventricular end-systolic diameter.

Publication bias

The clinical efficacy rate was defined as the primary efficacy endpoint. Egger's test of the clinical efficacy rate demonstrated no significant publication bias ($P = 0.557$) (Figure 9).

DISCUSSION

CHF is a severe manifestation or late stage of various heart diseases with high mortality and readmission rates[39]. The prevention and treatment of CHF have become a global public health concern. The pathogenesis of CHF is mainly related to ventricular remodeling. The overactivation of neuroendocrine and cytokine factors is closely related to the occurrence

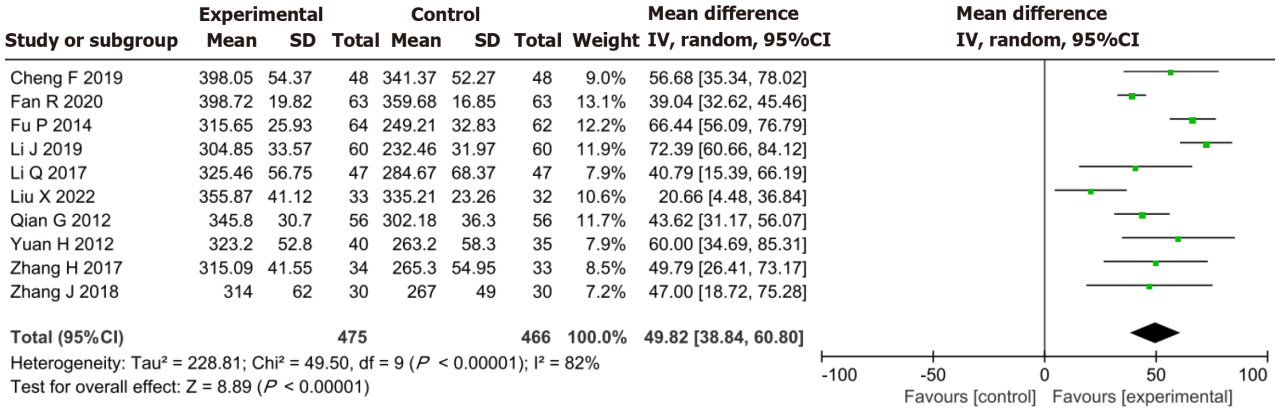

Figure 6 Meta-analysis results for 6-min walk test.

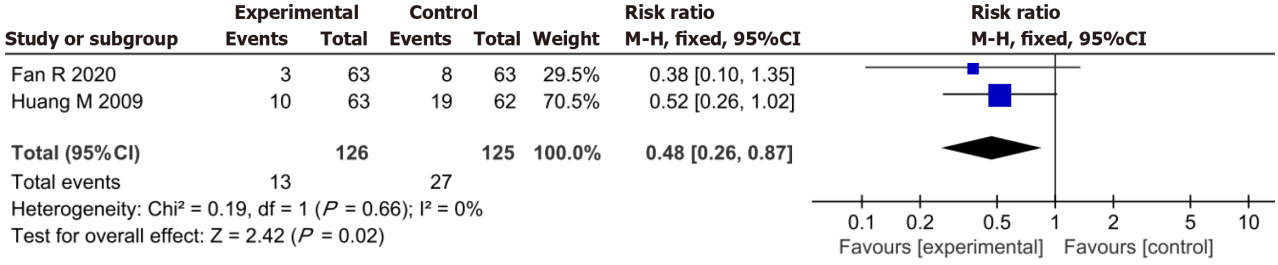

Figure 7 Meta-analysis results for readmission rate.

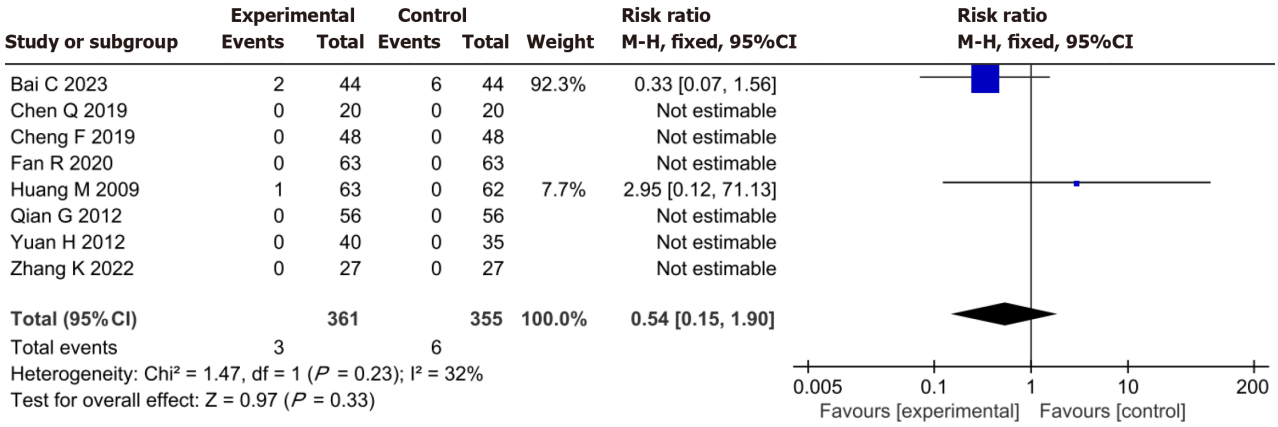

Figure 8 Meta-analysis results for adverse events.

of ventricular remodeling. As the understanding of the pathogenesis of CHF has deepened, the treatment concept for CHF has produced a major shift from traditional cardiotonic, diuretic, and vasodilator approaches to the inhibition of excessive activation of the neuroendocrine system and ventricular remodeling[40,41]. An increasing number of studies have demonstrated that YXST can improve coronary blood flow, alleviate symptoms, such as shortness of breath caused by myocardial ischemia, and inhibit myocardial fibrosis and ventricular remodeling through its anti-inflammatory and antioxidant properties. This suggests that YXST may serve as a complementary treatment strategy for CHF[16]. This study included 20 RCTs involving 1845 patients. This is the first systematic evaluation and meta-analysis of YXST for the treatment of CHF intending to provide evidence-based support for the clinical use of YXST.

Our findings revealed that the YXST combination group significantly improved the clinical effective rate by 23% and 6-MWT by 49.82 m compared to the conventional treatment group. This suggests that YXST effectively reduces the signs and symptoms of HF and enhances exercise tolerance in patients with CHF. Furthermore, the combination group of YXST reduced NT-proBNP by 1.03 ng/L and BNP by 80.95 ng/L, indicating its role in slowing down the progression of CHF, as BNP and NT-proBNP are important reference indexes for measuring the overall prognostic efficacy of CHF. In terms of cardiac function, the combination group of YXST significantly increased LVEF by 6.69%, reduced LVEDD by 3.92 mm, and LVESD by 4.34 mm. LVEF represents the ratio of stroke volume to the left ventricular end-diastolic volume. The parameter serves as an objective indicator of the severity of HF. Mortality in patients with HF is closely correlated with

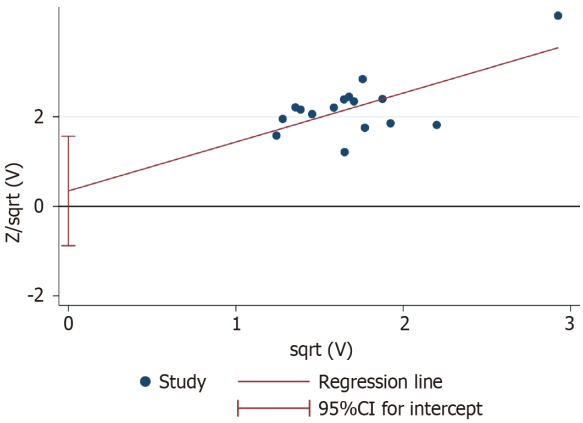

Figure 9 Egger's test for publication bias.

the LVEF. Additionally, LVESD and LVEDD are indicative of the volume load on the left ventricle. Increases in LVEDD and LVESD signify cardiac dilation and compromised ventricular compliance. Both LVEF and LVEDD reflect the extent of left ventricular remodeling. These three outcome indicators suggest that YXST improves cardiac function and reverses ventricular remodeling to a certain extent. This confirms that YXST improves the patients' clinical symptoms and cardiac function, which may be the reason for the reduction in the readmission rate.

Regarding safety endpoints, the YXST combination group exhibited an adverse event rate of 0.83% (3/361), whereas the conventional drug group had an adverse event rate of 1.69% (6/355). Adverse event rates were comparable between the two groups. This suggests that YXST has a favorable safety profile. The adverse events that occurred in both groups mainly involved gastrointestinal events. As the researchers did not identify a correlation between these adverse events and YXST, we hypothesized that they may have been caused by conventional medications such as aspirin. However, owing to the narrow study base and sample size, more studies are required to further explore the safety of YXST.

HFpEF is the most common type of CHF, accounting for more than 50% of all cases[42]. An observational study in a western country demonstrated that the 1-year mortality rate of patients with HFpEF was 20%–29%, whereas the 5-year mortality rate was as high as 53%–74%[43]. SGLT2i and angiotensin receptor/neprilysin inhibitors (ARNI) are commonly used for HFpEF and they effectively improve its prognosis[18,44]. However, apart from SGLT2i and ARNI, few beneficial drugs are available for HFpEF. The current treatment regimens are still inadequate for the management of all patients with HFpEF[45]. In this study, we evaluated the clinical efficacy of YXST in treating HFpEF. The results of the HFpEF subgroup analysis demonstrated that YXST significantly increased the clinical effective rate by 19%, 6-MWT by 44.61 m, and decreased NT-proBNP by 0.73 ng/L in patients with HFpEF. This suggests that YXST can reduce clinical symptoms, enhance exercise tolerance, and improve the overall prognosis of patients with HFpEF. Therefore, we hypothesized that YXST has the potential to complement SGLT2i and ARNI in the treatment of HFpEF.

According to the TCM theory, CHF is attributed to prolonged involvement of the heart, leading to a deficiency of Yangqi and blood stasis. The key to the treatment of CHF is to benefit Qi, warm Yang, and invigorate blood circulation to eliminate blood stasis[22]. The compositional characteristics of YXST, with multiple drugs and components, determine its pharmacological mechanism of action through multitarget synergistic effects. Moreover, YXST regulates neuroendocrine and cytokine levels through various pathological and physiological pathways, thereby enhancing its effectiveness in preventing and treating CHF. A previous study has reported that *Panax ginseng* C. A. Mey. (Renshen), *Astragalus membranaceus* (Fisch.) Bunge. (Huangqi), and *Salvia miltiorrhiza* Bge. (Danshen) are the main contributors to the blood-entry components of YXST[46]. Ginsenoside Rb1 inhibits calcium ion channel activity in the cell membrane and enhances myocardial contractility. *Astragalus membranaceus* (Fisch.) Bunge. (Huangqi) is mainly composed of saponins and flavonoids. Total *Astragalus* saponin can increase coronary blood flow and relieve myocardial ischemia. *Salvia* officinalis is mainly composed of *Salvia* quinone/ketones and salvianolic acid components, which can reduce blood viscosity and enhance blood fluidity[46]. Gao[47] discovered that YXST could protect the myocardium at the metabolic level, mainly by regulating energy metabolism and the inflammatory immune response, thus exerting an anti-HF effect using ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry coupled with principal component analysis. Owing to the limited number of mechanistic studies related to YXST, further research is required to elucidate the specific mechanisms of action of the drug.

The study has some limitations: (1) The study only included a sample size of 1845, which may result in a lack of precision in the study's findings due to insufficient statistical validity; (2) the included studies may have potential selectivity and implementation biases, which may have reduced the confidence in the meta-analysis; (3) the duration of each included study ranged from 1 to 48 wk, and the lack of long-term follow-up results did not confirm the long-term effects of YXST on CHF; and (4) YXST is a common proprietary Chinese medicine that is currently being used mainly in China, leading to the fact that the experimental centers of the published clinical trials were all in China. This meta-analysis predominantly explains the role of YXST in people of Chinese ethnicity, and how the drug works in other ethnicities is not clear. In the future, more multicenter, double-blind, stratified RCTs are needed to further investigate the effects of factors such as ethnicity and treatment duration on the clinical efficacy of YXST and to provide high-quality evidence-based confirmation of the clinical significance of the drug.

CONCLUSION

YXST effectively improves clinical symptoms and cardiac function in patients with CHF while maintaining a favorable safety profile, suggesting its potential as a therapeutic strategy for CHF.

FOOTNOTES

Co-first authors: Sheng-Hua Lu and Yun-Feng Yu.

Author contributions: Lu SH acquisition of data, analysis and interpretation of data, drafting the article, final approval; Yu YF acquisition of data, analysis and interpretation of data, drafting the article, final approval; Dai SS interpretation of data, revising the article, final approval; Hu YQ interpretation of data, revising the article, final approval; Liu JH conception and design of the study, critical revision, final approval. All authors seriously revised and approved the final manuscript.

Supported by Hunan Provincial Chinese Medicine Research Program Commissioned Key Projects, No. D2023005.

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: Sheng-Hua Lu 0009-0004-8101-5841; Yun-Feng Yu 0000-0002-7309-5608; Jian-He Liu 0000-0003-2473-858X.

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

REFERENCES

1 **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; Authors/ Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**: 891-975 [PMID: 27207191 DOI: 10.1002/ejhf.592]

2 **Writing Committee Members**; ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *J Card Fail* 2022; **28**: e1-e167 [PMID: 35378257 DOI: 10.1016/j.cardfail.2022.02.010]

3 **Zhang Y**, Gao C, Greene SJ, Greenberg BH, Butler J, Yu J, Zheng Z, Ma G, Wang L, Yang P, Ji X, Xu D, Wang J, Zhang Y, Liu Y, Zhao Y, Qi H, Zhai M, Feng J, Huang Y, Zhou Q, Zhang J. Clinical performance and quality measures for heart failure management in China: the China-Heart Failure registry study. *ESC Heart Fail* 2023; **10**: 342-352 [PMID: 36224725 DOI: 10.1002/ehf2.14184]

4 **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. *Eur Heart J* 2021; **42**: 3599-3726 [PMID: 34447992 DOI: 10.1093/eurheartj/ehab368]

5 **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]

6 **Sandri M**, Viehmann M, Adams V, Rabald K, Mangner N, Höllriegel R, Lurz P, Erbs S, Linke A, Kirsch K, Möbius-Winkler S, Thiery J, Teupser D, Hambrecht R, Schuler G, Gielen S. Chronic heart failure and aging - effects of exercise training on endothelial function and mechanisms of endothelial regeneration: Results from the Leipzig Exercise Intervention in Chronic heart failure and Aging (LEICA) study. *Eur J Prev Cardiol* 2016; **23**: 349-358 [PMID: 26015451 DOI: 10.1177/2047487315588391]

7 **Wang H**, Liu YJ, Yang JF. [Epidemiology of heart failure]. *Linchuang Xinxueguanbing Zazhi.* 2023; **39**: 243-247 [DOI: 10.13201/j.issn.1001-1439.2023.04.001]

8 **Emmons-Bell S**, Johnson C, Roth G. Prevalence, incidence and survival of heart failure: a systematic review. *Heart* 2022; **108**: 1351-1360

[PMID: 35042750 DOI: 10.1136/heartjnl-2021-320131]

9 **Virani SS**, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation* 2020; **141**: e139-e596 [PMID: 31992061 DOI: 10.1161/CIR.0000000000000757]

10 **Shu H**, Hang W, Peng Y, Nie J, Wu L, Zhang W, Wang DW, Zhou N. Trimetazidine Attenuates Heart Failure by Improving Myocardial Metabolism *via* AMPK. *Front Pharmacol* 2021; **12**: 707399 [PMID: 34603021 DOI: 10.3389/fphar.2021.707399]

11 **Zhu MJ**. [Evaluation and consideration of the curative effects of traditional Chinese medicine in the treatment of chronic heart failure]. *Beijing Zhongyiyao Daxue Xuebao* 2023; **46**: 902-907

12 **Gao F**, Fu Q, Bao SY, Ao WL. [Research progress of TCM in treatment of CHF]. *Zhongyiyao Xinxi* 2022; **39**: 85-89 [DOI: 10.19656/j.cnki.1002-2406.20220516]

13 **Zang YB**, Wan JJ, Zhang Z, Huang S, Liu X, Zhang W. An updated role of astragaloside IV in heart failure. *Biomed Pharmacother* 2020; **126**: 110012 [PMID: 32213428 DOI: 10.1016/j.biopha.2020.110012]

14 **Liu HX**. [Interpretation of Consensus of Experts on Clinical Application of Yangxinshi Tablets in Treatment of Coronary Heart Disease]. *Shijie Zhongyiyao* 2020; **15**: 637-642 [DOI: 10.3969/j.issn.1673-7202.2020.04.034]

15 **Guo ZG**, Yu CX, Song XQ. [Effect of Yangxinshi Tablets on myocardial apoptosis in rats with heart failure]. *Zhongguo Laonianxue Zazhi* 2018; **38**: 3032-3035 [DOI: 10.3969/j.issn.1005-9202.2018.12.082]

16 **Wang H**, Cao YJ, Zhao ZY. [Progress of Yangxin tablet in the treatment of cardiovascular diseases and its mechanism of action]. *Zhongxiyi Jiehe Xinnaoxueguanbing Zazhi* 2023; **21**: 3188-3192 [DOI: 10.12102/j.issn.1672-1349.2023.17.016]

17 **Chen YR**, Lu SH, Wang Z, Cheng Y. [Based on network pharmacology and molecular docking to investigate the mechanism of Yangxinshi Tablet against myocardial fibrosis]. *Zhongxiyi Jiehe Xinnaoxueguanbing Zazhi* 2023; **21**: 1195-1201 [DOI: 10.12102/j.issn.1672-1349.2023.07.006]

18 **McDonagh TA**, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, 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, Skibelund AK; ESC Scientific Document Group. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023; **44**: 3627-3639 [PMID: 37622666 DOI: 10.1093/eurheartj/ehad195]

19 **Bai CY**, Li R. [Effect of Yangxin Tablet as an adjuvant therapy on patients with coronary heart disease and heart failure]. *Sichuan Shenglikexue Zazhi* 2023; **45**: 423-425

20 **Bai JB**. [Evaluation of the clinical effect of Yangxinshi tablet in the intervention of heart failure caused by coronary heart disease]. *Yixue Shiliao Yu Jiankang* 2019; **14**: 128

21 **Cheng F**, Wei YJ, Xu HJ, Gao Z, Chen JG, Zhou M. [Clinical study on Yangxinshi Tablets combined with levocarnitine in treatment of diastolic heart failure]. *Xiandai Yaowu Yu Linchuang* 2019; **34**: 1007-1011 [DOI: 10.7501/j.issn.1674-5515.2019.04.026]

22 **Chen QY**. [Clinical study of Yangxinshi tablet treating chronic heart failure with Qi deficiency and blood stasis syndrome]. M.Sc. Thesis, Anhui University of Chinese Medicine, 2019; 1-47

23 **Fan RY**, Li WG, Liu YM, Liu P, Wang H. [Effect of Yangxinshi Tablet on cardiac function, neutrophil lymphocyte ratio and bilirubin in patients with chronic heart dysfunction]. *Jiefangjun Yixue Zazhi* 2020; **38**: 42-45 [DOI: 10.13704/j.cnki.jyyx.2020.07.015]

24 **Gao YN**, Zhang J. [Clinical observation of Yangxinshi Tablet in the treatment of type 2 diabetes mellitus complicated with chronic heart failure]. *Shijie Zhongyiyao* 2021; **16**: 961-964 [DOI: 10.3969/j.issn.1673-7202.2021.06.020]

25 **Gu JL**, Ye K, Wang XL, Zhou H, Xue JG. [Clinical observation on Yangxinshi Tablets on heart failure of coronary heart disease]. *Zhongguo zhongyi jizhneg* 2016; **25**: 868-871 [DOI: 10.3969/j.issn.1004-745X.2016.05.035]

26 **Fu P**, Huang ZD, Xie D. [Observation on curative effect of Yangxinshi Tablet treating heart failure caused by dilated cardiomyopathy]. *Shijie Zhongyiyao* 2014; **9**: 577-578 [DOI: 10.3969/j.issn.1673-7202.2014.05.01]

27 **Huang M**, Li HH, Zhang XN. [Clinical observation of Yangxinshi Tablet for treatment of diastolic heart failure]. *Zhongxiyi Jiehe Xinnaoxueguanbing Zazhi* 2009; **7**: 135-136 [DOI: 10.3969/j.issn.1672-1349.2009.02.004]

28 **Li J**, Zhou XL. [Clinical study on Yangxinshi Tablets combined with bisoprolol in the treatment of coronary heart disease and heart failure]. *Shijie Zhongyiyao* 2019; **14**: 3278-3281 [DOI: 10.3969/j.issn.1673-7202.2019.12.039]

29 **Li Q**. [Effect of Yangxinshi Tablets combined with Trimetazidine Hydrochloride Tablets on vascular endothelial function in coronary heart disease complicated with chronic heart failure]. *Hebei Yiexue Zazhi* 2017; **39**: 1222-1224 [DOI: 10.3969/j.]

30 **Liu XM**. [Intervention studies of Yangxinshi on exercise intensity and quality of life on heart failure with preserved ejection fraction]. M.Sc. Thesis, Shandong University of Chinese Medicine, 2022; 1-46

31 **Qian GQ**, Wei FP. [Observation of Yangxinshi Tablet treating 56 cases of heart failure with dilated cardiomyopathy]. *Zhejiang Zhongyi Zazhi* 2012; **47**: 850-851 [DOI: 10.3969/j.issn.0411-8421.2012.11.051]

32 **Qu JW**. [The effect of Yangxinshi on patients with chronic heart failure]. *Xibu Yixue* 2008; **20**: 989-990 [DOI: 10.3969/j.issn.1672-3511.2008.05.039]

33 **Wang HL**, Cheng XM, Guo JX, Guo YM. [Yangxinshi Tablet combined with western medicine to treat 60 cases of refractory heart failure]. *Zhongguo Meirong Yixue Zazhi* 2011; **20**: 502 [DOI: 10.3969/j.issn.1008-6455.]

34 **Yuan H**. [Clinical observation of Yangxinshi Tablet in adjuvant treatment of 75 cases of diastolic heart failure]. *Haixia Yaoxue Zazhi* 2012; **24**: 145-146 [DOI: 10.3969/j.issn.1006-3765.2012.02.075]

35 **Sun ML**, Wang P, Qiu TG, Liu WT. [Clinical observation of Yangxinshi Tablets in treatment of heart function in chronic heart failure with Qi deficiency and blood stasis syndrome]. *Shijie Zhongyiyao* 2016; **11**: 1507-1509 [DOI: 10.3969/j.issn.1673-7202.2016.08.031]

36 **Zhang H**, Niu TF. [Clinical observation of Yangxinshi Tablet treating 34 cases of diastolic heart failure of Qi deficiency and blood stasis syndrome]. *Zhongxiyi Jiehe Xinnaoxueguanbing Zazhi* 2017; **24**: 3148-3150 [DOI: 10.3969/j.issn.1672-1349.2017.24.020]

37 **Zhang JL**. [Effects of Yangxinshi Tablet on cardiac function and plasma levels of brain natriuretic peptide of patients with chronic heart disease]. *Shijie Zhongyiyao* 2018; **13**: 2148-2150 [DOI: 10.3969/j.issn.1673-7202.2018.09.012]

38 **Zhang K**. Effect of loading treatment with Yangxin's tablets on cardiac function and quality of life in patients with HFrEF (qi deficiency and blood stasis type). M.Sc. Thesis, Nanjing University of Chinese Medicine, 2022; 1-35

39 **Tomasoni D**, Adamo M, Lombardi CM, Metra M. Highlights in heart failure. *ESC Heart Fail* 2019; **6**: 1105-1127 [PMID: 31997538 DOI: 10.1002/ehf2.12555]

40 **Chen J**, Chen S, Zhang B, Liu J. SIRT3 as a potential therapeutic target for heart failure. *Pharmacol Res* 2021; **165**: 105432 [PMID: 33508434 DOI: 10.1016/j.phrs.2021.105432]

41 **Frantz S**, Hundertmark MJ, Schulz-Menger J, Bengel FM, Bauersachs J. Left ventricular remodelling post-myocardial infarction: pathophysiology, imaging, and novel therapies. *Eur Heart J* 2022; **43**: 2549-2561 [PMID: 35511857 DOI: 10.1093/eurheartj/ehac223]

42 **Lloji A**, Sreenivasan J, Novograd J, Aronow WS, Pan S, Lanier GM. Heart failure with preserved ejection fraction: key stumbling blocks for experimental drugs in clinical trials. *Expert Opin Investig Drugs* 2022; **31**: 463-474 [PMID: 35443138 DOI: 10.1080/13543784.2022.2069009]

43 **Dunlay SM**, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2017; **14**: 591-602 [PMID: 28492288 DOI: 10.1038/nrcardio.2017.65]

44 **Solomon SD**, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP; PARAGON-HF Investigators and Committees. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med* 2019; **381**: 1609-1620 [PMID: 31475794 DOI: 10.1056/NEJMoa1908655]

45 **Meier ML**, Pierce KN. New therapies for the treatment of heart failure with preserved ejection fraction. *Am J Health Syst Pharm* 2022; **79**: 1424-1430 [PMID: 35524990 DOI: 10.1093/ajhp/zxac129]

46 **Liu H**, Li J, Guo CJ, Meng PP, Li Y, Yu HC. [Study and clinical efficacy of Yangxinshi Tablets in treatment of cardiovascular diseases]. *Zhongguo Xunzheng Xinxueguan Yixue Zazhi* 2022; **5**: 638-640 [DOI: 10.3969/j.issn.1674-4055.2022.05.33]

47 **Gao Y**. [Study on the anti-heart failure mechanism of Yangxinshi Tablet based on omics and network pharmacology]. MD Thesis, Second Military Medical University, 2017; 1-137

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2231-2236

DOI: 10.12998/wjcc.v12.i13.2231

ISSN 2307-8960 (online)

CASE REPORT

Intra-thyroid esophageal duplication cyst: A case report

Hong-Guo Lin, Ming Liu, Xue-Yang Huang, Da-Sheng Liu

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: Sharma D, India

Received: January 28, 2024
Revised: March 9, 2024
Accepted: March 29, 2024
Published online: May 6, 2024

Hong-Guo Lin, Ming Liu, Xue-Yang Huang, Da-Sheng Liu, Department of Vascular Thyroid Surgery, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510006, Guangdong Province, China

Corresponding author: Da-Sheng Liu, MD, Doctor, Department of Vascular Thyroid Surgery, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, No. 55 Neihuan West Road, Panyu District, Guangzhou 510006, Guangdong Province, China.
804232372@qq.com

Abstract

BACKGROUND

Esophageal cysts are relatively rare in clinical practice, with most of the literature comprising case reports. Esophageal cysts protruding into the thyroid gland are easily misdiagnosed as thyroid tumors. No such cases have been reported so far.

CASE SUMMARY

This article reports the case of a 31-year-old adult male diagnosed with thyroid nodules before admission. The patient underwent left thyroidectomy and isthmusectomy. During the surgery, esophageal cysts were identified in the esophageal muscle and thyroid glands. The pathology results confirmed a nodular goiter combined with esophageal cysts. Postoperatively, the patient developed a neck infection and underwent another operation and broad-spectrum antibiotic treatment for recovery.

CONCLUSION

We report the first clinical case of an esophageal cyst located within the thyroid gland that was successfully treated surgically. Esophageal cyst located within the thyroid gland cause difficulties in diagnosis. In the present study, the contents of the esophageal cysts were calcified foci, and a small amount of fluid mixture, which were easily misdiagnosed as thyroid nodules and misled the surgical methods.

Key Words: Esophageal cysts; Thyroid; Diagnosed; Surgery; Case report

Core Tip: We reported on a very special patient. The diagnosis of a nodular goiter combined with esophageal cysts was made by his symptoms, physical examination, laboratory tests and intraoperative frozen pathological examination. Esophageal cysts embedded in the thyroid gland are rare in clinical practice and can cause difficulties in diagnosis. The patient was successfully treated surgically.

Citation: Lin HG, Liu M, Huang XY, Liu DS. Intra-thyroid esophageal duplication cyst: A case report. *World J Clin Cases* 2024; 12(13): 2231-2236
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2231.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2231

INTRODUCTION

Esophageal cysts are defined as congenital developmental abnormalities of the esophagus. Esophageal cysts located within the thyroid gland are extremely rarely, and no relevant medical literature of such cases have been reported. This article reports the case of a 31-year-old adult male diagnosed with thyroid nodules before admission. The patient underwent left thyroidectomy and isthmusectomy. During the surgery, esophageal cysts were identified in the esophageal muscle and thyroid glands. The pathology results confirmed a nodular goiter combined with esophageal cysts. Postoperatively, the patient developed a neck infection and underwent another operation and broad-spectrum antibiotic treatment for recovery.

CASE PRESENTATION

Chief complaints

The patient underwent thyroid ultrasound which revealed mixed nodule in the isthmus of the thyroid for 5 years.

History of present illness

A 31-year-old man was admitted to the local community hospital. Thyroid color Doppler ultrasound revealed a mixed nodule in the isthmus of the thyroid gland: No abnormalities were found in the right lobe of the thyroid gland (American College of Radiology Thyroid Imaging Reporting and Data System, ACR TR 3), but a solid nodule was found in the left lobe of the thyroid gland (ACR TR 5). The physical examination and laboratory test results were normal, and the patient had no history of swallowing obstruction.

History of past illness

Previously in good health.

Personal and family history

Deny bad personal history. Deny family medical history.

Physical examination

Physical examination was unremarkable, and sensation of swallowing obstruction was denied.

Laboratory examinations

The laboratory examination showed that all blood indicators were basically normal.

Imaging examinations

After admission, thyroid color Doppler ultrasound was performed again (Figure 1), and a nodule was located in the middle of the left lobe of the thyroid gland, classified as Thyroid Imaging Reporting and Data System (TI-RADS) 4A. The possibility of nodular goiter combined with calcification was not excluded and fine-needle aspiration (FNA) biopsy was recommended. The other thyroid nodules were classified as TI-RADS 3, considering the nodular goiter.

FINAL DIAGNOSIS

Combined with the paraffin pathology results after the first operation, the final diagnoses was esophageal cyst was embedded in the thyroid gland.

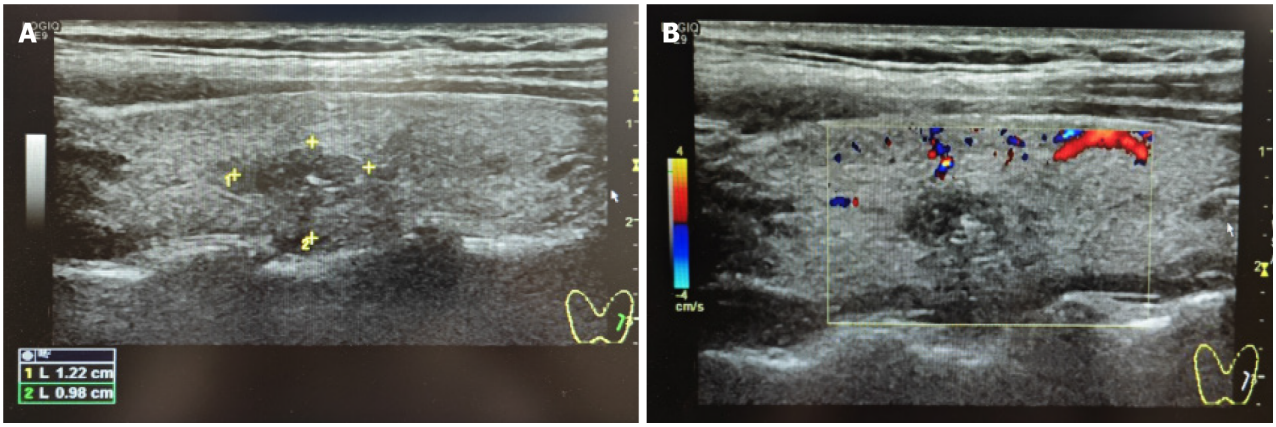

Figure 1 Ultrasound examination showing a hypoechoic nodule in the left thyroid gland. A: Nodule area; B: Nodule blood supply.

TREATMENT

Left thyroid lobectomy and isthmusectomy were performed under general anesthesia with tracheal intubation. Intraoperative frozen pathological examination showed that the nodule in the isthmus of the thyroid gland was consistent with nodular goiter. Furthermore, thyroid tissue was found in the left lobe of the thyroid gland, and a small focus of lymphoepithelial cysts was observed.

On postoperative day 3, the patient developed redness, swelling, and pain at the surgical site, accompanied by foul-smelling liquid discharge. Body temperature was 38.9 ℃ and routine blood examination showed that the white blood cell count was 10.78 × 10^9/L, neutrophil percentage was 77.4%, erythrocyte sedimentation rate was 54 mm/h, C-reactive protein was 59.20 mg/L, and calcitonin was 0.06 ng/L. Thyroid computed tomography (CT) revealed multiple scattered free gases in the neck, soft tissue swelling and exudation, and a small local effusion (Figure 2), while esophageal radiography showed no evident fistula signs (Figure 3). Emergency debridement for neck infections was performed in the operating room. A large amount of purulent fluid with a foul smell was observed in the surgical area. The recurrent laryngeal nerve was swollen, and a fistula with a diameter of approximately 4 mm × 5 mm was observed in the muscular layer of the anterior wall of the esophagus (Figure 4). Combined with the preoperative color Doppler ultrasound and paraffin pathology results after the first operation (Figure 5), it was considered that an esophageal cyst was embedded in the thyroid gland, which caused an esophageal fistula after thyroidectomy. The muscular layer of the fistula was sutured using a 3-0 Vicryl absorbable thread, and a drainage tube was left in place at the surgical site after repeated flushing with saline solution. After surgery, gastric tube feeding was performed, and food intake was prohibited. On day 11 after surgery, the gastric tube was removed, and the patient was initiated on a full liquid diet.

OUTCOME AND FOLLOW-UP

One month after surgery, the patient resumed a normal diet and did not experience any discomfort during follow-up for 2 years.

DISCUSSION

Esophageal cysts are rare in clinical practice, clear data on the true incidence of esophageal cysts are not available[1]. Congenital esophageal cysts can be classified as either duplicate, bronchogenic, gastric, or inclusion body cysts[2]. Esophageal cysts are typically asymptomatic, and 80% of cases are diagnosed in childhood. Cysts that continue to grow can cause esophageal obstruction[3]. Most esophageal cysts are located in the middle and lower parts of the esophagus, and approximately 10% of patients have esophageal cysts that communicate with the esophagus and grow along or attach to it. Surgical resection or endoscopy is the primary treatment for esophageal cysts[4].

Esophageal cysts are defined as congenital malformations of the foregut caused by the abnormal splitting of the posterior part of the embryonic foregut at 3-4 wk of gestation. Their origins may be either esophageal, bronchial, neural, gastrointestinal, and pericardial. Esophageal and bronchial cysts originate from the foregut and contain a ciliated epithelium, making them difficult to distinguish histologically.

Pathologically, the Palmer standard is usually used, which includes: (1) Attachment to the esophageal wall; (2) Presence of gastrointestinal epithelium; and (3) Presence of two layers of the muscularis propria[5].

Esophageal cysts are most commonly found in the mediastinum, and most patients have no clinical symptoms, although some patients may be diagnosed with nonspecific gastrointestinal symptoms during endoscopic examinations [6]. Treatment of asymptomatic patients with esophageal cysts remains controversial. Currently, there are no clear clinical guidelines. Close observation can be performed for small cysts without clinical symptoms; however, complete surgical

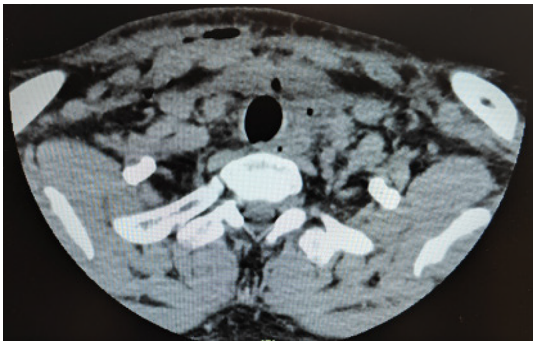

Figure 2 Thyroid computed tomography image showing multiple scattered free gases in the subcutaneous tissue on the right side of the lower neck and around the thyroid gland.

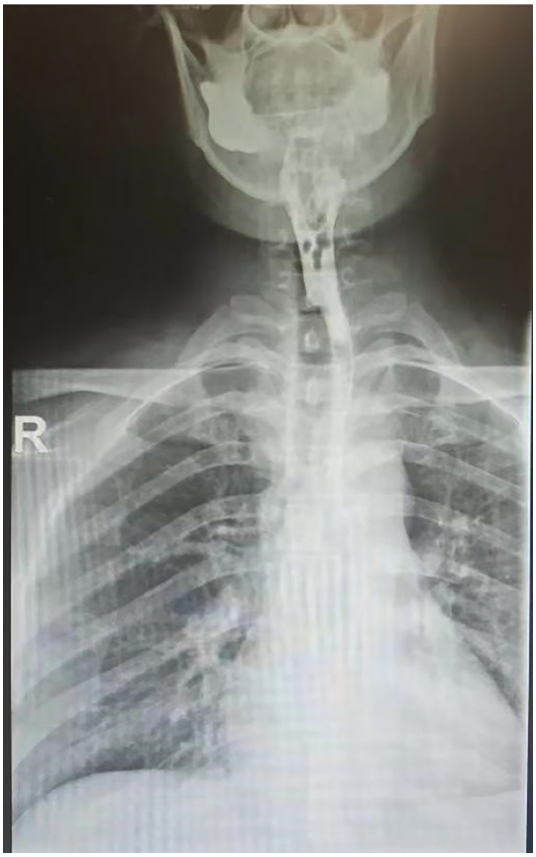

Figure 3 Esophageal contrast imaging showing no evident signs of fistula.

resection is recommended when the cyst enlarges and compresses the adjacent organs, causing symptoms[7]. Some patients may experience acute symptoms, such as ulcers, bleeding, and infection. This may be due to the presence of gastrointestinal epithelial cells in the cyst[8].

In the present case, the esophageal cyst presented as a thyroid nodule. After surgical resection, pathological results confirmed the presence of an esophageal cyst. The cyst was closely adhered to the esophageal muscularis propria, but was not completely connected to the esophageal lumen. During the initial surgery, the ruptured esophageal muscularis propria was not sutured or repaired that resulted in a postoperative infection, which eventually required a second surgery.

Most esophageal cysts are discovered incidentally. CT and magnetic resonance imaging (MRI) can better show the morphology and relationship with the surrounding tissues. Endoscopic ultrasound (EUS) can further show whether a mass is located in the esophageal muscle layer. EUS-guided FNA (EUS-FNA) can also be used to diagnose tumors qualitatively. However, the complications of EUS-FNA in cystic masses, including infection, bleeding, and mediastinitis, are common, with the incidence reaching as high as 14%. As such, EUS-FNA should not be routinely used for the biopsy of esophageal masses without mucosal abnormalities[9]. The differences in the nature of the cyst contents can also cause difficulties in diagnosis. In the present study, the contents of the esophageal cysts were calcified foci, and a small amount of fluid mixture, which were easily misdiagnosed as thyroid nodules and misled the surgical methods.

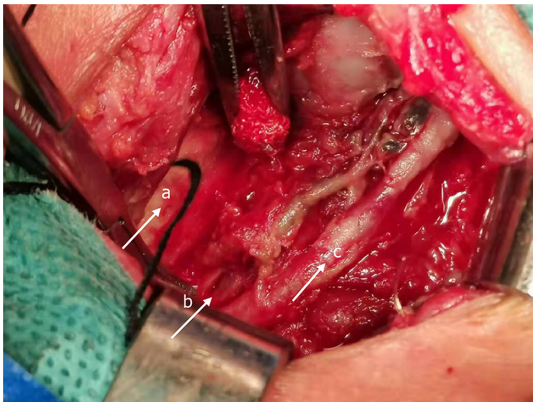

Figure 4 Intraoperative exploration showing a fistula with a diameter of about 0.5 cm visible in the muscular layer of the anterior wall of the esophagus. a: Trachea; b: Esophageal seromuscular layer rupture; c: Recurrent laryngeal nerve.

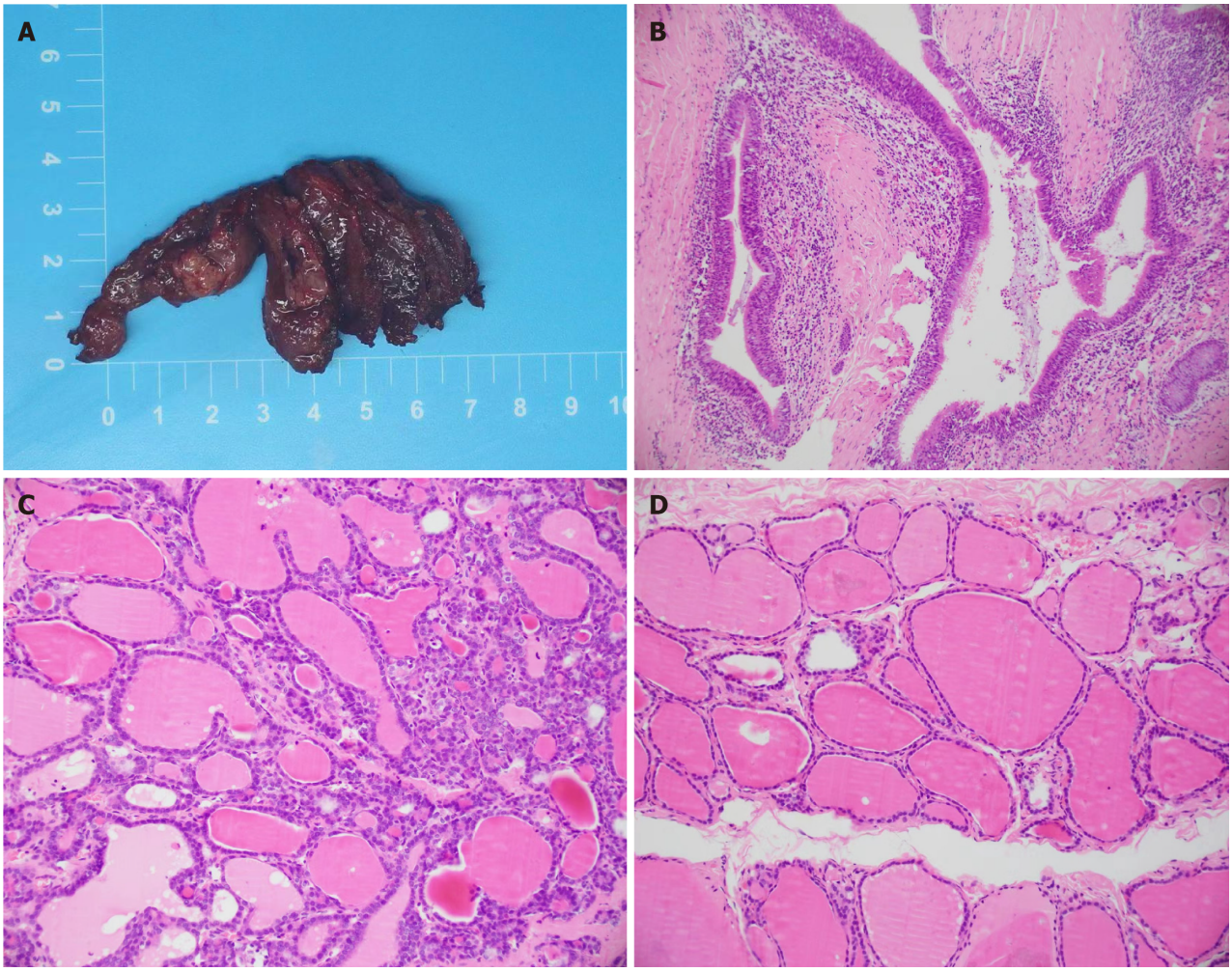

Figure 5 Histopathological analysis of the resected specimen. A: The resected specimen: Cyst in the left thyroid gland; B-D: Haematoxylin and eosin staining, the cyst wall is ciliated columnar epithelial (× 100).

CONCLUSION

Esophageal cysts most commonly found in the mediastinum, and most patients have no clinical symptoms.Most esophageal cysts are discovered incidentally. CT and MRI can better show the morphology and relationship with the surrounding tissues.Esophageal cysts embedded in the thyroid gland are rare in clinical practice and can cause difficulties in diagnosis.Herein, we report the first clinical case of an esophageal cyst located within the thyroid gland that was successfully treated surgically.

ACKNOWLEDGEMENTS

We thank the patient for his participation in this study. We have obtained the patient's support and informed consent form.

FOOTNOTES

Author contributions: Lin HG reviewed the literature and wrote the manuscript; Liu M and Huang XY perfected the data collection; Liu DS was the main provider of this case and revised the manuscript and directed the writing of the article. All authors gave final approval for the version to be submitted.

Supported by The Research Project of Guangzhou Science and Technology Plan, No. 2024A03J0042.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

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: Da-Sheng Liu 0009000526976296.

S-Editor: Zheng XM
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Wootton-Gorges SL**, Eckel GM, Poulos ND, Kappler S, Milstein JM. Duplication of the cervical esophagus: a case report and review of the literature. *Pediatr Radiol* 2002; **32**: 533-535 [PMID: 12107589 DOI: 10.1007/s00247-002-0693-8]
2 **Martin JT**, Cibull ML, Zwischenberger JB, Reda HK. Infection of an esophageal cyst following endoscopic fine-needle aspiration. *Int J Surg Case Rep* 2011; **2**: 144-146 [PMID: 22096709 DOI: 10.1016/j.ijscr.2011.03.005]
3 **Eichmann D**, Engler S, Oldigs HD, Schroeder H, Partsch CJ. Radiological case of the month. Denouement and discussion: congenital esophageal duplication cyst as a rare cause of neonatal progressive stridor. *Arch Pediatr Adolesc Med* 2001; **155**: 1067-1068 [PMID: 11529812 DOI: 10.1001/archpedi.155.9.1067]
4 **Nelms CD**, White R, Matthews BD, Ballinger WE Jr, Sing RF, Heniford BT. Thoracoabdominal esophageal duplication cyst. *J Am Coll Surg* 2002; **194**: 674-675 [PMID: 12022610 DOI: 10.1016/s1072-7515(02)01164-x]
5 **Markert DJ**, Grumbach K, Haney PJ. Thoracoabdominal duplication cyst: prenatal and postnatal imaging. *J Ultrasound Med* 1996; **15**: 333-336 [PMID: 8683671 DOI: 10.7863/jum.1996.15.4.333]
6 **Wiechowska-Kozłowska A**, Wunsch E, Majewski M, Milkiewicz P. Esophageal duplication cysts: endosonographic findings in asymptomatic patients. *World J Gastroenterol* 2012; **18**: 1270-1272 [PMID: 22468092 DOI: 10.3748/wjg.v18.i11.1270]
7 **Lee SY**, Kim HY, Kim SH, Jung SE, Park KW. Thoracoscopic resection of a cervical esophageal duplication cyst in a 3-month-old infant: a case report. *J Pediatr Surg* 2013; **48**: 873-875 [PMID: 23583149 DOI: 10.1016/j.jpedsurg.2012.12.046]
8 **Lee HS**, Jeon HJ, Song CW, Lee SW, Choi JH, Kim CD, Ryu HS, Hyun JH, Lee SY, Kim KT. Esophageal duplication cyst complicated with intramural hematoma--case report. *J Korean Med Sci* 1994; **9**: 188-196 [PMID: 7986394 DOI: 10.3346/jkms.1994.9.2.188]
9 **Wiersema MJ**, Vilmann P, Giovannini M, Chang KJ, Wiersema LM. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology* 1997; **112**: 1087-1095 [PMID: 9097990 DOI: 10.1016/s0016-5085(97)70164-1]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2237-2242

DOI: 10.12998/wjcc.v12.i13.2237

ISSN 2307-8960 (online)

CASE REPORT

Magnetic resonance imaging findings of radiation-induced breast angiosarcoma: A case report

Wen-Pei Wu, Chih-Wei Lee

Specialty type: Oncology

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: Singh R, India

Received: November 26, 2023
Peer-review started: November 26, 2023
First decision: February 5, 2024
Revised: February 17, 2024
Accepted: April 3, 2024
Article in press: May 6, 2024
Published online: May 6, 2024

Wen-Pei Wu, Department of Medical Imaging, Changhua Christian Hospital, Changhua 50006, Taiwan

Chih-Wei Lee, Department of Radiology, Changhua Christian Medical Foundation Changhua Christian Hospital, Changhua 50006, Taiwan

Corresponding author: Chih-Wei Lee, MD, Doctor, Department of Radiology, Changhua Christian Medical Foundation Changhua Christian Hospital, No. 135 Nanhsiao Street, Changhua 50006, Taiwan. 133559@cch.org.tw

Abstract

BACKGROUND

Breast conservation surgery (BCS) with adjuvant radiotherapy has become a gold standard in the treatment of early-stage breast cancer, significantly reducing the risk of tumor recurrence. However, this treatment is associated with adverse effects, including the rare but aggressive radiation-induced angiosarcoma (RIAS). Despite its rarity and nonspecific initial presentation, RIAS presents a challenging diagnosis, emphasizing the importance of imaging techniques for early detection and accurate diagnosis.

CASE SUMMARY

We present a case of a 48-year-old post-menopausal woman who developed skin ecchymosis on the right breast seven years after receiving BCS and adjuvant radiotherapy for breast cancer. Initial mammography and ultrasound were inconclusive, showing post-treatment changes but failing to identify the underlying angiosarcoma. Contrast-enhanced breast magnetic resonance imaging (MRI) revealed diffuse skin thickening and nodularity with distinctive enhan-cement kinetics, leading to the diagnosis of RIAS. This case highlights the crucial role of MRI in diagnosing and determining the extent of RIAS, facilitating timely and appropriate surgical intervention.

CONCLUSION

Breast MRI is crucial for detecting RIAS, especially when mammography and ultrasound are inconclusive.

Key Words: Radiation-induced angiosarcoma; Radiotherapy; Breast conserving surgery; Breast cancer; Magnetic resonance imaging; Case report

Core Tip: Radiation-induced angiosarcoma (RIAS) of the breast is extremely rare and aggressive complication of the radiotherapy. The diagnosis is difficult clinically, radiologically and even pathologically. Mammography and ultrasound findings of RIAS are nonspecific and may be occult on the initial conventional breast imaging. Breast magnetic resonance imaging can provide better morphologic characterization and extent of disease, which is critical in surgical planning and preventing delays in diagnosis.

Citation: Wu WP, Lee CW. Magnetic resonance imaging findings of radiation-induced breast angiosarcoma: A case report. *World J Clin Cases* 2024; 12(13): 2237-2242
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2237.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2237

INTRODUCTION

Breast conservation surgery (BCS) with adjuvant radiotherapy is becoming the gold standard treatment for patients with early breast cancer (stage I and II) over the decades[1-3]. The use of radiotherapy reduces the chance of tumor recurrence and subsequent morbidity and mortality[4,5]. However, the adverse cutaneous effects of radiotherapy include early and late reactions, including erythema, hyperpigmentation, telangiectasia, chronic radiation dermatitis and radiation-induced fibrosis[6]. However, radiotherapy has been associated with development of secondary soft-tissue sarcomas, with angiosarcoma emerging as the most common subtype, so called radiation-induced angiosarcoma (RIAS)[7-9]. RIAS is a rare and aggressive complication of radiation therapy. In patients undergoing BCS and adjuvant radiotherapy, the estimated incidence of RIAS is 0.05%–0.3%[10].

Mammography and ultrasound are reported to show mostly post-treatment changes, whereas contrast-enhanced breast magnetic resonance imaging (MRI) has been reported to be more sensitive in detecting skin enhancement of RIAS.

In this case report, we present the clinical course and MRI findings in a patient with RIAS presenting 7 years after treatment of breast cancer.

CASE PRESENTATION

Chief complaints

A 48-year-old post-menopausal woman presented with skin ecchymosis on her right breast, which had developed several months earlier.

History of present illness

The patient noticed a non-painful skin ecchymosis around the previous surgical scar on her right breast, which had been enlarging over the past several months (Figure 1).

History of past illness

Seven years ago, the patient underwent BCS for breast cancer on the right breast, followed by adjuvant radiotherapy. The pathology of the tumor showed a 0.6 cm dimension, classified as ypT1bN0M0. Axillary lymph node dissection was performed with no tumor found in the lymph nodes. The patient received a total radiotherapy dose of 60 Gy over 30 fractions and was on Tamoxifen 20 mg daily for 5 years. Follow-up examinations showed no clinical evidence of recurrent tumor or upper-extremity lymphedema.

Personal and family history

The patient had no relevant personal or family history of breast cancer or other genetic disorders.

Physical examination

Physical examination revealed a non-painful skin ecchymosis around the surgical scar on the right breast.

Laboratory examinations

The patient had no specific laboratory examinations in relation to the diagnosis of the condition.

Imaging examinations

Mammography (Figure 2A) and ultrasound (Figure 2B) showed negative results for recurrent breast carcinoma but indicated post-operative changes such as skin thickening. Despite these findings, the clinician suspected the condition

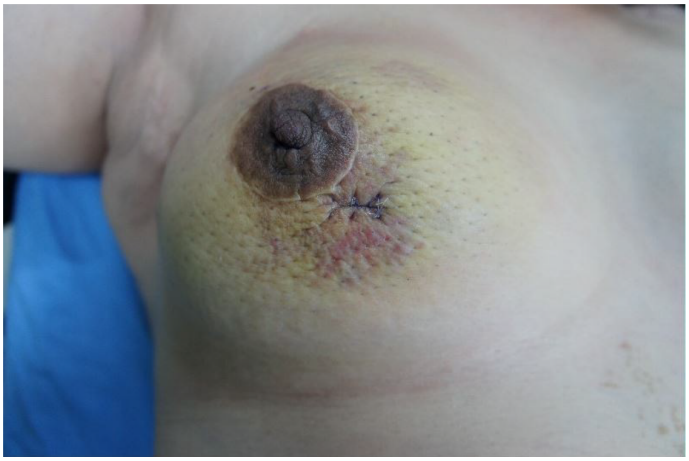

Figure 1 A skin ecchymotic plaque around the surgical scar on the right breast.

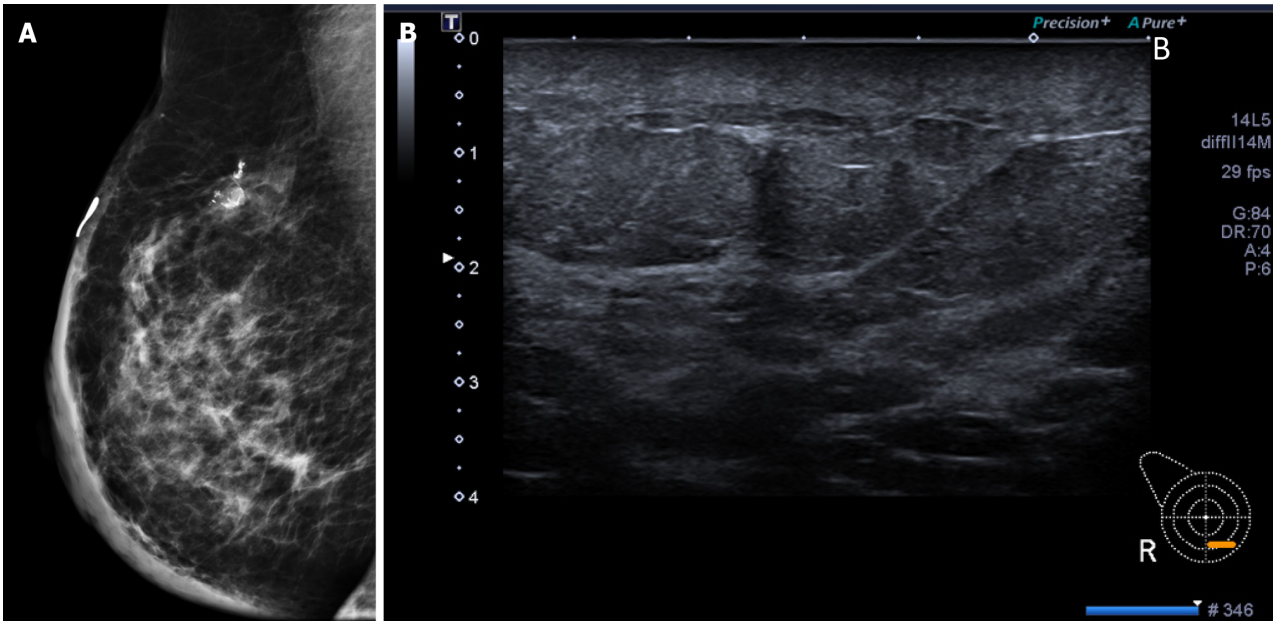

Figure 2 Mammography and ultrasound findings. A: The mammography (medio-lateral oblique view) showed dystrophic calcifications in the upper hemisphere and diffuse skin thickening, misdiagnosed as post-operative changes initially; B: The B-mode ultrasound showed non-specific findings except skin thickenings.

could be either a breast hematoma or recurrent breast carcinoma. For the problem solving, contrast-enhanced breast MRI (Figure 3) was performed and revealed diffuse skin thickening and nodularity, which showed hyperintensity on T2-weighted images and isointensity on T1-weighted images, with fast arterial enhancement on post-contrast dynamic series. The enhancement kinetics of cutaneous lesion shows rapid wash-in and wash-out (type 3 curve)[11]. No discrete intraparenchymal masses were present. Consequently, a diagnosis of radiation-induced angiosarcoma of breast or local tumor recurrence was made.

FINAL DIAGNOSIS

The final diagnosis was radiation-induced angiosarcoma of the breast, confirmed by excision biopsy findings.

TREATMENT

Given the MRI findings indicative of diffuse involvement of the right breast with angiosarcoma and the natural course of the disease, the patient elected to undergo right simple mastectomy. The timeline of this case report was illustrated as Figure 4.

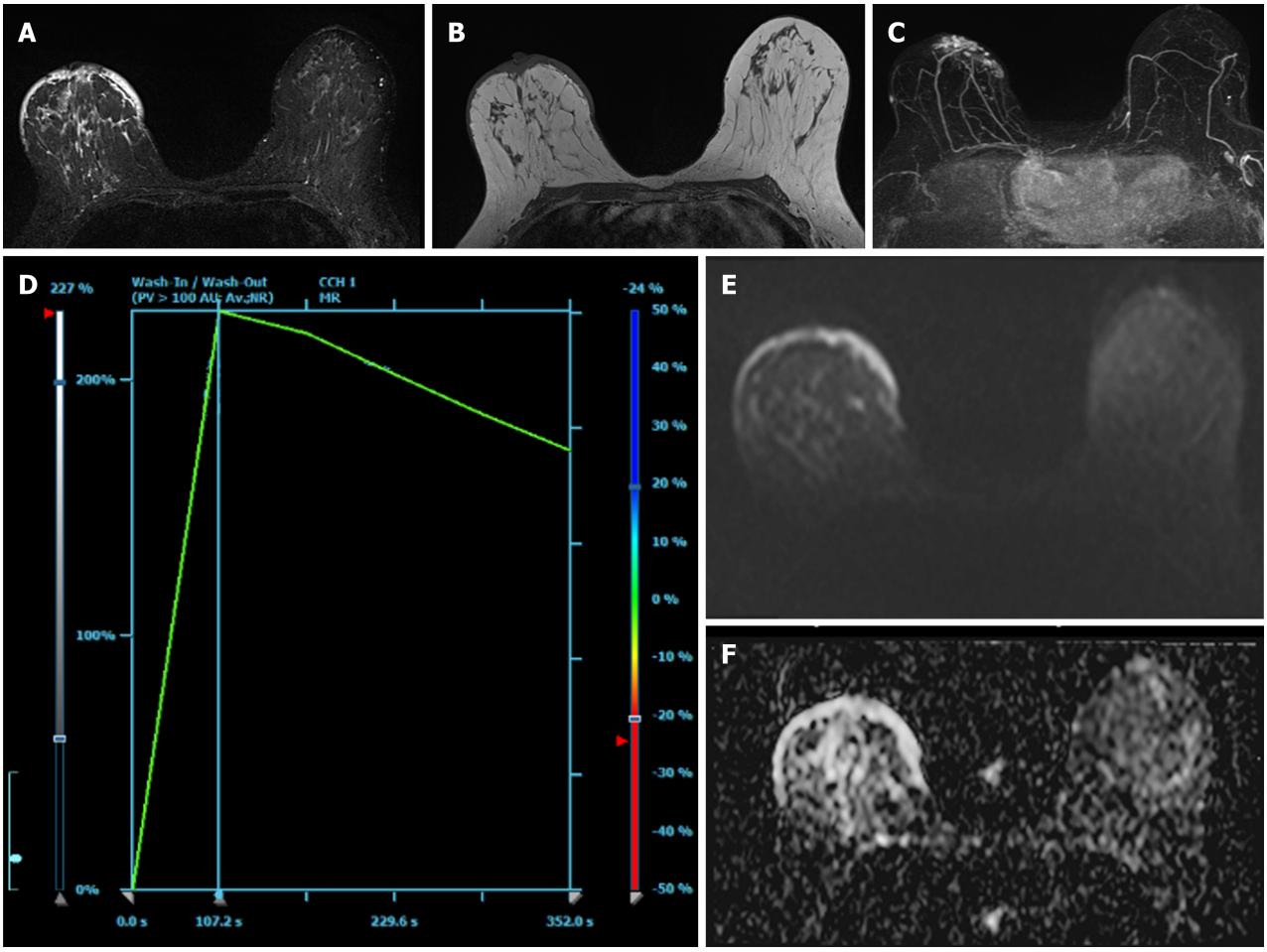

Figure 3 Illustrates the findings from contrast-enhanced breast magnetic resonance imaging, revealing diffuse skin thickening and nodularity. A: Presurgical breast magnetic resonance imaging depicts diffuse skin thickening with hyperintensity on T2-weighted images; B: Diffuse skin thickening is observed on T1-weighted images; C: Diffuse skin thickening enhances on the maximum-intensity projection of postcontrast dynamic images; D: The enhancement kinetics of cutaneous lesions show fast wash-in and wash-out (type 3 curve); E: The axial diffusion-weighted image exhibits hyperintensity; F: The corresponding apparent diffusion coefficient map shows hyperintensity, indicating diffuse vasogenic edematous changes in the skin.

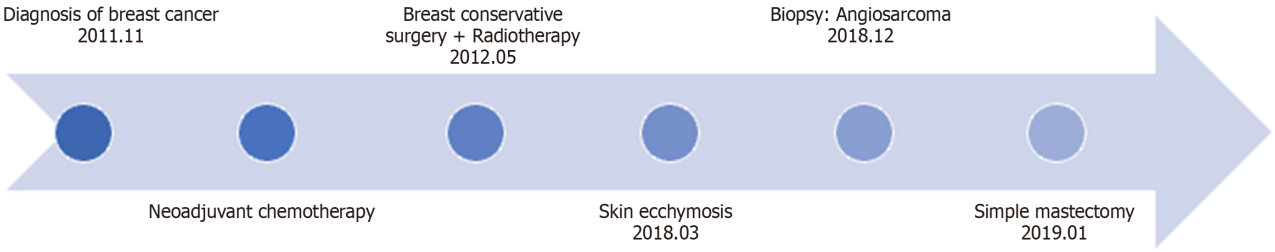

Figure 4 Case report timeline.

OUTCOME AND FOLLOW-UP

The mastectomy procedure was successful, with a gross examination revealing an irregular firm tumor measuring 12.1 cm in the greatest dimension. All margins were tumor-free. There was no mention of distant metastases on subsequent positron emission tomography/computed tomography scans. No recurrence or metastases observed during follow-up.

DISCUSSION

Angiosarcoma of the breast is a rare, highly aggressive malignant tumor of the vascular endothelium by the World Health Organization[12]. It accounts for 0.05% of all reported breast cancers, making them the rarest in that category[7,13,14]. It can be either primary or secondary. Primary angiosarcoma occurs in young women, with a median age of onset of

40 years. Secondary angiosarcoma occurs in older women with a history of BCS and radiotherapy[15], or chronic lymphedema, so called Stewart-Treves angiosarcomas[16].

The clinical differential diagnosis of angiosarcoma may include recurrent breast carcinoma, radiation-related morphea, and malignant melanoma. Results of mammography and ultrasound are not diagnostic for angiosarcoma and are typically negative in early disease. Clinical suspicion is the key to making an early diagnosis. Diagnosis prior to surgery, either by core needle biopsy or fine needle aspiration, is difficult. Chen *et al*[17] reported that a false negative result of core needle biopsy can achieve 37%. In this situation, a full-thickness incisional or excisional biopsy is required to ensure adequate sampling of the lesion.

Because the rarity and seeming harmless presentation, physicians and patients may frequently neglect initial symptoms and clinical findings with consequent diagnostic delay[18-20]. Chikarmane *et al*[21] reported that over half of the patients with RIAS have skin thickenings with post-radiation and lumpectomy changes on mammogram and ultrasound. Only one-quarter of RIAS were observed to involve intraparenchymal regions, presenting as irregular masses. Due to post-radiation alterations such as skin thickening, identifying predominantly cutaneous lesions on mammography and ultrasound may pose particular challenges.

The important role of breast MRI plays in the diagnosis and determination of disease extent. Salminen *et al*[7] reported that the spectrum of RIAS imaging findings was broad, but the majority of patients (63%) had enhancing skin thickening or discrete plaque-like enhancing in the skin. In our case, the cutaneous lesion demonstrated rapid arterial enhancement and washout on the dynamic series. Associated diffuse skin thickenings were hyperintense on T2-weighted images and isointense on T1-weighted images. Sanders *et al*[22] hypothesized in his study that the T2 hyperintense skin thickening with persistent enhancement could be related to post-radiation inflammatory changes, and foci with rapid early arterial enhancement and washout could represent tumor foci. Our case has the same findings on the breast MRI. In the patient with RIAS, contrast-enhanced breast MRI study could have important diagnostic potential to evaluate the true extent of disease.

We present this case to emphasize that, due to the nonspecific findings on mammography or ultrasound, breast MRI offers superior morphological characterization and assessment of disease extent. This is crucial for surgical planning and avoiding diagnostic delays. If an enhancing cutaneous lesion is detected on contrast-enhanced breast MRI at a postoperative and irradiated site, clinicians should consider the possibility of cutaneous angiosarcoma.

CONCLUSION

This case emphasizes the importance of considering radiation-induced angiosarcoma in patients presenting with skin changes post-radiotherapy for breast cancer. MRI plays a critical role in diagnosing and assessing the extent of the disease, especially when other imaging modalities are inconclusive. Early diagnosis and appropriate surgical intervention are crucial for managing this rare but aggressive complication.

FOOTNOTES

Author contributions: Lee CW designed the research; Wu WP performed the research; Wu WP and Lee CW contributed new reagents/analytic tools; Wu WP and Lee CW analyzed the data; Wu WP and Lee CW wrote the paper.

Informed consent statement: Informed consent was obtained from the individual in this case report prior to study.

Conflict-of-interest statement: All authors declare that they have no conflicts of interest relevant to this case report.

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: Taiwan

ORCID number: Wen-Pei Wu 0000-0002-4808-160X; Chih-Wei Lee 0000-0002-9499-4231.

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

REFERENCES

1 **Franceschini G**, Martin Sanchez A, Di Leone A, Magno S, Moschella F, Accetta C, Masetti R. New trends in breast cancer surgery: a therapeutic approach increasingly efficacy and respectful of the patient. *G Chir* 2015; **36**: 145-152 [PMID: 26712068 DOI: 10.11138/gchir/2015.36.4.145]

2 **Fisher B**, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; **347**: 1233-1241 [PMID: 12393820 DOI: 10.1056/NEJMoa022152]

3 **Veronesi U**, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, Aguilar M, Marubini E. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002; **347**: 1227-1232 [PMID: 12393819 DOI: 10.1056/NEJMoa020989]

4 **Overgaard M**, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, Kjaer M, Gadeberg CC, Mouridsen HT, Jensen MB, Zedeler K. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997; **337**: 949-955 [PMID: 9395428 DOI: 10.1056/NEJM199710023371401]

5 **Ragaz J**, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, Wilson KS, Knowling MA, Coppin CM, Paradis M, Coldman AJ, Olivotto IA. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997; **337**: 956-962 [PMID: 9309100 DOI: 10.1056/NEJM199710023371402]

6 **Bray FN**, Simmons BJ, Wolfson AH, Nouri K. Acute and Chronic Cutaneous Reactions to Ionizing Radiation Therapy. *Dermatol Ther (Heidelb)* 2016; **6**: 185-206 [PMID: 27250839 DOI: 10.1007/s13555-016-0120-y]

7 **Salminen SH**, Sampo MM, Böhling TO, Salo J, Tarkkanen M, Blomqvist CP, Hukkinen K. Radiation-associated angiosarcoma of the breast: analysis of diagnostic tools in a registry-based population. *Acta Radiol* 2022; **63**: 22-27 [PMID: 33349000 DOI: 10.1177/0284185120980142]

8 **Billings SD**, McKenney JK, Folpe AL, Hardacre MC, Weiss SW. Cutaneous angiosarcoma following breast-conserving surgery and radiation: an analysis of 27 cases. *Am J Surg Pathol* 2004; **28**: 781-788 [PMID: 15166670 DOI: 10.1097/01.pas.0000126055.33916.0b]

9 **Rubino C**, Shamsaldin A, Lê MG, Labbé M, Guinebretière JM, Chavaudra J, de Vathaire F. Radiation dose and risk of soft tissue and bone sarcoma after breast cancer treatment. *Breast Cancer Res Treat* 2005; **89**: 277-288 [PMID: 15754127 DOI: 10.1007/s10549-004-2472-8]

10 **Cohen-Hallaleh RB**, Smith HG, Smith RC, Stamp GF, Al-Muderis O, Thway K, Miah A, Khabra K, Judson I, Jones R, Benson C, Hayes AJ. Radiation induced angiosarcoma of the breast: outcomes from a retrospective case series. *Clin Sarcoma Res* 2017; **7**: 15 [PMID: 28794852 DOI: 10.1186/s13569-017-0081-7]

11 **Mercado CL**. BI-RADS update. *Radiol Clin North Am* 2014; **52**: 481-487 [PMID: 24792650 DOI: 10.1016/j.rcl.2014.02.008]

12 **Tan PH**, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, Lazar AJ, Morris EA, Sahin A, Salgado R, Sapino A, Sasano H, Schnitt S, Sotiriou C, van Diest P, White VA, Lokuhetty D, Cree IA; WHO Classification of Tumours Editorial Board. The 2019 World Health Organization classification of tumours of the breast. *Histopathology* 2020; **77**: 181-185 [PMID: 32056259 DOI: 10.1111/his.14091]

13 **Iacoponi S**, Calleja J, Hernandez G, Sainz de la Cuesta R. Primary breast angiosarcoma in a young woman. *Int J Surg Case Rep* 2016; **24**: 101-103 [PMID: 27232295 DOI: 10.1016/j.ijscr.2016.05.015]

14 **Russo D**, Campanino MR, Cepurnaite R, Gencarelli A, De Rosa F, Corvino A, Menkulazi M, Tammaro V, Fuggi M, Insabato L. Primary High-Grade Angiosarcoma of the Breast in a Young Woman With Breast Implants: A Rare Case and a Review of Literature. *Int J Surg Pathol* 2020; **28**: 906-912 [PMID: 32423273 DOI: 10.1177/1066896920924087]

15 **Buatti JM**, Harari PM, Leigh BR, Cassady JR. Radiation-induced angiosarcoma of the breast. Case report and review of the literature. *Am J Clin Oncol* 1994; **17**: 444-447 [PMID: 8092119 DOI: 10.1097/00000421-199410000-00018]

16 **STEWART FW**, TREVES N. Lymphangiosarcoma in postmastectomy lymphedema; a report of six cases in elephantiasis chirurgica. *Cancer* 1948; **1**: 64-81 [PMID: 18867440 DOI: 10.1002/1097-0142(194805)1:1<64::aid-cncr2820010105>3.0.co;2-w]

17 **Chen KT**, Kirkegaard DD, Bocian JJ. Angiosarcoma of the breast. *Cancer* 1980; **46**: 368-371 [PMID: 7190060 DOI: 10.1002/1097-0142(19800715)46:2<368::aid-cncr2820460226>3.0.co;2-e]

18 **Daniels BH**, Ko JS, Rowe JJ, Downs-Kelly E, Billings SD. Radiation-associated angiosarcoma in the setting of breast cancer mimicking radiation dermatitis: A diagnostic pitfall. *J Cutan Pathol* 2017; **44**: 456-461 [PMID: 28169467 DOI: 10.1111/cup.12917]

19 **Cabete J**, Lencastre A, Fidalgo A, Lobo L, João A, Serrão V. Postradiation cutaneous angiosarcoma of the breast: a diagnosis to keep in mind. *Breast J* 2014; **20**: 89-90 [PMID: 24237660 DOI: 10.1111/tbj.12215]

20 **Moe M**, Bertelli G. Breast angiosarcoma following lumpectomy and radiotherapy for breast cancer: a case with short latent period and false negative result on biopsies. *Ann Oncol* 2007; **18**: 801 [PMID: 17229767 DOI: 10.1093/annonc/mdl482]

21 **Chikarmane SA**, Gombos EC, Jagadeesan J, Raut C, Jagannathan JP. MRI findings of radiation-associated angiosarcoma of the breast (RAS). *J Magn Reson Imaging* 2015; **42**: 763-770 [PMID: 25504856 DOI: 10.1002/jmri.24822]

22 **Sanders LM**, Groves AC, Schaefer S. Cutaneous angiosarcoma of the breast on MRI. *AJR Am J Roentgenol* 2006; **187**: W143-W146 [PMID: 16861502 DOI: 10.2214/AJR.05.1940]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2243-2247

DOI: 10.12998/wjcc.v12.i13.2243

ISSN 2307-8960 (online)

CASE REPORT

Rim ^{18}F-fluorodeoxyglucose uptake of hepatic cavernous hemangioma on positron emission tomography/computed tomography: A case report

Yong-An Hu, Ya-Xin Guo, Qi-Feng Huang

Specialty type: Nuclear science and technology

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: Kupeli S, Türkiye

Received: November 28, 2023
Revised: February 21, 2024
Accepted: April 3, 2024
Published online: May 6, 2024

Yong-An Hu, Ya-Xin Guo, Qi-Feng Huang, Department of Nuclear Medicine, Jinhua Hospital of Zhejiang University, Jinhua Municipal Central Hospital, Jinhua 321000, Zhejiang Province, China

Corresponding author: Qi-Feng Huang, MD, Doctor, Department of Nuclear Medicine, Jinhua Hospital of Zhejiang University, Jinhua Municipal Central Hospital, No. 365 Renmin East Road, Jinhua 321000, Zhejiang Province, China. 1156225010@qq.com

Abstract

BACKGROUND

Peripheral FDG accumulation in a hepatic hemangioma presenting in a patient with prolonged fever is rare. Therefore, clinicians should pay close attention to patients with hepatic mass.

CASE SUMMARY

A 54-year-old woman with a 4-wk history of daily fevers was admitted to our hospital. A whole body ^{18}F-Fluordesoxyglucose (PET-FDG) positron emission tomography/computed tomography (PET/CT) was performed to elucidate the source of the fever. However, whole body ^{18}F-FDG PET/CT raised the suspicion of a malignant lesion because of peripheral FDG accumulation (SUVmax 3.5 g/mL) higher than that of the normal liver parenchyma (SUVmax 1.6 g/mL) surrounding a hypoactive area, and no other abnormalities were showed. Subsequently, the patient underwent liver mass resection. Histopathology showed a hepatic cavernous hemangioma with fatty infiltration around the lesion. The fever disappeared four days after surgery and the patient did not present any complications during follow-up.

CONCLUSION

Fatty infiltration in the peripheral parts of hepatic cavernous hemangioma may lead to subacute inflammation which further activate the Kupffer cells. This may cause prolonged fever and peripheral rim FDG accumulation on PET/CT.

Key Words: ^{18}F-Fluordesoxyglucose positron emission tomography/computed tomography; Hepatocellular carcinoma; Fever; Fatty infiltration; Case report

Core Tip: Most of the hepatic cavernous hemangiomas (HCHs) are small, asymptomatic, and detected incidentally. The typical characteristics of HCHs on computed tomography or magnetic resonance imaging make their diagnosis straightforward. It has been suggested that low uptake of fluorodeoxyglucose could be useful to distinguish between benign hemangioma and malignant liver lesions. However, in the case presented here, a pathologically confirmed hepatic cavernous hemangioma showed a SUVmax (maximum standardized uptake value) in the margin of the lesion which was higher than that of the normal liver parenchyma. Therefore, clinicians should pay close attention to patients with hepatic mass.

Citation: Hu YA, Guo YX, Huang QF. Rim ^{18}F-fluorodeoxyglucose uptake of hepatic cavernous hemangioma on positron emission tomography/computed tomography: A case report. *World J Clin Cases* 2024; 12(13): 2243-2247
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2243.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2243

INTRODUCTION

Cavernous hemangioma is the most common benign hepatic tumor, with a prevalence of 0.4% to 20% in the general population and is believed to arise from vascular malformations although some studies have suggested it might originate from hepatic areas of focal necrosis and regeneration[1,2]. It can occur in any age group, but is most prevalent in middle-aged women (the female to male ratio is 5:1)[3]. Hepatic cavernous hemangioma usually presents as a solitary lesion, but 2%-30% of patients may present with multiple lesions. Most of the hepatic cavernous hemangiomas are small, asymptomatic, and detected incidentally, but large ones can occasionally cause symptoms or complications such as fever, jaundice, nausea, vomiting, rupture. Giant lesions can stretch the Glissonean capsule causing pain that may influence the patient's quality of life[4].

The typical characteristics of hepatic cavernous hemangiomas on computed tomography (CT) or magnetic resonance imaging (MRI) are progressive peripheral nodal enhancement at dynamic imaging and delayed centripetal fill-in, making their diagnosis straightforward[5]. Stable appearances on serial imaging and the absence of vascular flow on Doppler ultrasound are also helpful diagnostic cues for hepatic cavernous hemangiomas. However, atypical hemangiomas can be confused with malignant lesions such as intrahepatic cholangiocarcinoma, hepatocellular carcinoma, mixed hepatocellular-cholangiocarcinoma, and angiosarcoma[6]. Fluordesoxyglucose (FDG) uptake of hepatic cavernous hemangiomas is usually low[7]. Thus, ^{18}F-FDG positron emission tomography/CT (PET/CT) is suggested to distinguish benign lesions from malignant lesions when CT and MRI suspect cavernous hepatic hemangioma but cannot exclude malignancy because of its larger size and degeneration[8]. Treatment depends on the size of the tumor and the symptoms. Asymptomatic patients and patients with hepatic lesion size ≤ 5 cm or with growth rate ≤ 3 mm per year do not require treatment[9]. Otherwise, therapy most often is surgical resection of the lesion, after which recurrence or growth of residual small lesions is rare[10]. A few cases were reported of orthotopic liver transplantation for large or diffuse bilateral lesions[11]. Transcatheter arterial embolization and radiation therapy are alternatives in patients unfit for surgery[12,13].

CASE PRESENTATION

Chief complaints

A 54-year-old woman with a 4-wk history of daily fevers was admitted to our hospital.

History of present illness

The patient had daily fevers (up to 39.2 °C) for 4 wk of unknown origin.

History of past illness

She was in good health and her past medical history was unremarkable.

Personal and family history

The patient denied any family history of malignancy.

Physical examination

Body temperature was 38.4 °C, blood pressure was 117/82 mmHg, heart rate was 85 beats/min, respiratory rate was 20 breaths/min and her oxygen saturation was 98%.

Laboratory examinations

Blood tests indicated an elevation in neutrophils (81.5%), C-reactive protein (118.2 mg/L), alkaline phosphatase (147.0 IU/L), and γ-glutamyl transpeptidase (59.9 U/L).

Imaging examinations

Abdominal ultrasound was performed showed a 10.0 cm × 7.0 cm heterogeneous hyperechoic mass in the left liver lobe. On dynamic contrast-enhanced CT, peripheral nodular enhancement in the arterial phase and gradual fill-in in the delayed phase were seen in the mass, which are findings typical for cavernous hemangioma (Figure 1). A whole body 18F-FDG PET/CT was performed to elucidate the source of the fever. However, whole body 18F-FDG PET/CT raised the suspicion of a malignant lesion because of peripheral FDG accumulation (SUVmax 3.5 g/mL) higher than that of the normal liver parenchyma (SUVmax 1.6 g/mL) surrounding a hypoactive area, and no other abnormalities were showed (Figure 2).

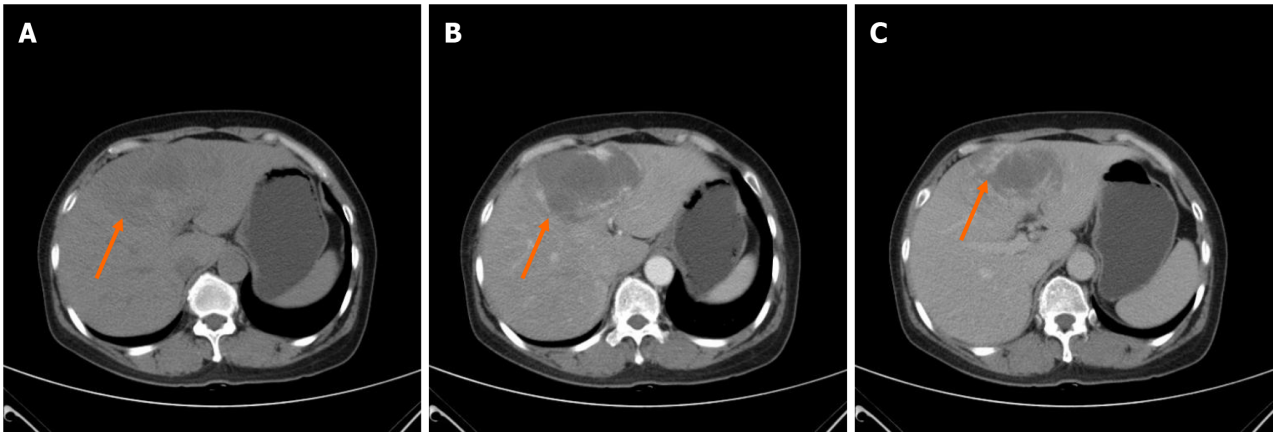

Figure 1 Abdominal computed tomography pre-operation showed a slightly low intensity mass of 10.0 cm × 7.0 cm (orange arrow) was seen in the left liver lobe on plain computed tomography with peripheral nodular enhancement in the arterial phase and gradual fill-in in the delayed phase. A: Plain computed tomography; B: The arterial phase; C: The delayed phase.

FINAL DIAGNOSIS

Hepatic cavernous hemangioma.

TREATMENT

Preoperative needle biopsy was not undertaken given the risk of bleeding because the tumor was highly vascular. Subsequently, the patient underwent liver mass resection. At gross examination, the tumor was a dark red mass of 10 cm in diameter. Histopathology showed a hepatic cavernous hemangioma with fatty infiltration around the lesion (Figure 3).

OUTCOME AND FOLLOW-UP

The fever disappeared four days after surgery and the patient did not present any complications during follow-up.

DISCUSSION

While it has been suggested that low uptake of FDG could be useful to distinguish between benign hemangioma and malignant liver lesions, in the case presented here, a pathologically confirmed hepatic cavernous hemangioma showed a SUVmax (maximum standardized uptake value) in the margin of the lesion which was higher than that of the normal liver parenchyma[7,8,14]. We suspect that this may result from the fatty infiltration. Uptake of FDG in focal fatty infiltration of the liver has been reported and has been attributed to activation of Kupffer cells[15]. A mouse model provided evidence that lipid accumulation in the liver leads to subacute hepatic 'inflammation' through nuclear factor (NF)-kappa activation and downstream cytokine production and that Kupffer cells may activated[16]. However, as the latter reference mentions, the approximately twofold activation of hepatic NF-κB is in contrast to the much greater, many-fold activation that typifies acute inflammatory reactions. Therefore, it remains speculative whether the fever in the patient described here could have been related to the uptake of FDG in the hemangioma. Fever has seldom been reported in hepatic hemangioma[17]. One study suggested that necrotic changes within the hemangioma may cause fever[18]. However, necrotic changes have not been seen in our patient. Moreover, no histologic evidence was found of infection of the hemangioma, which conceivably would constitute a differential explanation of the fever and of the FDG accumulation. Moreover, the peripheral nature of the FDG accumulation would be unexpected in case of infection and it seems unlikely

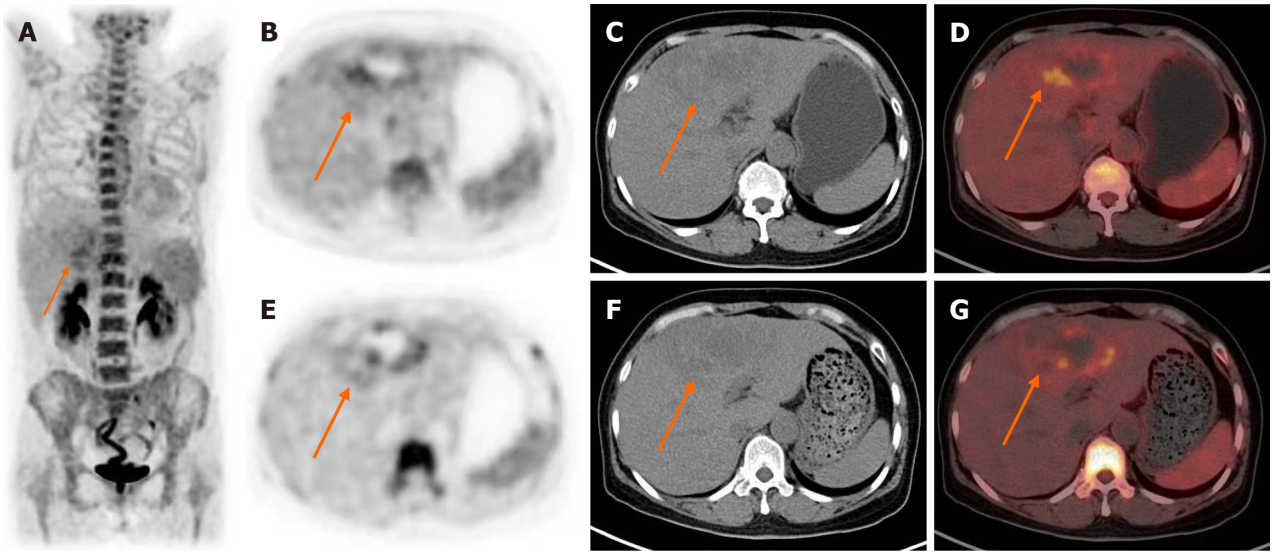

Figure 2 ^{18}F-Fluordesoxyglucose positron emission tomography/computed tomography pre-operation showed the liver lesion (orange arrow) with peripheral fluorodeoxyglucose accumulation (SUVmax 3.5) higher than that of the normal liver parenchyma (SUVmax 1.6) surrounds a hypoactive area. A: Whole body ^{18}F-Fluordesoxyglucose positron emission tomography; B and E: Axial positron emission tomography; C and F: Computed tomography; D and G: Combined positron emission tomography/computed tomography slices.

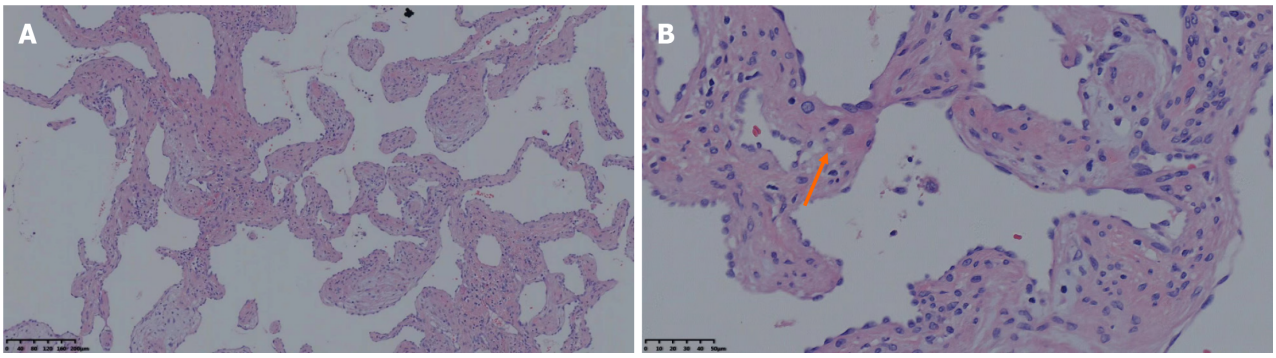

Figure 3 The result of histopathological examination. Hematoxylin and Eosin staining showed numerous dilated blood vessels adjacent to hepatocytes with fatty cell (orange arrow). A: Under low magnification (× 40); B: Under high magnification (× 100).

that any inflammatory infiltrate would have cleared entirely. Still, this we cannot formally rule out this possibility.

CONCLUSION

Fatty infiltration in the peripheral parts of hepatic cavernous hemangioma may lead to subacute inflammation which further activate the Kupffer cells. This may cause prolonged fever and peripheral rim FDG accumulation. We observed peripheral FDG accumulation in a hepatic hemangioma presenting in a patient with prolonged fever. This probably relates to fatty infiltration at the border of the hemangioma and resulting Kupffer cell activation. Since the fever disappeared after resection of the hemangioma, this might suggest that it may have been caused by inflammation induced by the hemangioma.

FOOTNOTES

Author contributions: All authors were involved in the preparation of this manuscript. Hu YA participated in data collection and wrote the manuscript; Guo YX participated in literature search and wrote the manuscript; Huang QF wrote and revised the manuscript; all authors have read and agreed to the published version of the manuscript.

Supported by Zhejiang Province Public Welfare Technology Application Research Project, No. LGF21H180007.

Informed consent statement: Written informed consent has been obtained from the patient to publish this paper.

Conflict-of-interest statement: All authors declare that they have no conflicts of interest.

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: Qi-Feng Huang 0000-0002-1611-207X.

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

REFERENCES

1 **Ojili V**, Tirumani SH, Gunabushanam G, Nagar A, Surabhi VR, Chintapalli KN, Ryan J. Abdominal Hemangiomas: A Pictorial Review of Unusual, Atypical, and Rare Types. *Can Assoc Radiol J* 2013; **64**: 18-27 [DOI: 10.1016/j.carj.2011.08.004]
2 **Brogna A**, Ferrara R, Bucceri AM, Virgilio C, Scalisi G. An atypical case of hepatic cavernous hemangioma. *Cases J* 2009; **2**: 181 [PMID: 19946491 DOI: 10.1186/1757-1626-2-181]
3 **Choi BY**, Nguyen MH. The diagnosis and management of benign hepatic tumors. *J Clin Gastroenterol* 2005; **39**: 401-412 [PMID: 15815209 DOI: 10.1097/01.mcg.0000159226.63037.a2]
4 **Abdel Wahab M**, El Nakeeb A, Ali MA, Mahdy Y, Shehta A, Abdulrazek M, El Desoky M, Abdel Wahab R. Surgical Management of Giant Hepatic Hemangioma: Single Center's Experience with 144 Patients. *J Gastrointest Surg* 2018; **22**: 849-858 [PMID: 29488123 DOI: 10.1007/s11605-018-3696-y]
5 **Oldhafer KJ**, Habbel V, Horling K, Makridis G, Wagner KC. Benign Liver Tumors. *Visc Med* 2020; **36**: 292-303 [PMID: 33005655 DOI: 10.1159/000509145]
6 **Lin S**, Zhang L, Li M, Cheng Q, Zheng S. Atypical hemangioma mimicking mixed hepatocellular cholangiocarcinoma: Case report. *Medicine (Baltimore)* 2017; **96**: e9192 [PMID: 29390333 DOI: 10.1097/MD.0000000000009192]
7 **Higashiyama S**, Kawabe J, Hayashi T, Kurooka H, Oe A, Kotani J, Kawamura E, Shiomi S. A case of cavernous hemangioma in which malignancy was preoperatively excluded by FDG-PET. *Ann Nucl Med* 2008; **22**: 327-330 [PMID: 18535885 DOI: 10.1007/s12149-007-0101-4]
8 **Shimada K**, Nakamoto Y, Isoda H, Saito H, Arizono S, Shibata T, Togashi K. FDG PET for giant cavernous hemangioma: important clue to differentiate from a malignant vascular tumor in the liver. *Clin Nucl Med* 2010; **35**: 924-926 [PMID: 21206221 DOI: 10.1097/RLU.0b013e3181f9de11]
9 **Jiang H**, Chen Z, Prasoon P, Wu H, Zeng Y. Surgical Management for Giant liver Hemangiomas Greater Than 20 cm in Size. *Gut Liver* 2011; **5**: 228-233 [PMID: 21814606 DOI: 10.5009/gnl.2011.5.2.228]
10 **Leon M**, Chavez L, Surani S. Hepatic hemangioma: What internists need to know. *World J Gastroenterol* 2020; **26**: 11-20 [PMID: 31933511 DOI: 10.3748/wjg.v26.i1.11]
11 **Prodromidou A**, Machairas N, Garoufalia Z, Kostakis ID, Tsaparas P, Paspala A, Stamopoulos P, Sotiropoulos GC. Liver Transplantation for Giant Hepatic Hemangioma: A Systematic Review. *Transplant Proc* 2019; **51**: 440-442 [PMID: 30879561 DOI: 10.1016/j.transproceed.2019.01.018]
12 **Hanks BA**, Suhocki PV, DeLong DM, Doan PL, Liu E, Tsai AL, Burke CT, Bernard SA, O'Neil BH, Morse MA. The efficacy and tolerability of transarterial chemo-embolization (TACE) compared with transarterial embolization (TAE) for patients with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol* 2008; **26** [DOI: 10.1200/jco.2008.26.15_suppl.4595]
13 **Shimizu S**, Mizumoto M, Okumura T, Li Y, Baba K, Murakami M, Ishida T, Nakamura M, Hiroshima Y, Iizumi T, Saito T, Numajiri H, Nakai K, Hata M, Sakurai H. Proton beam therapy for a giant hepatic hemangioma: A case report and literature review. *Clin Transl Radiat Oncol* 2021; **27**: 152-156 [PMID: 33665385 DOI: 10.1016/j.ctro.2021.01.014]
14 **Mergo PJ**, Ros PR. Benign lesions of the liver. *Radiol Clin North Am* 1998; **36**: 319-331 [PMID: 9520985 DOI: 10.1016/s0033-8389(05)70025-7]
15 **Kim YH**, Kim JY, Jang SJ, Chung HW, Jang KS, Paik SS, Song SY, Choi YY. F-18 FDG uptake in focal fatty infiltration of liver mimicking hepatic malignancy on PET/CT images. *Clin Nucl Med* 2011; **36**: 1146-1148 [PMID: 22064098 DOI: 10.1097/RLU.0b013e3182335f60]
16 **Cai D**, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, Shoelson SE. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nat Med* 2005; **11**: 183-190 [PMID: 15685173 DOI: 10.1038/nm1166]
17 **Yoshimizu C**, Ariizumi S, Kogiso T, Sagawa T, Taniai M, Honda G, Egawa H, Tokushige K. Giant Hepatic Hemangioma Causing Prolonged Fever and Indicated for Resection. *Intern Med* 2022; **61**: 1849-1856 [PMID: 34803101 DOI: 10.2169/internalmedicine.8405-21]
18 **Yang YG**, Chen WF, Mai WH, Li XF, Zhou HL, Liu LJ, Li MY. Spontaneous intracapsular hemorrhage of a giant hepatic cavernous hemangioma: a rare case report and literature review. *BMC Gastroenterol* 2021; **21**: 84 [PMID: 33622256 DOI: 10.1186/s12876-021-01666-z]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2248-2253

DOI: 10.12998/wjcc.v12.i13.2248

ISSN 2307-8960 (online)

CASE REPORT

Recovering from prolonged cardiac arrest induced by electric shock: A case report

Jian Zhang, Yan-Ru Qiao, Ya-Dong Yang, Guo-Zheng Pan, Chong-Qing Lv

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: Mallet RT, United States

Received: December 11, 2023
Peer-review started: December 11, 2023
First decision: February 8, 2024
Revised: February 29, 2024
Accepted: March 28, 2024
Article in press: March 28, 2024
Published online: May 6, 2024

Jian Zhang, Yan-Ru Qiao, Guo-Zheng Pan, Chong-Qing Lv, Department of General Surgery, Shengli Oilfield Central Hospital, Dongying 257000, Shandong Province, China

Ya-Dong Yang, Department of Emergency Medicine, Shengli Oilfield Central Hospital, Dongying 257000, Shandong Province, China

Corresponding author: Chong-Qing Lv, Doctor, Researcher, Surgeon, Department of General Surgery, Shengli Oilfield Central Hospital, No. 31 Jinan Road, Dongying 257000, Shandong Province, China. lvchongqing2006@163.com

Abstract

BACKGROUND

Cardiac arrest (CA) induced by electric shock is a rare occurrence, particularly in cases of prolonged CA. Currently, there is limited literature on similar incidents, and we present a relevant case report.

CASE SUMMARY

A 27-year-old Asian male man, experiencing respiratory CA due to electric shock, was successfully restored to sinus rhythm after 50 min of cardiopulmonary resuscitation and 8 electrical defibrillation sessions. In the subsequent stages, the patient received multiple organ function protection measures, leading to a successful recovery and eventual discharge from the hospital.

CONCLUSION

Prolonging resuscitation time can enhance the chances of survival for patients, this study provide valuable insights into the management of electric shock-induced CA.

Key Words: Electric shock; Cardiac arrest; Prolonged cardiopulmonary resuscitation; Cerebral resuscitation; Case report

Core Tip: The successful management of a young patient experiencing respiratory cardiac arrest due to electrical injury was accomplished through prolonged cardiopulmonary resuscitation. This study emphasizes the significance of persisting in rescue efforts for individuals with cardiac and respiratory arrest, particularly among young patients without significant organ dysfunction. By extending the duration of resuscitation and implementing early measures for brain protection, not only can normal autonomic circulation be restored but also complete recovery of brain function can be achieved.

Citation: Zhang J, Qiao YR, Yang YD, Pan GZ, Lv CQ. Recovering from prolonged cardiac arrest induced by electric shock: A case report. *World J Clin Cases* 2024; 12(13): 2248-2253
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2248.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2248

INTRODUCTION

Timely and proficient implementation of cardiopulmonary resuscitation (CPR) is crucial for the successful resuscitation of patients who undergo electric shock-induced cardiac arrest (CA), a critical and urgent condition in the emergency department. Prolonging the CPR duration as much as possible can potentially save more lives. Early hyperbaric oxygen intervention treatment plays a crucial role in protecting a patient's brain function and prognosis when vital signs are stable. Patients with respiratory CA secondary to electric shock were successfully treated with prolonged CPR, as illustrated by a case report. This aims to contribute valuable insights for fellow professionals in the field.

CASE PRESENTATION

Chief complaints

The electrical shock led to a 50-min respiratory CA.

History of present illness

A 27-year-old healthy young man suffered from respiratory and CA due to accidental electric shock (AC 380 V). The family members at the scene cut off power and began to implement CPR within 5 min. Paramedics arrived at the scene in 15 min and continued CPR, while transferring the patient to the emergency department of our hospital.

History of past illness

He used to be healthy.

Personal and family history

The parents are in good health and have no reported family history of genetic disease, infectious disease, or similar conditions.

Physical examination

Upon arrival at the emergency department, the patient displayed no spontaneous respiration or heartbeat. Immediate measures, including electrocardiography monitoring, tracheal intubation, continuous external chest compression, and intravenous administration of rapid fluid rehydration, adrenaline, and dopamine were implemented. Approximately 20 min later after receiving rescue medication, the patient regained a spontaneous heartbeat, only to suffer from repeated ventricular fibrillation. The patient achieved sinus rhythm after 8 electric defibrillation attempts, a 150 mg amiodarone intravenous push, and a 1 mg/min intravenous drip. However, the patient remained unconscious with frequent convulsions and was transferred to the emergency intensive care unit (EICU) for advanced life support. Physical examination within the EICU: The patient's temperature was 36.2 °C, heart rate was 99 beats/min, and ventilator-assisted breathing was provided (PS mode: PS 8 cm H_2O, PEEP 4 cm H_2O, FiO_2 55%). Saturation of peripheral oxygen (SPO_2) was 85%, blood pressure was 137/88 mmHg. The patient was in a coma state, with a Glasgow Coma Scale score of E1VTM1. No burns were detected on the entire skin surface. The pupils were equicircular, with a diameter of approximately 4 mm. The neck was soft, with no resistance observed. Corneal reflex was absent. The abdomen was soft, with bowel sounds occurring approximately once per minute, and abdominal wall reflex was not elicited. Both bilateral Babinsky signs and meningeal irritation signs were negative.

Laboratory examinations

The results of peripheral blood examination and arterial blood gas analysis are presented in Table 1.

Imaging examinations

The aforementioned information is referenced in the section dedicated to treatment.

Table 1 Blood examination

Blood examination	WBC (× 10^9/L)	RBC (× 10^{12}/L)	Hg (g/L)	PLT (× 10^9/L)	ALT (U/L)	AST (U/L)	TBIL (μmol/L)	Troponin (μg/L)	Myoglobin (μg/L)	CKMB (μg/L)	Arterial blood gas analysis					
											pH	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	HCO_3 (mmol/L)	Lac (mmol/L)	BE (mmol/L)
Day 1	21.1	6.12	166	397	163	290	11	15.4	3811	79.2	7.27	59.2	37.8	17	12.9	-9.13
Day 2	21	5.48	146	309	164	125	6.1	9.76	2028	50.2	7.361	189.5	40.4	26.5	1	0.48
Reference value	3.5-9.5	4.3-5.8	130-175	125-350	9-52	14-36	3-22	0.02-0.25	0-140	0-25	7.35-7.45	80-100	35-45	22-26	1.0-1.7	-3.0 to 3.0

WBC: White blood cell; RBC: Red blood cell; Hg: Hemoglobin; PLT: Platelet; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; CKMB: Creatine kinase-MB.

FINAL DIAGNOSIS

Electrical injury, respiratory and CA, and postcardiac arrest syndrome.

TREATMENT

The patient underwent a sequence of interventions, including administration of amiodarone to stabilize cardiac rhythm, rapid rehydration with succinyl gelatin, acid correction using sodium bicarbonate, sedation and muscle relaxation through midazolam and bensulfuron atracurium, cerebral protection *via* temperature control blanket, maintenance of blood pressure with norepinephrine, oxiracetam to safeguard the brain, mannitol for prevention and treatment of brain edema and pulmonary edema, coenzyme Q10 to protect the myocardium, omeprazole to preserve gastric mucosa, reduced glutathione to enhance liver function, ceftriaxone sodium to prevent infection, and other supportive treatments.

Two days post-admission, the patient underwent a repeated blood test (Table 1). The abdominal physical examination showed no positive signs, and bowel sounds were approximately 4 per minute. Enteral nutrition was administered, and ambulatory electroencephalography examination revealed severe abnormal brain waves (low voltage) (Figure 1). The computed tomography scan of the head, however, revealed no apparent abnormalities (Figure 2). Troxerutin brain protein was added to promote neurological function recovery following a neurology consultation.

OUTCOME AND FOLLOW-UP

The patient's respiratory function improved 4 d post-admission, with Venturi oxygen used instead of mechanical ventilation, SPO_2 was maintained at 96%. Seven days post-admission, the patient remained unconscious and was subjected to tracheotomy and hyperbaric oxygen therapy. By day 10, the patient could open his eyes, accompanied by significant agitation and coughing, and the sedation drugs were gradually tapered off while increasing the frequency of awakenings. By day 14, the patient could communicate simplistically, and his vital signs stabilized to facilitate a transfer to the general

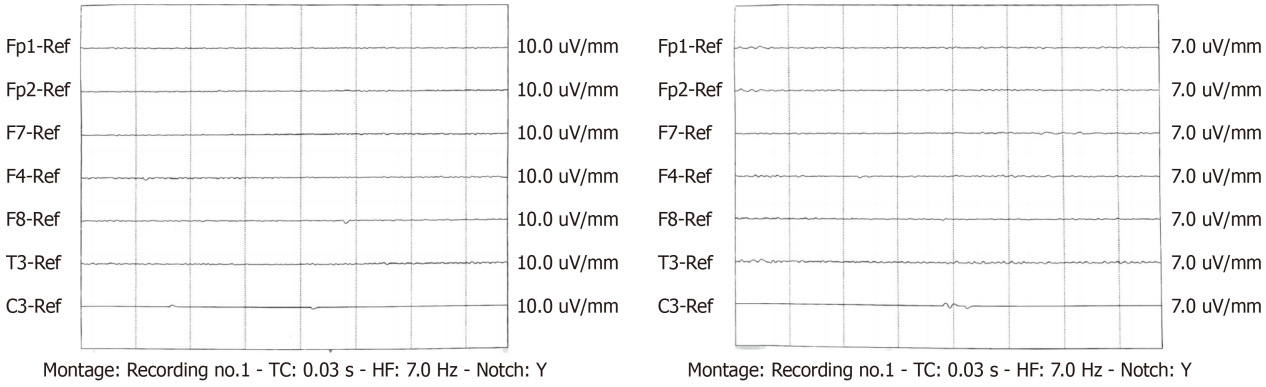

Figure 1 The ambulatory electroencephalography examination revealed pronounced abnormal brain waves characterized by low voltage.

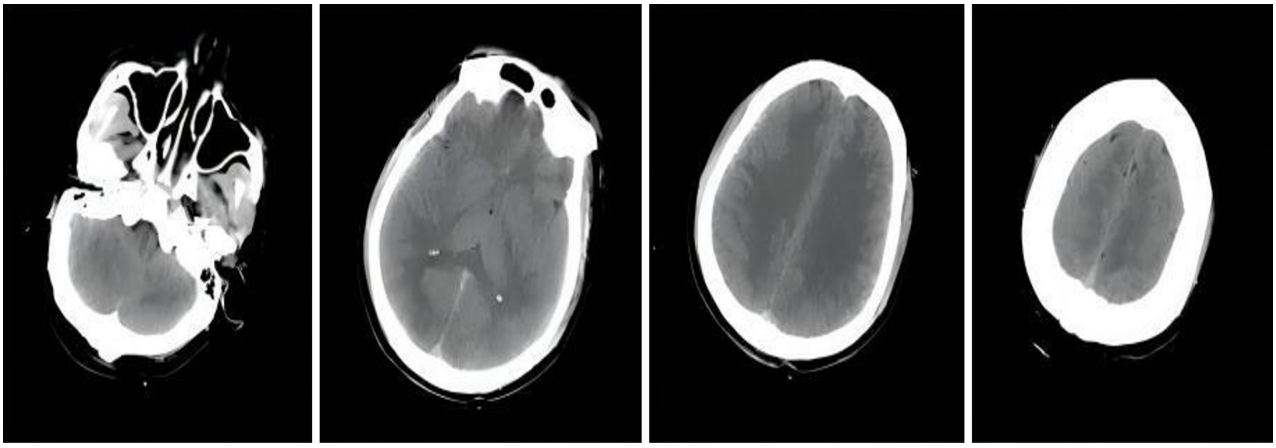

Figure 2 Computed tomography scan of the head showed no obvious abnormalities.

ward. By day 18, his condition notably improved, exhibiting autonomous eating, speaking after removal of the tracheal cannula, and mild physical activities. By day 20, the patient could communicate normally. Finally, by day 26 of admission, the patient's consciousness, activity, and speech returned to normal, resulting in discharge without lingering deficits in memory. The patient remained asymptomatic after a 6-month follow-up period post-discharge.

DISCUSSION

Electrical injury results in tissue damage and dysfunction upon entry of the current into the body, clinically manifesting as localized damage at the shock site, systemic injuries, particularly to the cardiovascular and nervous systems, and, in severe cases, respiratory and CA. The severity of electric injury is contingent on the intensity, type, voltage, contact resistance, duration, and pathway of the current within the body. Electric current typically follows the course of blood vessels and nerves, and when it traverses the heart, it can elicit respiratory depression or arrest, ventricular fibrillation, or CA[1]. In this case report, the patient promptly entered a coma subsequent to electric shock. Continuous CPR was immediately administered, which bought time for subsequent treatment. An decrease of 1 min in emergency response time could enhance patient survival rates by over 15%[2]. The essence of improving survival rates lies in promptly restoring heartbeat and respiration. The guidelines for CPR emphasize that the first 5 min post-CA constitute a golden window for CPR rescue. Beyond this critical period, the likelihood of resuscitation success precipitously declines, corresponding to a decrease in the CPR success rate for each additional minute[3,4]. Moreover, abbreviating emergency response time outside hospitals is a critical strategy for professional teams to optimize the CPR success rate in patients experiencing CA[5].

The probability of successful CPR for patients with CA decreases to less than 3% if spontaneous rhythm recovery is not achieved within 20 min, and clinical CPR may be terminated if there is still no detectable cardiac electrical activity after 30 min. However, given that most patients with electrical injuries are young adults with normal heart and lung function, medical professionals should embrace the concept of ultra-long CPR and endeavor to extend the CPR time in clinical practice, actively rescuing and saving lives[6].

Due to changes in societal roles, elderly individuals seldom encounter respiratory and CA caused by external or human factors, which sets them apart significantly from non-elderly adult patients. The primary etiologies of out-of-hospital CA (OHCA) among the elderly encompass cardiogenic and respiratory ailments as well as asphyxia. Owing to physiological deterioration, exacerbation of chronic underlying conditions, and diminished drug responsiveness fo-

llowing hypoxia, the success rate of resuscitation substantially diminishes with advancing age. Elderly individuals afflicted with cerebrovascular disease, dementia, cerebellar atrophy, and associated disorders frequently manifest a profound decline in swallowing function leading to an augmented risk of aspiration during meals. Furthermore, those suffering from multiple chronic diseases accompanied by respiratory tract infections may experience impaired cough reflexes and compromised airway protection functions that can further impede recovery from OHCA.

This case report presents a young male patient who underwent continuous CPR for 50 min, ultimately restoring autonomous rhythm and sinus rhythm after electrical defibrillation, providing compelling evidence for the effectiveness of long CPR.

Modern medical resuscitation strategies prioritize cardiopulmonary and cerebral resuscitation. Even during the resuscitation process, interventions such as hypothermia, dehydration, cranial pressure reduction, hyperbaric oxygen, and cerebral nerve protection should be implemented to ensure effective cerebral resuscitation. The timeliness and efficacy of cerebral resuscitation are crucial for patient recovery. Following successful CPR in this case, the patient received hypothermia, dehydration, brain tissue protection and early hyperbaric oxygen therapy. Hyperbaric oxygen therapy has been extensively used in cerebral resuscitation, and literature indicates that it can alleviate post-CPR organ ischemia and hypoxia, facilitating brain function recovery[7]. Therefore, it is recommended to administer hyperbaric oxygen therapy promptly.

In summary, the successful treatment in this case can be attributed to the following factors: (1) Implementation of effective rescue measures, including continuous and uninterrupted chest compressions, defibrillation, prompt establishment of an artificial airway with adequate ventilation, and appropriate administration of cardiovascular drugs, contributed significantly to the successful treatment in this case; (2) Despite the patient's heart stopping for over 50 min and complete loss of reflexes with no response to pain stimuli, medical staff and family members demonstrated unwavering persistence in resuscitation efforts without easily relinquishing treatment in what appeared to be a seemingly hopeless situation. This steadfast determination ultimately led to successful recovery; and (3) Continued preservation of organ function after resuscitation is crucial, particularly for vital organs such as the heart, brain, lungs, and kidneys. It is imperative to target control blood pressure levels, oxygen saturation levels, carbon dioxide partial pressure as well as body temperature. Early initiation of enteral nutrition can prevent dysbiosis-induced secondary infections. Additionally, the timely application of hyperbaric oxygen therapy following CPR greatly improves cerebral recovery outcomes, leading to enhanced prognosis through reduced disability rates or mortality risks and minimized occurrence of vegetative states. As a result, it contributes to an overall enhancement in patients' quality of life.

CONCLUSION

For patients experiencing sudden cardiac and respiratory arrest secondary to electrical injuries, particularly those aged between young and middle-aged without significant organ dysfunction, the pursuit of rescuing should not be relinquished lightly. Extending the duration of CPR, implementing early brain protection measures, and employing active and comprehensive treatments can result not only in the establishment of a normal autonomous circulation but also in the full restoration of brain function.

FOOTNOTES

Co-first authors: Jian Zhang and Yan-Ru Qiao.

Co-corresponding authors: Ya-Dong Yang and Chong-Qing Lv

Author contributions: Lv CQ designed the study; Yang YD and Qiao YR collectd the data; Zhang J and Pan GZ wrote the original draft; Zhang J and Qiao YR contributed equally to this work as co-first authors; Yang YD and Lv CQ contributed equally to this work as co-corresponding authors.

Informed consent statement: Written informed consent was obtained from the patient 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: China

ORCID number: Chong-Qing Lv 0000-0002-8781-6920.

S-Editor: Zheng XM
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Fish R**. Electric shock, Part II: Nature and mechanisms of injury. *J Emerg Med* 1993; **11**: 457-462 [PMID: 8228110 DOI: 10.1016/0736-4679(93)90250-b]
2 **Yan S**, Gan Y, Jiang N, Wang R, Chen Y, Luo Z, Zong Q, Chen S, Lv C. The global survival rate among adult out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation: a systematic review and meta-analysis. *Crit Care* 2020; **24**: 61 [PMID: 32087741 DOI: 10.1186/s13054-020-2773-2]
3 **Merchant RM**, Topjian AA, Panchal AR, Cheng A, Aziz K, Berg KM, Lavonas EJ, Magid DJ; Adult Basic and Advanced Life Support, Pediatric Basic and Advanced Life Support, Neonatal Life Support, Resuscitation Education Science, and Systems of Care Writing Groups. Part 1: Executive Summary: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2020; **142**: S337-S357 [PMID: 33081530 DOI: 10.1161/CIR.0000000000000918]
4 **Bai Z**, Wang L, Yu B, Xing D, Su J, Qin H. The success rate of cardiopulmonary resuscitation and its correlated factors in patients with emergency prehospital cardiac arrest. *Biotechnol Genet Eng Rev* 2023; 1-10 [PMID: 37130224 DOI: 10.1080/02648725.2023.2202516]
5 **Sladjana A**, Gordana P, Ana S. Emergency response time after out-of-hospital cardiac arrest. *Eur J Intern Med* 2011; **22**: 386-393 [PMID: 21767757 DOI: 10.1016/j.ejim.2011.04.003]
6 **Liu W**, Liu LN, Lin CW, Wang HY, Wang XD. Successful Recovery After Prolonged Cardiopulmonary Resuscitation and Rescue Thrombolytics in a Patient with Cardiac Arrest Secondary to Presumed Massive Pulmonary Embolism. *Risk Manag Healthc Policy* 2021; **14**: 4253-4256 [PMID: 34703337 DOI: 10.2147/RMHP.S317205]
7 **Schmitz J**, Liebold F, Hinkelbein J, Nöhl S, Thal SC, Sellmann T. Cardiopulmonary resuscitation during hyperbaric oxygen therapy: a comprehensive review and recommendations for practice. *Scand J Trauma Resusc Emerg Med* 2023; **31**: 57 [PMID: 37872558 DOI: 10.1186/s13049-023-01103-y]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2254-2262

DOI: 10.12998/wjcc.v12.i13.2254

ISSN 2307-8960 (online)

CASE REPORT

Young patient with a giant gastric bronchogenic cyst: A case report and review of literature

Xu-Ren Lu, Xu-Guang Jiao, Qi-Hang Sun, Bo-Wen Li, Qing-Shun Zhu, Guang-Xu Zhu, Jian-Jun Qu

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: Utano K, Japan

Received: December 17, 2023
Revised: February 9, 2024
Accepted: April 2, 2024
Published online: May 6, 2024

Xu-Ren Lu, Qi-Hang Sun, Bo-Wen Li, School of Clinical Medicine, Shandong Second Medical University, Weifang 261000, Shandong Province, China

Xu-Ren Lu, Xu-Guang Jiao, Qi-Hang Sun, Bo-Wen Li, Qing-Shun Zhu, Guang-Xu Zhu, Jian-Jun Qu, Department of Gastrointestinal Surgery Medical Center, The First Affiliated Hospital, Shandong Second Medical University, Weifang 261000, Shandong Province, China

Corresponding author: Jian-Jun Qu, Doctor, Chief Doctor, Department of Gastrointestinal Surgery Medical Center, The First Affiliated Hospital, Shandong Second Medical University, No. 151 Guangwen Street, Kuiwen District, Weifang 261000, Shandong Province, China. 1035123330@qq.com

Abstract

BACKGROUND

Gastric bronchogenic cysts (BCs) are extremely rare cystic masses caused by abnormal development of the respiratory system during the embryonic period. Gastric bronchial cysts are rare lesions that were first reported in 1956; as of 2023, only 33 cases are available in the PubMed online database. BCs usually have no clinical symptoms in the early stage, and imaging findings also lack specificity. Therefore, they are difficult to diagnose before histopathological examination.

CASE SUMMARY

A 34-year-old woman with respiratory distress presented at our hospital. Endoscopic ultrasound revealed an anechoic mass between the spleen, left kidney and gastric fundus, with hyperechogenic and soft elastography textures and with a size of approximately 6.5 cm × 4.0 cm. Furthermore, a computed tomography scan demonstrated high density between the posterior stomach and the spleen and the left kidney, with uniform internal density and a small amount of calcification. The maximum cross section was approximately 10.1 cm × 6.1 cm, and the possibility of a cyst was high. Because the imaging findings did not suggest a malignancy and because the patient required complete resection, she underwent laparotomy surgery. Intraoperatively, this cystic lesion was found to be located in the posterior wall of the large curvature of the fundus and was approximately 8 cm × 6 cm in size. Finally, the pathologists verified that the cyst in the fundus was a gastric BC. The patient recovered well, her symptoms of chest tightness disappeared, and the abdominal drain was removed on postoperative day 6, after which she was discharged on day 7 for 6 months of follow-up. She had no tumor recurrence or postoperative complications during the follow-up.

CONCLUSION
This is a valuable report as it describes an extremely rare case of gastric BC. Moreover, this was a very young patient with a large BC in the stomach.

Key Words: Bronchogenic cyst; Stomach; Endoscopic ultrasound-guided fine needle aspiration; Endosonography; Case report

Core Tip: Gastric bronchogenic cysts (BCs) represent uncommon congenital anomalies, often manifesting as indistinct cystic formations on preoperative evaluations. Herein, we document a noteworthy instance of a sizable gastric BC occurring in a young female patient. The definitive diagnosis of gastric BC was established through histopathological examination following laparotomy resection. The analysis of the reported cases revealed that gastric BC often mimics gastrointestinal stromal tumors on preoperative imaging. We recommend elective radical surgical resection for young patients with large cysts, as they might progress to malignancies.

Citation: Lu XR, Jiao XG, Sun QH, Li BW, Zhu QS, Zhu GX, Qu JJ. Young patient with a giant gastric bronchogenic cyst: A case report and review of literature. *World J Clin Cases* 2024; 12(13): 2254-2262
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2254.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2254

INTRODUCTION

Bronchogenic cysts (BCs) are uncommon developmental malformations that result from the aberrant development of the primitive tracheobronchial tube, leading to the formation of cystic lesions. These lesions are typically congenital, meaning they are present at birth, and can cause various symptoms depending on their location and size[1]. The lesions can be divided into mediastinal, intrapulmonary, and ectopic types according to their location[2]. The tumor is primarily located in the mediastinum if it occurs early in gestation, as opposed to the thoracic cavity if it arises later in development[3]. Abdominal BCs, especially those situated within the gastric wall, are exceptionally uncommon occurrences[4]. Dewing *et al*[5] were the pioneers in describing gastric bronchial cysts in 1956, and as of 2023, only a few cases have been described in reports available in the PubMed online database. For patients with BCs, there is a wide range for the age at diagnosis, which has ranged from 17 to 81 years, and it has a higher prevalence in females, with a median age of development of 43 years[1]. BCs of the gastric region typically manifest along the posterior wall of the gastric body and the lesser curvature of the stomach[6]. In previous reports, it has been observed that a significant proportion of patients were asymptomatic [7]. However, among those who exhibited symptoms, epigastric pain and vomiting were the most prevalent[8]. Most gastric BCs are easily misdiagnosed as gastrointestinal stromal tumors (GISTs) before surgery[9]; however, fortunately, their prognosis is good[10]. In the current investigation, we have documented a rare instance of a gastric BCs occurring in a 34-year-old patient. Furthermore, we have undertaken a thorough examination of the existing literature (Table 1) to delve into the clinical manifestations associated with these cysts, aiming to contribute to a deeper understanding of their nature and incidence.

CASE PRESENTATION

Chief complaints

A 34-year-old Chinese woman presented to the gastrointestinal surgery clinic with a complaint of respiratory distress for 5 d.

History of present illness

A 34-year-old Chinese female patient presented with chest tightness and shortness of breath for 5 d with no nausea, vomiting, sour regurgitation, belching, dysphagia, melena, or weight loss.

History of past illness

She had a history of psoriasis.

Personal and family history

Her father died of lymphoma. In addition, the patient denied any family history of other malignancies.

Table 1 Thirty-three cases

Ref.	Age	Gender	Size (cm)	Location	Symptom	Preoperative diagnosis	Intervention
Braffman *et al*[24], 1988	64	Female	15 × 8	Posterior wall	Epigastric pain		Resection
Matsubayashi *et al*[25], 2003	62	Male	10 × 3 × 3	Posterior wall		Lymphangioma/benign	Resection
Hedayati *et al*[26], 2003	59	Female	7 × 5	Posterior wall		Adrenocortical cancer	Laparoscopic
Rubio *et al*[27], 2005	26	Male			Epigastric pain		
Melo *et al*[12], 2005	39	Female	4 × 2.5 × 1	Gastric fundus	Rib pain	GIST	Laparoscopic resection
Song *et al*[28], 2005	62	Female	1.7	Lesser curvature		Benign stromal tumor	Resection
Wakabayashi *et al*[29], 2007	37	Male	5	Lesser curvature	Epigastric pain	A duplication cyst	Exploration
Sato *et al*[19], 2008	60	Female	3			Benign cyst of the gastric submucosa	
Shibahara *et al*[17], 2009	43	Male	9 × 4	Lesser curvature	Epigastric pain	Gastric cancer	
Jiang *et al*[30], 2010	25	Female	3 × 2.5 × 2.0	Gastric fundus	Epigastric pain	GIST	Laparotomy
Tan *et al*[10], 2010	30	Female	5.1 × 3.6 × 4.6	Posterior wall of the stomach			Laparoscopic wedge resection
Kurokawa *et al*[31], 2013	71	Male	3.2	Gastric cardia	Throat discomfort	Cyst	Laparoscopic
Yang and Guo[6], 2013	50	Male	8.0 × 6.0	Gastric fundus		Retroperitoneal mass	Laparotomy
Yang and Guo[6], 2013	37	Female	10 × 6	Posterior wall of the stomach		GIST	Wedged gastrectomy
Sun *et al*[32], 2015	67	Male	4.1 × 3.2	Gastric fundus	Dull epigastric pain	GIST	Laparotomy
Tu *et al*[1], 2016	17	Female	3 × 2.5	Gastric cardia	Epigastric pain	Cyst	Laparotomy
Chhaidar *et al*[33], 2017	65	Female	7 × 8	Gastric cardia	Epigastric pain	GIST	Total gastrectomy
Xiao *et al*[13], 2020	62	Female	6.4 × 4.9	Lesser curvature of the gastric cardia	Right lower abdominal pain	GIST	Laparoscopic
He *et al*[15], 2020	55	Female	7 × 6 × 2	Gastric cardia	Intermittent epigastric pain	Benign cyst of the gastric submucosa	Da vinci robotic-assisted laparoscopic
Sun *et al*[7], 2020	68	Male	10 × 8 × 8	Fundus of stomach		Retroperitoneal mass	Laparotomy
Erbenová *et al*[34], 2021	30	Female		Gastric cardia		Tumor of gastric cardia	Laparoscopic
Lou *et al*[8], 2022	38	Female	5 × 2.6	Gastric fundus	Upper abdominal pain	Lymphatic cyst	Laparoscopic
Wang *et al*[35], 2022	76	Male	3.1 × 3.0	Gastroesophageal junction	Abdominal pain and distension	GIST	Laparoscopic
Li *et al*[36], 2022	35	Male		Posterior wall of the gastric cardia		Abdomystic Lymphangioma	Laparotomy
Lv *et al*[37], 2023	23	Male		Greater curvature	Abdominal discomfort		
Qian and Xu[16], 2023	50	Male	2 × 1.5	Posterior gastric fundus wall		Schwannoma or low-grade stromal tumor	Gastroscope
Qian *et al*[38], 2023	45	Female	3 × 2	Gastric cardia	Upper abdominal pain	GIST	Laparoscope

Ma *et al*[39], 2023	46	Female	5 × 4.5 × 3.5	Gastric body	Abdominal pain	GIST	
Lin and Cao[40], 2023	47	Male	8 × 7	Posterior wall of the fundus	Pain in the right chest		
Liu and Li[41], 2023	65	Male	4 × 3	Gastric cardia	Blech		
Terayama *et al*[42], 2023	37	Female	3	Gastric cardia	Asymptomatic	Bronchogenic cyst	Resection
Terayama *et al*[42], 2023	47	Male	5	Gastric cardia	Asymptomatic	Gastric bronchogenic cyst	Resection
Terayama *et al*[42], 2023	37	Male	3.5	Gastric cardia	Asymptomatic		Resection

GIST: Gastrointestinal stromal tumor.

Physical examination

Her abdomen was smooth and flat, and there was no gastrointestinal type or mild upper abdominal tenderness without rebound pain or an overt mass. The bowel sounds were normal.

Laboratory examinations

No abnormalities were found in routine blood or urine analyses or liver or kidney function tests.

Imaging examinations

Endoscopic ultrasound (EUS) revealed a 65 mm × 40 mm single cyst. The images also showed that the cyst was located at the bottom of the gastric wall. Anechoic masses were detected between the spleen, left kidney, and gastric fundus with punctate hyperechogenicity. Elastography revealed a soft texture. These findings suggested the presence of a cyst within the stomach (Figure 1). Additionally, an enhanced computed tomography (CT) scan revealed a cystic mass measuring 101 mm × 61 mm in size. There was no contrast enhancement, and the mass was located within the posterior wall of the gastric fundus, spleen and left kidney with regular and smooth outlines. The mass appeared to have a slightly high and uniform density with a small, calcified shadow in the posterior gastric region. No septation was observed. It also showed an extraluminal growth pattern with an obvious border, and the gastric wall was affected by pressure (Figure 2). Moreover, no significant enlargement of lymph nodes was observed in the vicinity of the stomach or retroperitoneal region. Before surgery, an EUS examination was performed to determine which layer of the gastric wall the cyst had originated from. However, because the cyst wall was evaluated by CT, because there was calcification on the cyst wall, and because the contents of the cyst were mainly liquid components according to the density, there was concern that fine needle aspiration (FNA) may cause rupture of the cyst before surgery and would increase the risk of infection. Second, we suspected that the patient's chest tightness was caused by compression of the diaphragm muscle by the large cyst. To eliminate the patient's symptoms and because the patient strongly desired surgery, after consultation and discussion with many experts, we decided to prudently remove the cyst and obtain a complete pathological specimen so that a safe postoperative examination could be performed to obtain the most accurate diagnosis. Based on these two points, we did not use preoperative FNA.

FINAL DIAGNOSIS

After treatment, the patient's symptoms of chest tightness resolved. We suspected that the chest tightness was due to the large cyst exerting pressure on the diaphragm. Based on the obtained specimen, this mass was approximately 80 mm × 50 mm × 40 mm in size. Under microscopic examination, the cyst lining exhibited pseudostratified ciliated columnar epithelial cells, while the cyst wall displayed smooth muscle and small salivary gland tissue. Immunohistochemical staining revealed the following results: CK7 (+) TTF-1 (partial +), NapsinA (+), CK20 (-), Villin (-), SMA (+), Desmin (+), P63 (+), and elastic fiber (+) (Figure 3). The pathologists conclusively confirmed that the cystic mass located in the fundus was indeed gastric BCs.

TREATMENT

Given the young age of the patient, the large cyst with prominent gastric wall compression and chest tightness could have been associated with the cystic mass, and given that the patient wished to have the lesion completely removed, the patient underwent intra-abdominal mass resection under general anesthesia and nerve block anesthesia. Intraoperative observations of this cystic mass revealed it to be a smooth, single-port cyst originating from the posterior wall of the gastric fundus and extending along the greater curvature. Surgical exploration revealed no intra-abdominal ascites or

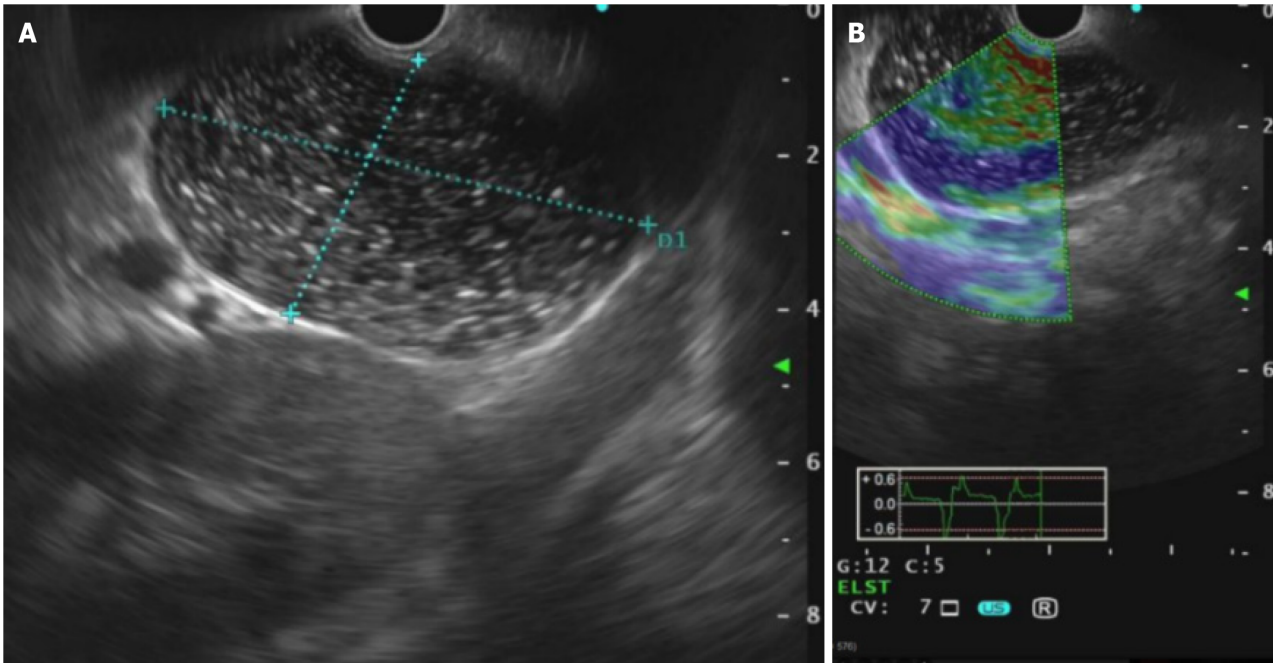

Figure 1 Imaging at admission. Endoscopic ultrasound revealed a 6.5 cm × 4.0 cm single cyst. The cyst, without any echoes or color flow signals, was located in the posterior wall of the gastric body. These results indicated the possibility of a cyst of the stomach.

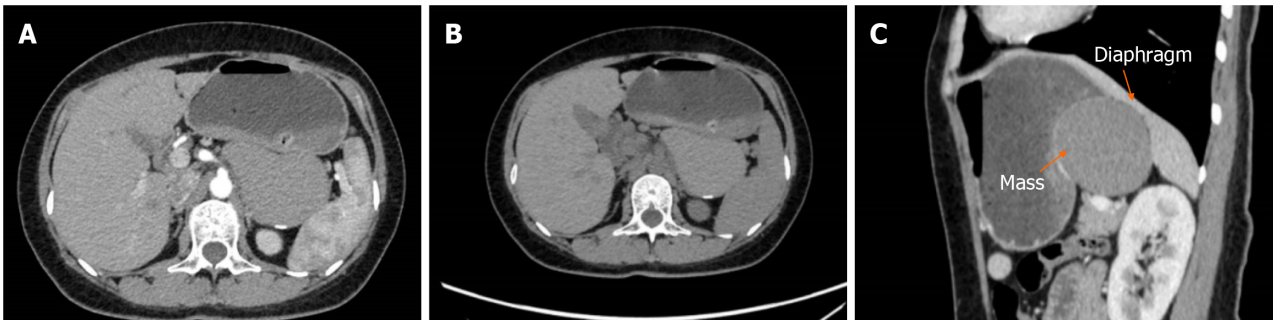

Figure 2 Imaging at admission. A: An enhanced computed tomography scan demonstrated a 10.1 cm × 6.1 cm mass. The mass was present in the posterior part of the stomach between the spleen and the left kidney; a large, slightly high-density swelling shadow with uniform internal density was shown; and a small calcification shadow could be seen at the rear. The computer tomography (CT) value was approximately 70 HU, and the gastric wall was compressed and changed; B: Noncontrast CT image; C: It can be clearly seen from the sagittal position that the diaphragm was compressed by the mass.

obvious abnormalities in the liver, abdominal wall, pelvic cavity, omenta, or mesentery. The cystic mass was then completely dissected from the stomach. It is worth noting that surgeons need to avoid cyst rupture during these types of surgery.

OUTCOME AND FOLLOW-UP

The patient recovered well, her symptoms of chest tightness completely disappeared, and the abdominal drain was removed on postoperative day 6, after which she was discharged on day 7 for 6 months of follow-up. The patient had no tumor recurrence or postoperative complications that occurred after surgery.

DISCUSSION

To conduct a comprehensive study on BCs of the stomach, a systematic literature review was undertaken using the PubMed database. The search was focused on articles published in English and employed the keyword "gastric BCs" to identify relevant studies. The final date for data collection was set as December 2023. The inclusion criteria stipulated that all patients must have a confirmed diagnosis of gastric BCs through pathological examination. Additionally, patients exhibiting imaging characteristics typical of gastric BCs were included, irrespective of age and sex. Conversely, patients

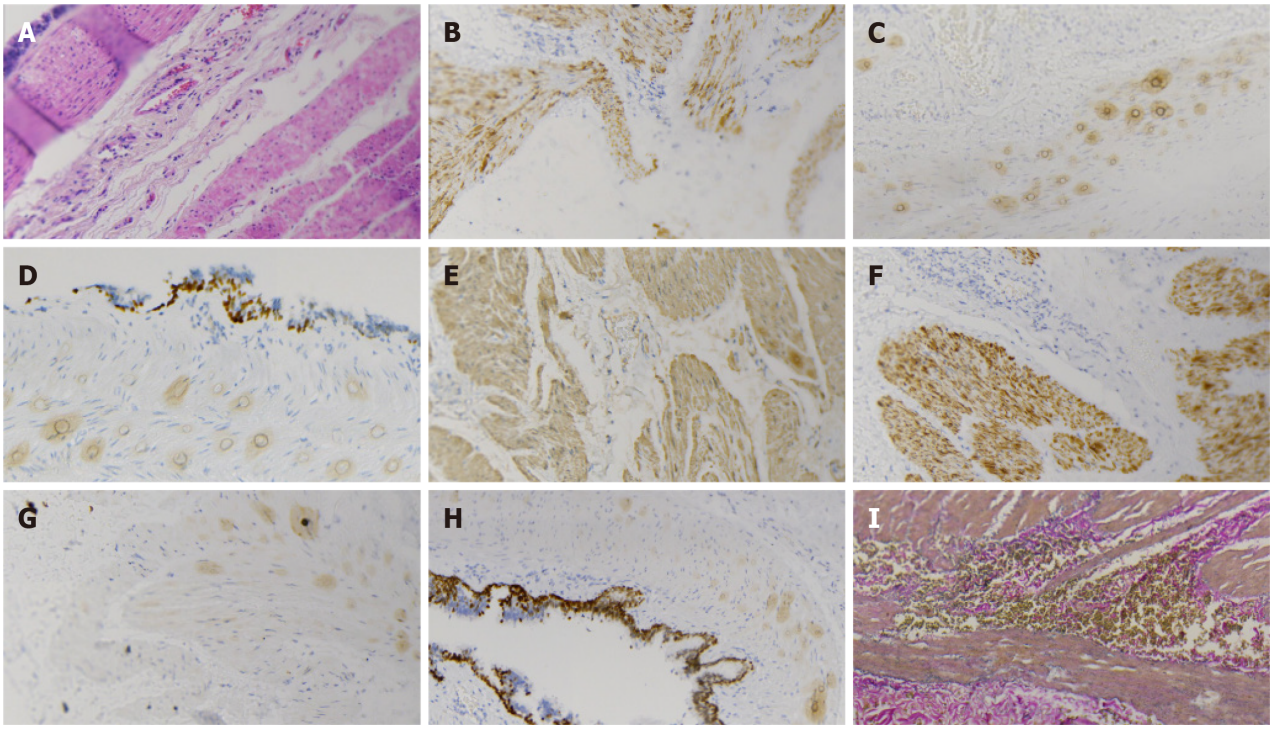

Figure 3 Histopathological analysis and immunohistochemical examination of the resected specimen. A: Microscopically, pseudostratified ciliated columnar epithelial cells could be observed in the cyst lining, and smooth muscle and small salivary gland tissue could be observed in the cyst; B: Napsin A (+); C: CK20 (-); D: P63 (+); E: SMA (+); F: Desmin (+); G: CK7 (+); H: TTF-1 (+); I: Elastic fiber (+).

lacking typical pathological or imaging features were excluded from the study. Based on our knowledge cutoff of December 2023, a total of 33 cases of gastric BCs were reported, meeting the specified search criteria. These cases are comprehensively listed in Table 1.

BCs are primitive-foregut-derived congenital cystic abnormalities[11]. Migration of BCs may ensue when their attachments to the trachea or esophagus fail to persist, resulting in their potential displacement within the anatomical structures of the body[12]. The primary sites of occurrence for BCs predominantly involve the thoracic region, notably within the mediastinum. However, on rare occasions, they may also manifest in the subdiaphragmatic region. BC of the stomach appears to be a disease detected at all ages (from 17 to 76 years of age), and there was no apparent sex difference (17 females and 16 males). The dimensions of BCs exhibited considerable variability, ranging from 1.7 to 15 cm, as indicated by available data from our cases and referenced literature. However, the majority of cyst diameters fell within the range of 3 to 7 cm. Regarding localization, our investigation revealed a predilection for cysts to be situated in the gastric cardia or posterior wall of the fundus. A large proportion of patients with BC have clinical manifestations of epigastric pain, while others generally experience nonspecific symptoms, which may be due to local tumor compression and infection[13]. Notably, four patients with gastric BC had elevated tumor marker levels. Elevated CA19-9 levels were present in two of the patients[10,14], and elevated CA72-4 levels were also present in patients with elevated CA72-4 levels [15,16]. Interestingly, these elevated tumor markers returned to normal after surgery, suggesting that there is a direct relationship between benign BCs and elevated tumor marker levels. However, the relationship between tumor markers and BC needs further study. It is worth noting that BCs of the stomach have been associated with the presence of gastric carcinoma. Chronic inflammation of the gastric mucosa, stemming from BCs, may have contributed to the development of these adenocarcinomas in the stomach, as reported in previous studies[17]. While the current investigation illustrates that EUS and other imaging modalities can aid in localizing the lesion, they are limited in their ability to offer qualitative diagnostic insights. Accurate preoperative diagnosis is challenging, and most patients are easily misdiagnosed with GIST. In summary, preoperative diagnosis of gastric BCs is challenging due to the absence of specific clinical manifestations, as well as inconclusive findings from laboratory tests and imaging studies. Moreover, the rarity of these lesions further complicates their diagnosis.

BCs are commonly detected through CT and magnetic resonance imaging (MRI). However, relying solely on imaging techniques to differentiate them from other types of cysts can be challenging due to the presence of similar radiological features among various cystic lesions. Ubukata *et al*[18] demonstrated that far greater clarity was achieved when using MRI than when using CT, especially for identifying the contents of the cystic lesions. In the present case, since the patient had metal dental implants, this patient was not suitable to undergo MRI. EUS is commonly employed to ascertain the specific layer of the gastric wall from which the lesion originates and to delineate its approximate location within the gastrointestinal tract[15]. Imaging alone cannot usually distinguish between nonneoplastic lesions and benign or malignant neoplasms. In clinically warranted situations, EUS-FNA biopsy has been previously established as a valuable tool for the unequivocal diagnosis of gastric BCs[19]. Its effectiveness is further emphasized by its sensitivity range of 86%-93%[20], diagnostic accuracy spanning 82%-95%, and an exceptionally low complication rate of merely 1%-3%[21].

Although the probability of complications is extremely low, there are risks of ulceration, infection and hemorrhage. EUS-FNA provides a new diagnostic and treatment approach for asymptomatic gastric BC patients. We recommend that EUS-FNA be performed first for elderly patients, patients in poor physical condition, asymptomatic patients, and patients who cannot undergo surgical treatment for various reasons in the short term; then subsequent treatment options should be discussed based on the results.

Through our systematic review of existing cases, we conclude that GIST is the most common preoperative diagnosis of gastro BCs. The two conditions are difficult to distinguish by imaging, and an accurate preoperative diagnosis can be obtained *via* EUS-FNA before surgery. However, there are risks such as infection and bleeding. During the operation, these masses can be distinguished by observing their nature. GISTs are brittle and prone to bleeding, while gastro BCs are composed mainly of cystic components[9]. Second, due to the rarity of BCs, clinicians lack understanding of this disease, which is also one of the reasons for the failure to obtain an accurate preoperative diagnosis of this disease.

The ultimate diagnosis typically hinges on a histopathological analysis of specimens obtained postoperatively. A review of the literature revealed that surgical resection was the most common option. Surgical removal will improve the symptoms of cyst compression and reduce the risk of BC transforming into a malignant tumor[22]. The findings from the current literature review indicate that asymptomatic patients harboring small masses require careful monitoring. Conversely, for symptomatic patients, particularly those who are young as exemplified in this case report, surgical resection is advisable. In the case presented, the patient's respiratory distress was attributed to the growing mass exerting pressure on the diaphragmatic muscle. In addition to routine laparoscopic resection, Lee *et al*[23] proposed endoscopic mucosal resection (EMR) for the treatment of gastric BC. They proposed that when a lesion is suspected to be a solid tumor on the basis of EUS and CT investigations and if there is a positive cushion sign, the differential diagnosis of a developmental cyst should be considered, and EMR could be used for curative treatment. Regardless of the operation method, care should be taken to avoid intraoperative cyst rupture and postoperative infection complications. Due to the large size of the cyst in this case, open surgery was chosen to obtain a sufficient surgical field of view and ensure complete resection.

Although gastric BCs are a very rare disease, when comparing our case with those reported in PubMed, it can be seen that there are no specific clinical manifestations or laboratory indicators associated with BC. Elevated tumor markers have been reported in some cases; however, the sample size was insufficient to support an association. Early detection of suspected lesions is a favorable factor affecting patient survival. In addition, CT, MRI, and EUS are popular methods for detecting gastric BCs. Surgical removal is the most common way to relieve symptoms; however, the recommendation of surgical intervention for asymptomatic patients remains controversial. Through our diagnosis and treatment and the postoperative follow-up of this patient, we would like to show that surgical resection is recommended for young patients with large cysts and clinical symptoms to eliminate symptoms and the uncertainty of transformation of gastro BCs into malignant tumors.

CONCLUSION

Although gastric BCs are a very rare disease, when comparing our case with those reported in PubMed, it can be seen that there are no specific clinical manifestations or laboratory indicators associated with BC. Elevated tumor markers have been reported in some cases; however, the sample size was insufficient to support an association. Early detection of suspected lesions is a favorable factor affecting patient survival. In addition, CT, MRI, and EUS are popular methods for detecting gastric BCs. Surgical removal is the most common way to relieve symptoms; however, the recommendation of surgical intervention for asymptomatic patients remains controversial. Through our diagnosis and treatment and the postoperative follow-up of this patient, we would like to show that surgical resection is recommended for young patients with large cysts and clinical symptoms to eliminate symptoms and the uncertainty of transformation of gastro BCs into malignant tumors.

FOOTNOTES

Author contributions: Qu JJ was responsible for the overall project progress, paper revision and submission; Lu XR and Jiao XG contributed to manuscript writing and editing and data collection; Sun QH and Zhu QS contributed to the data analysis; Li BW and Zhu GX contributed to the conceptualization and supervision. All the authors read and approved the final manuscript.

Supported by Weifang Municipal Health Commission Scientific Research Project, No. WFWSHKK-2021-028; and Shandong Province Medical Health Science and Technology Project, No. 202304010544.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest to disclose.

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: Bo-Wen Li 0009-0006-3328-8778; Jian-Jun Qu 0009-0000-4883-7326.

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

REFERENCES

1 **Tu C**, Zhu J, Shao C, Mao W, Zhou X, Lin Q, Li Z, Zhang J, Zhou Q, Chen W. Gastric bronchogenic cysts: A case report and literature review. *Exp Ther Med* 2016; **11**: 1265-1270 [PMID: 27073434 DOI: 10.3892/etm.2016.3067]
2 **McAdams HP**, Kirejczyk WM, Rosado-de-Christenson ML, Matsumoto S. Bronchogenic cyst: imaging features with clinical and histopathologic correlation. *Radiology* 2000; **217**: 441-446 [PMID: 11058643 DOI: 10.1148/radiology.217.2.r00nv19441]
3 **Gross DJ**, Briski LM, Wherley EM, Nguyen DM. Bronchogenic cysts: a narrative review. *Mediastinum* 2023; **7**: 26 [PMID: 37701638 DOI: 10.21037/med-22-46]
4 **Seddik H**, Adioui T, Rouibaa F, El Hamdi FZ, Aourarh A, Mahi M, Benkirane A, Zentar A. Gastric bronchogenic cyst presenting as a submucosal mass: a case report. *J Med Case Rep* 2012; **6**: 262 [PMID: 22937973 DOI: 10.1186/1752-1947-6-262]
5 **Dewing SB**, Roessel CW, Olmstead EV. Enterogenous cyst of the stomach wall, a rare benign lesion; case report. *Ann Surg* 1956; **143**: 131-135 [PMID: 13275911 DOI: 10.1097/00000658-195601000-00019]
6 **Yang X**, Guo K. Bronchogenic cyst of stomach: two cases report and review of the English literature. *Wien Klin Wochenschr* 2013; **125**: 283-287 [PMID: 23579880 DOI: 10.1007/s00508-013-0352-0]
7 **Sun B**, Wang AK, Chen H, Qian BL, Yi XK, Jiang Y, Li Q, Fu WG, Li J. Bronchogenic cyst of the stomach: A case report and literature review. *Exp Ther Med* 2020; **20**: 166 [PMID: 33093904 DOI: 10.3892/etm.2020.9295]
8 **Lou F**, Chen Q, Hu H. Gastric bronchogenic cyst in a young woman. *Asian J Surg* 2022; **45**: 1982-1984 [PMID: 35584996 DOI: 10.1016/j.asjsur.2022.04.038]
9 **Xiao J**, Zhang R, Chen W, Wu B. Ectopic bronchogenic cyst of the gastric cardia considered to be a gastrointestinal stromal tumor before surgery: a case report. *BMC Surg* 2020; **20**: 42 [PMID: 32122361 DOI: 10.1186/s12893-020-00704-z]
10 **Tan KK**, Nandini CL, Ho CK. A case of gastric bronchogenic cyst in Singapore with multiple intrigues. *ANZ J Surg* 2010; **80**: 286-287 [PMID: 20575959 DOI: 10.1111/j.1445-2197.2010.05260.x]
11 **St-Georges R**, Deslauriers J, Duranceau A, Vaillancourt R, Deschamps C, Beauchamp G, Pagé A, Brisson J. Clinical spectrum of bronchogenic cysts of the mediastinum and lung in the adult. *Ann Thorac Surg* 1991; **52**: 6-13 [PMID: 2069465 DOI: 10.1016/0003-4975(91)91409-o]
12 **Melo N**, Pitman MB, Rattner DW. Bronchogenic cyst of the gastric fundus presenting as a gastrointestinal stromal tumor. *J Laparoendosc Adv Surg Tech A* 2005; **15**: 163-165 [PMID: 15898909 DOI: 10.1089/Lap.2005.15.163]
13 **Xiao J**, Zhang X, Zhou H, Hong T, Li B, He X, Liu W. Subdiaphragmatic bronchogenic cysts: Case series and literature review. *Front Med (Lausanne)* 2022; **9**: 993091 [PMID: 36275826 DOI: 10.3389/fmed.2022.993091]
14 **Ikehata A**, Sakuma T. Gastric duplication cyst with markedly elevated concentration of carbohydrate antigen 19-9. *Am J Gastroenterol* 2000; **95**: 842-843 [PMID: 10710108 DOI: 10.1111/j.1572-0241.2000.01873.x]
15 **He WT**, Deng JY, Liang H, Xiao JY, Cao FL. Bronchogenic cyst of the stomach: A case report. *World J Clin Cases* 2020; **8**: 1525-1531 [PMID: 32368546 DOI: 10.12998/wjcc.v8.i8.1525]
16 **Qian W**, Xu G. Gastric fundus bronchogenic cyst with elevated CA72-4: A case report and literature review. *Asian J Surg* 2023; **46**: 4507-4508 [PMID: 37179180 DOI: 10.1016/j.asjsur.2023.04.133]
17 **Shibahara H**, Arai T, Yokoi S, Hayakawa S. Bronchogenic cyst of the stomach involved with gastric adenocarcinoma. *Clin J Gastroenterol* 2009; **2**: 80-84 [PMID: 26192170 DOI: 10.1007/s12328-008-0042-z]
18 **Ubukata H**, Satani T, Motohashi G, Konishi S, Goto Y, Watanabe Y, Nakada I, Tabuchi T. Intra-abdominal bronchogenic cyst with gastric attachment: report of a case. *Surg Today* 2011; **41**: 1095-1100 [PMID: 21773899 DOI: 10.1007/s00595-010-4398-6]
19 **Sato M**, Irisawa A, Bhutani MS, Schnadig V, Takagi T, Shibukawa G, Wakatsuki T, Imamura H, Takahashi Y, Sato A, Hikichi T, Obara K, Hashimoto Y, Watanabe K, Ohira H. Gastric bronchogenic cyst diagnosed by endosonographically guided fine needle aspiration biopsy. *J Clin Ultrasound* 2008; **36**: 237-239 [PMID: 18027836 DOI: 10.1002/jcu.20425]
20 **Matsui M**, Goto H, Niwa Y, Arisawa T, Hirooka Y, Hayakawa T. Preliminary results of fine needle aspiration biopsy histology in upper gastrointestinal submucosal tumors. *Endoscopy* 1998; **30**: 750-755 [PMID: 9932753 DOI: 10.1055/s-2007-1001416]
21 **O'Toole D**, Palazzo L, Arotçarena R, Dancour A, Aubert A, Hammel P, Amaris J, Ruszniewski P. Assessment of complications of EUS-guided fine-needle aspiration. *Gastrointest Endosc* 2001; **53**: 470-474 [PMID: 11275888 DOI: 10.1067/mge.2001.112839]
22 **Endo C**, Imai T, Nakagawa H, Ebina A, Kaimori M. Bronchioloalveolar carcinoma arising in a bronchogenic cyst. *Ann Thorac Surg* 2000; **69**: 933-935 [PMID: 10750790 DOI: 10.1016/s0003-4975(99)01402-2]
23 **Lee SH**, Park DH, Park JH, Kim HS, Park SH, Kim SJ, Oh MH. Endoscopic mucosal resection of a gastric bronchogenic cyst that was mimicking a solid tumor. *Endoscopy* 2006; **38** Suppl 2: E12-E13 [PMID: 17366384 DOI: 10.1055/s-2006-944862]
24 **Braffman B**, Keller R, Gendal ES, Finkel SI. Subdiaphragmatic bronchogenic cyst with gastric communication. *Gastrointest Radiol* 1988; **13**: 309-311 [PMID: 3169478 DOI: 10.1007/bf01889087]
25 **Matsubayashi J**, Ishida T, Ozawa T, Aoki T, Koyanagi Y, Mukai K. Subphrenic bronchopulmonary foregut malformation with pulmonary-

sequestration-like features. *Pathol Int* 2003; **53**: 313-316 [PMID: 12713567 DOI: 10.1046/j.1440-1827.2003.01475.x]

26 **Hedayati N**, Cai DX, McHenry CR. Subdiaphragmatic bronchogenic cyst masquerading as an "adrenal incidentaloma". *J Gastrointest Surg* 2003; **7**: 802-804 [PMID: 13129560 DOI: 10.1016/s1091-255x(03)00134-3]

27 **Rubio CA**, Orrego A, Willén R. Bronchogenic gastric cyst. A case report. *In Vivo* 2005; **19**: 383-385 [PMID: 15796201]

28 **Song SY**, Noh JH, Lee SJ, Son HJ. Bronchogenic cyst of the stomach masquerading as benign stromal tumor. *Pathol Int* 2005; **55**: 87-91 [PMID: 15693855 DOI: 10.1111/j.1440-1827.2005.01788.x]

29 **Wakabayashi H**, Okano K, Yamamoto N, Suzuki Y, Inoue H, Kadota K, Haba R. Laparoscopically resected foregut duplication cyst (bronchogenic) of the stomach. *Dig Dis Sci* 2007; **52**: 1767-1770 [PMID: 17404869 DOI: 10.1007/s10620-006-9580-8]

30 **Jiang L**, Jiang L, Cheng N, Yan L. Bronchogenic cyst of the gastric fundus in a young woman. *Dig Liver Dis* 2010; **42**: 826 [PMID: 19616489 DOI: 10.1016/j.dld.2009.06.014]

31 **Kurokawa T**, Yamamoto M, Ueda T, Enomoto T, Inoue K, Uchida A, Kikuchi K, Ohkohchi N. Gastric bronchogenic cyst histologically diagnosed after laparoscopic excision: report of a case. *Int Surg* 2013; **98**: 455-460 [PMID: 24229041 DOI: 10.9738/INTSURG-D-12-00038.1]

32 **Sun L**, Lu L, Fu W, Li W, Liu T. Gastric bronchogenic cyst presenting as a gastrointestinal stromal tumor. *Int J Clin Exp Pathol* 2015; **8**: 13606-13612 [PMID: 26722583]

33 **Chhaidar A**, Ammar H, Abdessayed N, Azzaza M, Gupta R, Abdennaceur N, Bdioui A, Mokni M, Ali AB. Large bronchogenic cyst of stomach: A case report. *Int J Surg Case Rep* 2017; **34**: 126-129 [PMID: 28391172 DOI: 10.1016/j.ijscr.2017.03.021]

34 **Erbenová A**, Placrová B, Špůrková Z, Horák P. Bronchogenic cyst of gastric cardia - case report and literature review. *Rozhl Chir* 2021; **100**: 507-511 [PMID: 35021843 DOI: 10.33699/PIS.2021.100.10.507-511]

35 **Wang HB**, Wang SL, Yu JW. A gastric bronchogenic cyst pre-operatively misdiagnosed as a gastrointestinal stromal tumor. *Asian J Surg* 2022; **45**: 2022-2023 [PMID: 35527127 DOI: 10.1016/j.asjsur.2022.04.067]

36 **Li C**, Zhang XW, Zhao CA, Liu M. Abdominal bronchogenic cyst: A rare case report. *World J Clin Cases* 2022; **10**: 12671-12677 [PMID: 36579087 DOI: 10.12998/wjcc.v10.i34.12671]

37 **Lv X**, Zhang M, Zhang T. A case of ectopic bronchogenic and enterogenous cysts over the gastric wall. *Asian J Surg* 2024; **47**: 1047-1048 [PMID: 37945402 DOI: 10.1016/j.asjsur.2023.10.098]

38 **Qian JW**, Qian ZH, Wu YY, Liu PF. Bronchogenic cyst of stomach: A case report. *Asian J Surg* 2023; **46**: 2896-2898 [PMID: 36805727 DOI: 10.1016/j.asjsur.2023.01.101]

39 **Ma P**, Gao F, Zhu W, Cao Y. Bronchial-origin gastric cyst: A rare case report. *Asian J Surg* 2023; **46**: 988-989 [PMID: 35961895 DOI: 10.1016/j.asjsur.2022.07.106]

40 **Lin Z**, Cao Q. Gastric bronchogenic cyst. *Rev Esp Enferm Dig* 2023; **115**: 665-666 [PMID: 37882202 DOI: 10.17235/reed.2023.9964/2023]

41 **Liu T**, Li J. Gastric cardia bronchogenic cyst with prolonged belching. *Rev Esp Enferm Dig* 2023 [PMID: 37539531 DOI: 10.17235/reed.2023.9865/2023]

42 **Terayama M**, Kumagai K, Kawachi H, Makuuchi R, Hayami M, Ida S, Ohashi M, Sano T, Nunobe S. Optimal resection of gastric bronchogenic cysts based on anatomical continuity with adherent gastric muscular layer: A case report. *World J Gastrointest Surg* 2023; **15**: 1216-1223 [PMID: 37405090 DOI: 10.4240/wjgs.v15.i6.1216]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2263-2268

DOI: 10.12998/wjcc.v12.i13.2263

ISSN 2307-8960 (online)

CASE REPORT

Airway management of a patient with linear immunoglobulin A bullous dermatosis: A case report

Olga C Nin, Robert Hutnik, Neil N Chheda, David Hutchinson

Specialty type: Anesthesiology

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: Esch M, Germany

Received: December 19, 2023
Peer-review started: December 19, 2023
First decision: January 10, 2024
Revised: January 24, 2024
Accepted: March 26, 2024
Article in press: March 26, 2024
Published online: May 6, 2024

Olga C Nin, Robert Hutnik, David Hutchinson, Department of Anesthesiology, University of Florida College of Medicine, Gainesville, FL 32610, United States

Neil N Chheda, Department of Otolaryngology, University of Florida College of Medicine, Gainesville, FL 32610, United States

Corresponding author: Olga C Nin, MD, Associate Professor, Department of Anesthesiology, University of Florida College of Medicine, 1600 SW Archer Road, PO Box 100254, Gainesville, FL 32610, United States. onin@anest.ufl.edu

Abstract

BACKGROUND

There is limited literature on managing the airway of patients with linear immunoglobulin A (IgA) bullous dermatosis, a rare mucocutaneous disorder that leads to the development of friable bullae. Careful clinical decision making is necessary when there is a risk of bleeding into the airway, and a multidisciplinary team approach may lead to decreased patient morbidity during these high-risk scenarios, especially when confronted with an unusual cause for bleeding.

CASE SUMMARY

A 45-year-old African American female presented to our ambulatory surgical center for right corneal transplantation due to corneal perforation after blunt trauma in the setting of cicatricial conjunctivitis and diffuse corneal neovascularization from linear IgA bullous dermatosis. The diagnosis of IgA dermatosis was recent, and the patient had been lost to follow-up. The severity of the disease and extent of airway involvement was unknown at the time of the surgery. Significant airway bleeding was noticed upon intubation and the otorhinolaryngology team had to be called to the operating room. The patient required transfer to the intensive care unit where a multidisciplinary team was involved in her case. The patient was extubated on postoperative day 4.

CONCLUSION

A multidisciplinary approach to treating this disease is the best course of action before a surgical procedure. In our case, key communication between the surgery, anesthesia, and dermatology teams led to the quick and safe treatment of our patient's disease. Ambulatory surgery should not be considered for these cases unless they are in full remission and there is no mucous membrane involvement.

Key Words: Airway management; Bleeding risk; Linear immunoglobulin A bullous dermatosis; Multidisciplinary approach; Outpatient procedure; Case report

Core Tip: Linear immunoglobulin A bullous dermatosis, a rare mucocutaneous disorder, can lead to significant airway bleeding due to the presence of friable bullae. Airway emergencies in ambulatory surgical centers can be very high risk. A multidisciplinary discussion of the disease and patient optimization needs to be performed before the day of surgery. These cases should be treated in the inpatient setting where resources are most easily accessible, and an ear, nose, and throat team should be available.

Citation: Nin OC, Hutnik R, Chheda NN, Hutchinson D. Airway management of a patient with linear immunoglobulin A bullous dermatosis: A case report. *World J Clin Cases* 2024; 12(13): 2263-2268
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2263.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2263

INTRODUCTION

Linear immunoglobulin A (IgA) bullous dermatosis (LABD) is an autoimmune mucocutaneous disease involving disruption of the dermoepidermal junction, resulting in the formation of blisters or bullae[1]. IgA autoantibodies attach to antigens in the skin's basement membrane and mucosa, causing these clinical findings. Lesions typically appear as clear or hemorrhagic bullae with an urticarial base on the face, trunk, buttocks, and skin overlying joint sites. In 60% to 80% of cases, mucosal membranes, including the eyes and oral cavity, are also affected[2]. Patients with mucosal involvement can experience morbidity related to corneal scarring and pharyngeal or esophageal stricture formation, requiring surgical intervention. There is limited literature on the intraoperative management of these patients, especially regarding airway instrumentation.

CASE PRESENTATION

Chief complaints

Decreased vision in the right eye.

History of present illness

A 45-year-old African American female presented to our ambulatory surgical center for right corneal transplantation due to corneal perforation in the setting of cicatricial conjunctivitis, as well as diffuse corneal neovascularization from LABD. At the time of the surgery, the severity of the disease was unknown. The patient had been lost to follow-up with dermatology and was not taking any medications for her LABD. The severity of the patient's history of LABD diagnosis was only discovered after the operating room case and an in-depth conversation with her dermatologist. The patient's LABD was considered idiopathic per her dermatologist, given the absence of any inciting medication or infection. She began experiencing skin rashes and blisters in 2017. In June 2019, she sought medical attention due to mucosal membrane involvement, but at that time no medical therapy was initiated. In January 2021, she developed visual problems with her right eye and, following a confirmatory skin biopsy, was officially diagnosed with LABD in February 2021. Dapsone therapy was initiated in April 2021. She was hospitalized in May 2021 for a corneal ulcer of the right eye and was treated with one dose of intravenous immunoglobulin (IVIG), rituximab infusions, and 25 mg of oral dapsone twice each day. The patient received 4 doses of rituximab and was lost to follow-up until August 2021. This case was emergent due to the risk of permanent visual loss. The surgery was scheduled at the freestanding outpatient surgical center due to the presence of necessary equipment, personnel, and materials.

History of past illness

The patient's medical history consisted of anxiety, depression, chronic benzodiazepine dependence, chronic back pain, hypertension, constipation, genital herpes, prior cocaine abuse, and LABD.

Personal and family history

The patient had a strong family history of autoimmune disease, with paternal cousins having sarcoidosis, systemic lupus erythematosus, and multiple sclerosis. The patient was married and lived a few hours away from our hospital location. She was of a lower socioeconomic background and had trouble affording medications for her treatment.

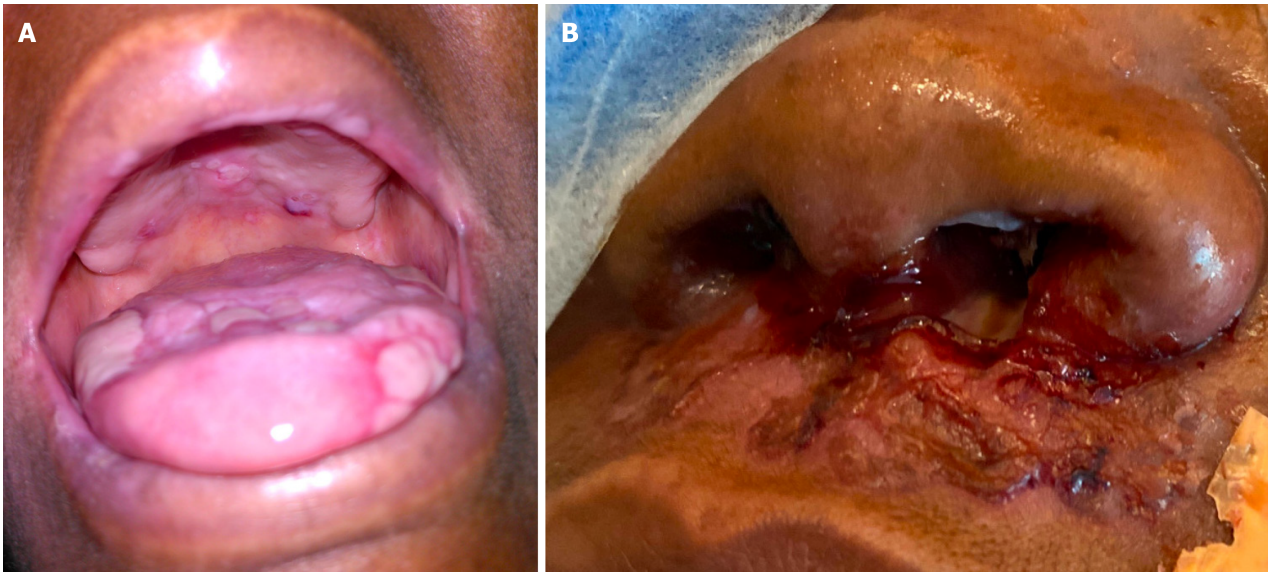

Figure 1 Preoperative tongue and nasal lesions. A: Preoperative tongue lesions; B: Preoperative nasal lesions.

Physical examination

The patient had visible nasal ulcers and some white ulcers on her tongue (Figure 1). There was no history of bleeding in her mouth or of previous anesthetic complications. The rest of the physical exam was normal.

Laboratory examinations

No laboratories were needed for preoperative evaluation before this emergent case.

Imaging examinations

Figure 1 shows the preoperative oral and nasal lesions.

MULTIDISCIPLINARY EXPERT CONSULTATION

On August 10, 2021, the patient presented to the free-standing ambulatory surgical center for a corneal transplant of the right eye under general anesthesia. On the day of surgery, an anesthetic preoperative evaluation and a focused physical examination were performed. The patient had visible clear nasal ulcers and white ulcers on her tongue (Figure 1). There was no history of bleeding in her mouth or of previous anesthetic complications. General anesthesia was indicated, given the type of surgery; therefore, airway manipulation was required. The decision was made to intubate using a C-MAC for optimal airway visualization due to the unknown extent of mucosal involvement of her disease, and complete visualization of the oropharynx was desirable. A peripheral intravenous catheter was placed, and 2 mg of intravenous midazolam was administered before proceeding to the operating room. She received a standard intravenous anesthesia induction with propofol, fentanyl, lidocaine, and rocuronium.

Upon careful placement of the C-MAC Mac 3 blade, ulcerative lesions were observed throughout the oropharynx, epiglottis, and vallecula. There was spontaneous and diffuse bleeding from lesions in the vallecula, even with minimal manipulation, and the airway was quickly secured using a wire-reinforced 7.0 endotracheal tube. A wire-reinforced tube was chosen so the endotracheal tube could be taped to the chin for surgical exposure. The ear, nose, and throat (ENT) team was called to the operating room to evaluate the bleeding, where they performed a visual examination by C-MAC, suctioned, and placed five epinephrine-soaked (0.1 mg/mL) cottonoids in the oropharynx. After a discussion between the ENT and ophthalmology teams, the decision was made to proceed with the surgery and transfer the patient intubated after surgery to our institution's main hospital surgical intensive care unit under the care of the ENT team. This hospital is located 20 min from our free-standing outpatient facility. Upon successful completion of the surgical procedure, the patient was transferred intubated to the surgical intensive care unit *via* ambulance.

The patient was transferred in stable condition to the main hospital by ambulance under the direct supervision of the attending anesthesiologist. To assess the extent of the ulcerative lesions before trial extubation, a bedside bronchoscopy was performed that revealed no ulcerative lesions in the trachea or bronchi. Ventilator weaning commenced, and extubation was planned in the operating room when clinically indicated. On postoperative day 1, the patient was taken to the operating room where a micro-suspended direct laryngoscopy was performed. Despite minimal manipulation, diffuse mucosal bleeding in the oral cavity and oropharynx was observed. The oral cavity was packed for hemostasis, and the patient remained intubated (Figure 2).

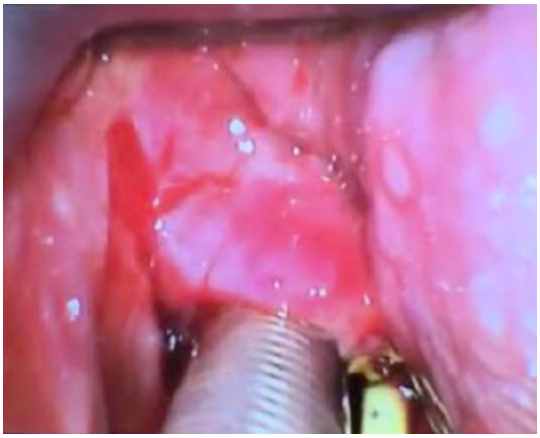

Figure 2 Hypopharynx of the airway in the operating room on postoperative day 1.

Due to the severity and extent of the disease, the dermatology team re-initiated dapsone therapy and prescribed a course of intravenous methylprednisolone and a single dose of both cyclophosphamide and IVIG. Overnight, the patient was observed to have a few isolated episodes of agitation that resulted in spontaneous bleeding; therefore, the oropharynx was repacked with epinephrine- and tranexamic acid-soaked Kerlix. On postoperative day 3, the ENT team removed the oral packing. On postoperative day 4, the patient returned to the operating room and was successfully extubated to cool, humidified air *via* a face mask. She received a dose of intravenous cyclophosphamide and was discharged 2 d later with a course of prednisone daily and dapsone with a follow-up for a second intravenous cyclophosphamide infusion planned in 1 mo. A timeline of this case can be seen in Figure 3.

FINAL DIAGNOSIS

Right corneal perforation due to cicatricial conjunctivitis and diffuse corneal neovascularization from LABD.

TREATMENT

Patient was treated with dapsone and a course of prednisone. In the hospital the patient was given a course of intravenous methylprednisolone and a single dose of both cyclophosphamide and IVIG. She subsequently received monthly IV cyclophosphamide home infusions.

OUTCOME AND FOLLOW-UP

The patient continues on monthly cyclophosphamide infusions and daily oral prednisone and dapsone. She is seeing her dermatologist monthly.

DISCUSSION

LABD is a markedly rare disease, so very few anesthesiologists have experience managing these patients. In Europe, the incidence is approximately 0.1 per million. It presents in a bimodal age distribution: children aged six months to 10 years old (mean age five years old, rarely persisting past puberty) and adults over 60 years old. LABD is typically triggered by infection but can also be drug-induced by exposure to antibiotics (most notably vancomycin), antihypertensives, and nonsteroidal anti-inflammatory drugs. While some LABD presentations are idiopathic, associations with other systemic diseases have been demonstrated, such as ulcerative colitis, systemic lupus erythematosus, and lymphoproliferative disorders. Up to 5% of reported cases of LABD have been associated with lymphoid malignancies including Hodgkin's or B-cell lymphoma. Idiopathic LABD may persist for decades with episodes of relapse/remission. In our patient, LABD was diagnosed in February 2021 and deemed idiopathic[3].

Diagnosis is confirmed by clinical, histopathological, and immunological data. Treatment varies depending on the degree of severity of disease and the potential inciting event. In suspected drug-induced LABD, removal of the offending medication may result in gradual resolution. The mainstay of treatment in LABD is dapsone (50-150 mg daily in adults), which can begin resolution of lesions within 72 h. Per a collection of case reports, median length of dapsone treatment is 26 mo[4]. Common side effects of dapsone include hemolytic anemia (G6PD deficiency), methemoglobinemia, motor

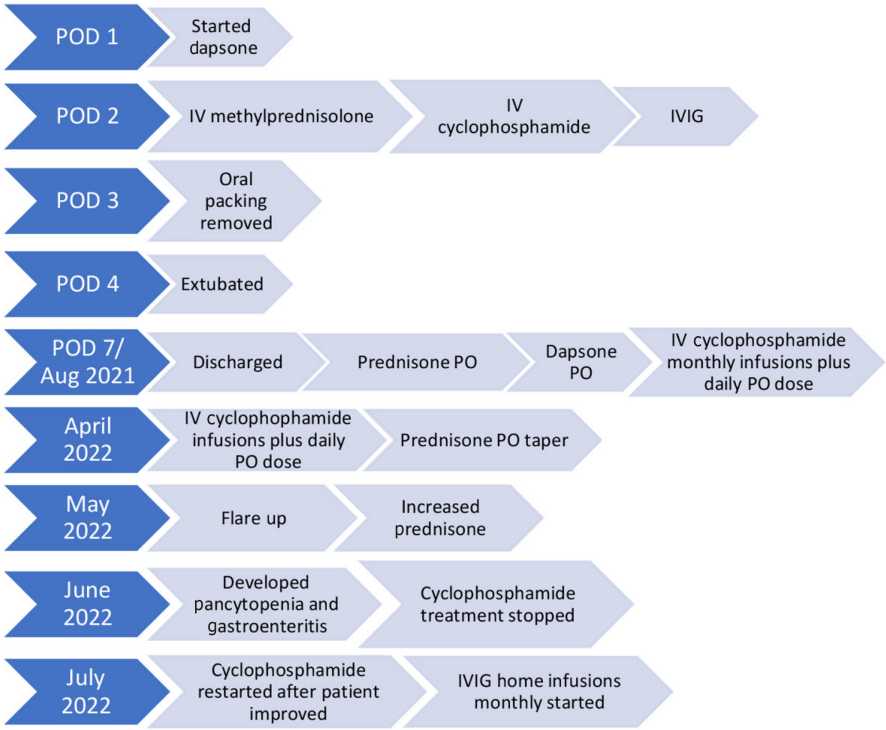

Figure 3 Timeline of case. IV: Intravenous; IVIG: Intravenous immunoglobulin; PO: By mouth.

neuropathy, hepatitis, cholestatic jaundice, and hypoalbuminemia. Routine complete blood count, liver function tests, and G6PD levels should be checked while on dapsone therapy. Immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil, and cyclophosphamide) and corticosteroids are other modalities used for treatment. Chronic use of cyclophosphamide can lead to the onset of malignancies, such as bladder cancer[5]. Other treatment options include colchicine, tetracyclines, sulfonamides, nicotinamides, and IVIG.

Dermatology input and medication management were key to improving our patient's outcome. She continued on dapsone and was also given intravenous methylprednisolone, IVIG, and a dose of cyclophosphamide to treat her mucous membrane lesions and allow for extubation.

For an anesthesiologist caring for patients with LABD, the most critical information needed is the presence of mucous membrane involvement and airway compromise. In the event of airway bleeding with this disease, ENT intervention to control bleeding with epinephrine and tranexamic acid is necessary to protect the airway as medical treatment begins to take effect. Our ambulatory surgical center and the ENT clinics are all in the same building, helping our team initiate treatment quickly.

For our case, the severity and details of the disease were unknown at the time of the surgery. The surgery was emergent and needed to proceed to try to save vision in her eye. In our health system, corneal transplants are only done at our ambulatory center; necessary supplies and equipment are not present in the hospital. The patient did not report as scheduled to the anesthesia preoperative clinic so the first time the patient was evaluated by the anesthesia team was on the day of her surgery. Given the emergent need to preserve her vision, the necessity of performing the surgery at our ambulatory center, and the absence of any history of airway bleeding, the decision was made to proceed. Going forward, such cases must be completed in the inpatient setting; our system now has plans in place to transfer necessary equipment and staff to the inpatient setting as necessary.

CONCLUSION

To our knowledge, this is the first case report of the anesthetic implications of LABD[4] involving the mucous membranes of the nasal cavities and oropharynx. Given the lack of information on this disease and its extent in this patient, our anesthesia team was unaware of the lesions we would encounter throughout both the oropharynx and hypopharynx. Upon intubation, we understood the extent of the lesions and their friability. In retrospect, we should have consulted the ENT team preoperatively for a preoperative nasopharyngoscopy to determine the extent of the lesions. Had the patient attended her preoperative clinic appointment, our team may have had more information available.

A multidisciplinary approach to treating this disease is the best course of action before a surgical procedure. Ambulatory surgery should not be considered for these cases unless they are in full remission and there is no mucous membrane involvement. In our case, key communication between the surgical services, anesthesia, and dermatology teams occurred after the surgery and led to quick and safe treatment. We present this case to bring forward important anesthetic considerations for this rare disease.

This manuscript was prepared in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 privacy regulations and adheres to applicable Enhancing the Quality and Transparency of Health Research guidelines (CARES [for CAse REportS] checklist). Written patient consent and written HIPAA authorization for the publication of this case report were obtained using a standardized consent form. Institutional Review Board consent was not required.

Learning points: (1) Mucous lesions in the oropharynx and hypopharynx can be extremely friable and cause bleeding upon minimal manipulation; (2) Early dermatology intervention and medication administration is key to a quick recovery from an acute exacerbation; and (3) Proper planning of operating room intervention in a hospital setting is vital to mitigate potential airway complications. These cases should not be done in an ambulatory setting.

ACKNOWLEDGEMENTS

The authors thank Bryan Penberthy, MFA, of the University of Florida College of Medicine Department of Anesthesiology's Communications & Publishing office for his editorial assistance with this manuscript.

FOOTNOTES

Author contributions: Chheda NN and Hutchinson D critically reviewed and revised the manuscript; Nin OC wrote the original draft and critically reviewed and revised the manuscript.

Informed consent statement: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict-of-interest statement: All authors declare that they have no conflict of interest to disclose.

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: United States

ORCID number: Olga C Nin 0009-0008-9490-8197.

S-Editor: Liu JH
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Chen S**, Mattei P, Fischer M, Gay JD, Milner SM, Price LA. Linear IgA bullous dermatosis. *Eplasty* 2013; **13**: ic49 [PMID: 23882302]
2 **Guide SV**, Marinkovich MP. Linear IgA bullous dermatosis. *Clin Dermatol* 2001; **19**: 719-727 [PMID: 11705681 DOI: 10.1016/s0738-081x(00)00185-1]
3 **Lammer J**, Hein R, Roenneberg S, Biedermann T, Volz T. Drug-induced linear IgA bullous dermatosis: a case report and review of the literature. *Acta Derm Venereol* 2019; **99**: 508-515 [PMID: 30809685 DOI: 10.2340/00015555-3154]
4 **Lings K**, Bygum A. Linear IgA bullous dermatosis: a retrospective study of 23 patients in Denmark. *Acta Derm Venereol* 2015; **95**: 466-471 [PMID: 25350667 DOI: 10.2340/00015555-1990]
5 **Vale ECSD**, Dimatos OC, Porro AM, Santi CG. Consensus on the treatment of autoimmune bullous dermatoses: dermatitis herpetiformis and linear IgA bullous dermatosis - Brazilian Society of Dermatology. *An Bras Dermatol* 2019; **94**: 48-55 [PMID: 31166403 DOI: 10.1590/abd1806-4841.2019940208]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2269-2274

DOI: 10.12998/wjcc.v12.i13.2269

ISSN 2307-8960 (online)

CASE REPORT

Deferred revascularization in diabetic patient according to combined invasive functional and intravascular imaging data: A case report

Arif Al Nooryani, Wael Aboushokka, Branko Beleslin, Biljana Nedeljkovic-Beleslin

Specialty type: Cardiac and cardiovascular systems

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: Ding H, China

Received: December 22, 2023
Peer-review started: December 22, 2023
First decision: January 10, 2024
Revised: January 25, 2024
Accepted: March 20, 2024
Article in press: March 20, 2024
Published online: May 6, 2024

Arif Al Nooryani, Wael Aboushokka, Department of Cardiology, Al Qassimi Hospital, Sharjah 1234, United Arab Emirates

Branko Beleslin, Department of Cardiology, Medical Faculty, University of Belgrade, Belgrade 11000, Serbia

Biljana Nedeljkovic-Beleslin, Institute of Endocrinology, Diabetes and Metabolic Disorders, Univeristy Clinical Center of Serbia, Belgrade 11000, Serbia

Biljana Nedeljkovic-Beleslin, Department of Internal Medicine/Endocrinology, Medical faculty, University of Belgrade, Belgrade 11000, Serbia

Corresponding author: Branko Beleslin, FACC, FESC, MD, PhD, Full Professor, Department of Cardiology, Medical Faculty, University of Belgrade, Dr Subotica 8, Belgrade 11000, Serbia. branko.beleslin@gmail.com

Abstract

BACKGROUND

Invasive functional evaluation by fractional flow reserve (FFR) is considered as a gold standard for the evaluation of intermediate coronary stenosis. However, in patients with diabetes due to accelerated progression of atherosclerosis the outcome may be worse even in the presence of negative functional testing.

CASE SUMMARY

We present a case of 55-year-old male diabetic patient who was admitted for chest pain. Diagnostic coronary angiography disclosed 2 intermediate stenoses of the obtuse marginal branch with no evidence of restenosis on previously implanted stent. Patient undergone invasive functional testing of intermediate lesion with preserved FFR (0.88), low coronary flow reserve (1.2) and very high index of microvascular resistance (84). Due to discrepancy in invasive functional parameters, intravascular imaging with optical coherence tomography showed fibrotic stenoses without signs of thin-sup fibroatheroma. Because of the preserved FFR and no signs of vulnerable plaque, the interventional procedure was deferred and the patient continued with optimal medications.

CONCLUSION

Combined functional and anatomic imaging of intermediate coronary stenosis in diabetic patients represent comprehensive contemporary decision pathway in the management of the patients.

Key Words: Fractional flow reserve; Coronary flow reserve; Index of microvascular resistance; Optical coherence tomography; Intermediate coronary stenosis; Case report

Core Tip: We present a case of the diabetic patient with moderate-to-severe coronary stenosis with preserved fractional flow reserve, low coronary flow reserve, high index of microvascular resistance and intravascular optical coherence tomography image demonstrating fibrotic plaque without signs of thin-cup fibroatheroma. Combined functional and anatomic imaging of intermediate coronary stenosis represent comprehensive contemporary decision pathway in the management of the patients.

Citation: Al Nooryani A, Aboushokka W, Beleslin B, Nedeljkovic-Beleslin B. Deferred revascularization in diabetic patient according to combined invasive functional and intravascular imaging data: A case report. *World J Clin Cases* 2024; 12(13): 2269-2274
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2269.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2269

INTRODUCTION

Fractional flow reserve (FFR) is considered as a functional gold standard for the evaluation of coronary stenosis, and the decision for management of intermediate coronary stenosis should be based on functional evaluation[1]. Still, there are some clinical conditions, such as patients with diabetes mellitus (DM) where the value of FFR is still not so well validated and defined. In fact, the previous data have shown that the outcome of deferred lesions according to negative FFR is worse in patients with DM in comparison to non-diabetic patients[2]. In addition, COMBINE optical coherence tomography (OCT) FFR trial has demonstrated additional value of intravascular OCT imaging in stratification of diabetic patients with the negative FFR[3].

CASE PRESENTATION

Chief complaints

We present a case of 55-year-old male diabetic patient who was admitted to our clinic for chest pain syndrome. His chest pain appeared occasionally during last 2 wk and had rather atypical presentation both at rest and after exertion. It was not accompanied by any other symptoms like dyspnea, fatigue or nausea. Due to recent appearance of chest pain of uncertain origin as well as previous implanted stent in left main coronary artery, the patient was referred directly to invasive coronary angiography without non/invasive functional testing.

History of present illness

Three years ago, he suffered from non-ST segment elevation myocardial infarction due to critical lesion of the ostial circumflex (Cx) artery which was treated with implantation of one drug-eluting stent (DES) with crossover from left main to Cx coronary artery (Figure 1). Following DES implantation from left main to Cx, 2 intermediate stenoses of the proximal part of the long second obtuse marginal branch (Figure 1A, orange arrows) were observed that were estimated to be not significant without a need for further intervention. Four years ago, he also had percutaneous coronary intervention with one DES implantation in the right coronary artery (RCA). Since the last coronary event, the patient has been free of any symptom, he was feeling physically and emotionally fit. His medications included aspirin, beta-blockers, and rosuvastatin.

History of past illness

Patient has been obese (102 kg), and has elevated HbA1c levels with no regular anti-diabetic therapy.

Personal and family history

Patient denies smoking, doesn't have hypertension, and denies alcohol abuse. He has elevated cholesterol levels treated with statins.

Physical examination

On physical examination there was no remarkable finding. His blood pressure was 130/80 mmHg. His heart sounds were normal, without significant murmurs. His lung fields were clear, and there were no signs of heart failure. His ECG was normal with sinus rhythm, heart rate of 62/min, without conduction and rhythm disturbances as well as ST-T changes.

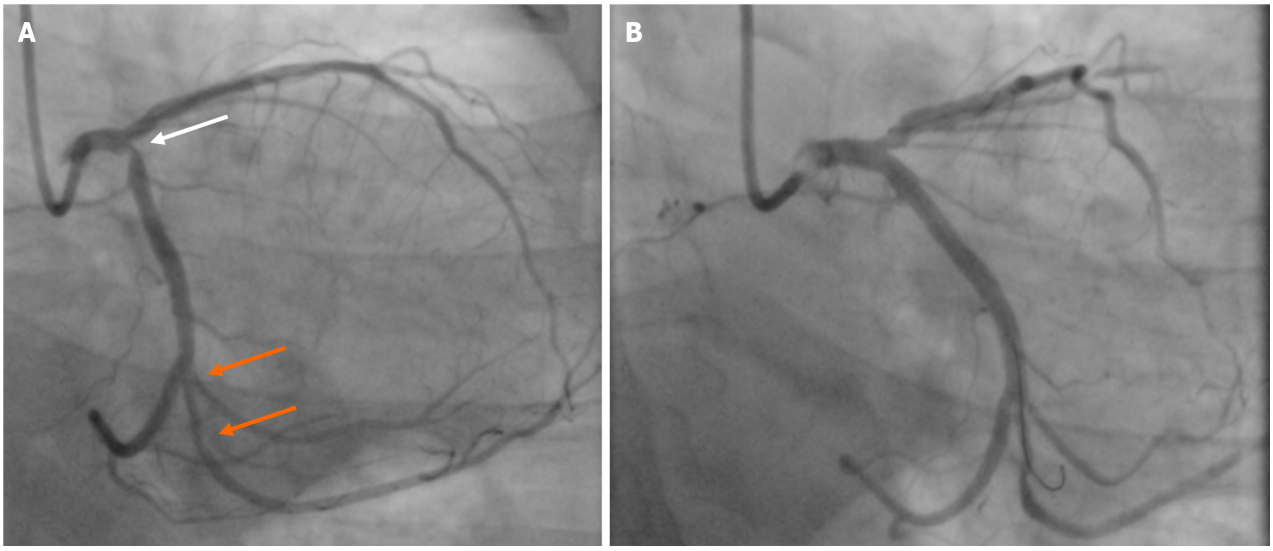

Figure 1 Angiographic images of left coronary artery before (A) and after (B) intervention. White arrow shows stenosis in the ostial part of circumflex artery stenosis, and two orange arrows depicts 2 tandem stenoses in the obtuse marginal branch. Coronary angiography after stenting from left main to circumflex coronary artery.

Laboratory examinations

The laboratory values showed normal blood count, elevated low density lipoprotein (LDL)-cholesterol of 2.3 mmol/L, HbA1c was 6.1%, and the renal function was preserved with estimated glomerular filtration rate of 75 mL/min/1.73m^2.

Imaging examinations

His cardiac ultrasound was normal with preserved ejection fraction, there were no wall motion abnormalities, the heart chambers were of normal dimensions as well as function and appearance of the valves. Coronary angiography showed no signs of restenosis in the left main to Cx stent, mild ostial stenosis/pinching of left anterior descending artery was unchanged to previous procedure, and 2 moderate-to-severe stenoses in the ostio-proximal part of the second obtuse marginal seem slightly tighter (Figure 2A) than 3 years ago. RCA was without signs of stenosis or restenosis. As there was no non-invasive functional testing for evaluation of myocardial ischemia, the decision was made to perform immediately invasive physiologic evaluation of the Cx obtuse marginal artery using Coroventis platform (Coroventis CoroFow Cardiovascular system, Abbot) and pressure wire (PressureWire X, Abbot) for the invasive functional assessment with FFR during hyperemia with i.v. adenosine, resting full-cycle ratio (RFR), coronary flow reserve (CFR) by thermodilution and index of microvascular resistance (IMR) for the assessment of microvascular dysfunction. FFR was preserved with a value of 0.88, RFR was also preserved with a value of 0.90 but CFR was very low (1.2) with a very high IMR of 84 (Figure 2B). As there was a discrepancy in functional parameters (FFR preserved, CFR low) pointing out to microvascular dysfunction, OCT imaging (DragonFly OpStar imaging catheter, Abbot) was also applied to evaluate the more detailed anatomical characteristics of the lesion. OCT imaging confirmed the significant fibrotic tandem stenoses but without signs of thin-cup fibroatheroma (Figure 3, co-registration of angiographic and OCT imaging, Ultreon 1.0 software for OCT intravascular imaging, Abbot) or plaque vulnerability.

FINAL DIAGNOSIS

The diagnosis was that the patient had non-flow limiting coronary stenoses without signs of vulnerable plaque by OCT, and with significantly deteriorated microvascular function according to low coronary CFR and high IMR, which might be clinically defined as microvascular disease producing angina or chest pain syndrome.

TREATMENT

As the patient had negative or normal FFR value with no intravascular imaging signs of vulnerable plaque, the revascularization was deferred and the patient was recommended to continue with aspirin and to increase dosage of lipid lowering therapy and add ezetimibe to optimize LDL-cholesterol levels. In addition, due to microvascular dysfunction, as demonstrated with very low CFR and very high IMR, diltiazem and ranolazine were added to his therapy. Gluformine was also added to control diabetes.

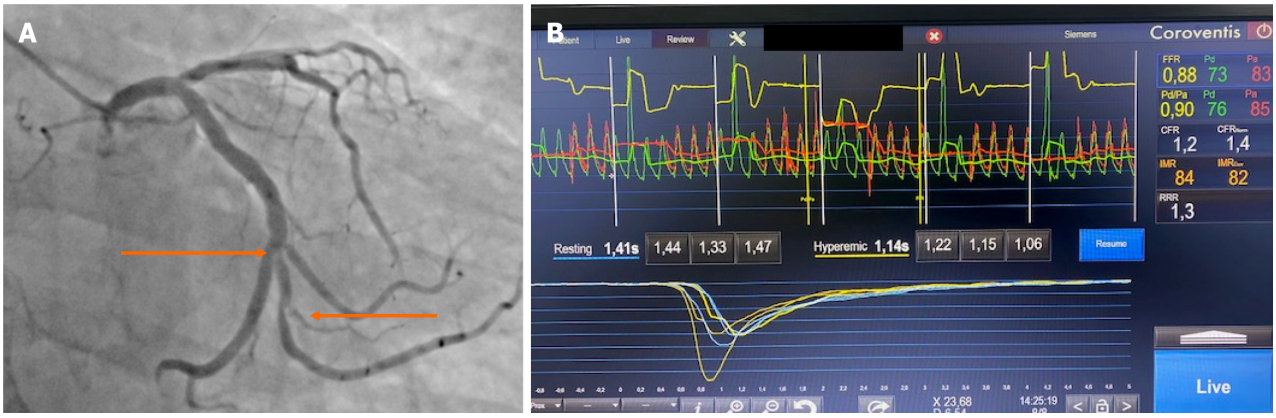

Figure 2 Invasive functional parameters of the obtuse marginal stenoses. A: Coronary stenoses in obtuse marginal branch are shown in orange arrows; B: Corresponding fractional flow reserve, coronary flow reserve, and index of microvascular resistance values.

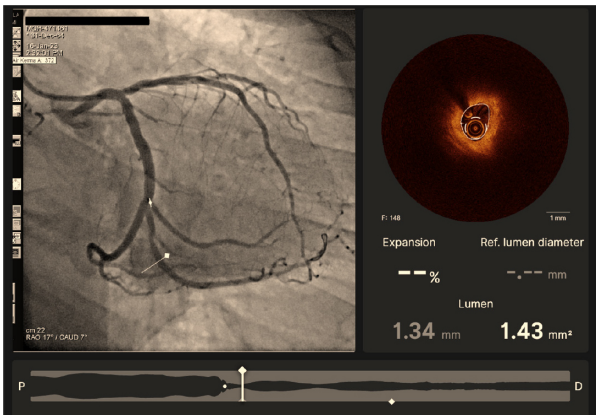

Figure 3 Co-registration images of angiography (left) and optical coherence tomography cross-section imaging (right).

OUTCOME AND FOLLOW-UP

His six-month follow-up was uneventful with very rare atypical chest pain episodes.

DISCUSSION

The optimal diagnostic strategy in patients with diabetes remains controversial and challenging. The previous studies have shown low event rates in asymptomatic patients but also disparities (different cardiovascular risk groups, different non-invasive and invasive testing) in the management and screening of those patients[4]. According to the latest European Society of Cardiology guidelines[5], functional stress testing and computed tomography angiography may be considered and indicated in patients with diabetes as well. On the other hand, earlier studies with stress echocardiography have demonstrated that significantly more patients with diabetes have ischemia on stress testing, and that the prognosis in patients without ischemia is still worse in diabatic than non-diabatic patients[6]. In addition, noninvasively measured (2D echocardiography) CFR provides independent prognostic information in diabetic and non-diabetic patients and negative dipyridamole stress echocardiography - an abnormal CFR is associated with almost twice worse prognoses in diabetic in comparison to non-diabetic patients[7]. Finally, Murthy *et al*[8] have demonstrated that abnormal CFR by positron emission tomography is independent predictor of cardiac mortality in patients with diabetes and without known coronary artery disease.

Regarding invasive functional testing, Kennedy *et al*[2] has shown that deferred revascularization in 250 patients according to FFR have been connected with worse outcome in patients with diabetes in comparison to non-diabetic patients, in terms of significant more revascularizations (16% *vs* 6%) in the mean follow-up time of 40 months. Although earlier studies[9,10] have not shown significant differences in the outcome between diabetic and non-diabetic patients according to FFR values this issue remains controversial. Therefore, COMBINE OCT FFR[3] investigated the impact of OCT-detected thin-cap fibroatheroma (TCFA) on clinical outcomes of patients with diabetes patients with FFR negative lesions. The study[3] revealed that among 550 enrolled diabetic patients with ≥ 1 FFR-negative lesions, TCFA-positive patients represented 25% of this population and were associated with a five-fold higher rate of MACE despite the absence of ischemia as demonstrated by negative FFR > 0.80. This discrepancy between the impact of vulnerable plaque and

ischemia on future adverse events may explain worse outcome in diabetic patients with negative FFR. On the other hand, diabetic patients with negative FFR and without TCFA remained to have very low event rate of 3.1% over mean follow-up of 18 months[3]. Still the question remains on the outcome of vulnerable plaques due to the low hard event rates and limited positive predictive value[11]. Regarding therapeutic options, serial intravascular imaging has demonstrated that lipid lowering therapy led to regression of coronary plaque volume and increase in fibroatheroma cup thickness proportional to decrease in cholesterol levels[12].

Our patient presented with anatomically significant but functionally non-significant coronary lesion without signs of plaque vulnerability as shown by thick-cap fibroatheroma, but with significant disturbance of coronary microcirculation as shown by low CFR and very high IMR. The microcirculatory dysfunction may be present in diabetic patients and the cause of positive functional testing and chest pain[13]. In fact, the traditional risk factors may all contribute to coronary microvascular dysfunction and structural remodeling of the microcirculation. In the WISE study[14], chest pain, diabetes, smoking, CAD severity were all independent predictors of hard cardiovascular events. The evaluation of microcirculatory dysfunction has gained a lot of interest in the last years and specific algorithms have been developed to interrogate this clinical condition[15]. Optimal therapy for microcirculatory dysfunction has not been established yet but calcium channel blockers, nebivolol, ranolazine, trimetazidine, ACE inhibitors have been associated with beneficial effects in microvascular angina[15].

CONCLUSION

The invasive functional evaluation combined with intravascular imaging have complementary diagnostic and prognostic role and therefore a contemporary evaluation of coronary stenosis, particularly in diabetic patients whenever possible and available should include both functional and intravascular imaging data for the best patient management and decision making.

ACKNOWLEDGEMENTS

The authors would like to thank research medical nurses Ruwaide Najeeb and chief Cath Lab medical nurse Fadwa el Rawi Ibrahim for their generous support in preparing the manuscript.

FOOTNOTES

Author contributions: Al Nooryani A contributed to conception, design, acquisition of data and final approval; Aboushokka W contributed to acquisition of data, analysis and interpretation; Beleslin B contributed to conception, design, acquisition of data, analysis, writing the case report; Nedeljkovic-Beleslin B contributed to analysis, interpretation and critical analysis.

Informed consent statement: Study participant provided informed written consent prior to diagnostic intervention.

Conflict-of-interest statement: All authors declare that they don't have conflict of interest.

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: United Arab Emirates

ORCID number: Arif Al Nooryani 0000-0002-0329-7954; Wael Aboushokka 0000-0002-6746-6742; Branko Beleslin 0000-0001-9452-8241; Biljana Nedeljkovic-Beleslin 0000-0002-1687-9297.

S-Editor: Zheng XM
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Neumann FJ**, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC

Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019; **40**: 87-165 [PMID: 30165437 DOI: 10.1093/eurheartj/ehy394]

2 **Kennedy MW**, Kaplan E, Hermanides RS, Fabris E, Hemradj V, Koopmans PC, Dambrink JH, Marcel Gosselink AT, Van't Hof AW, Ottervanger JP, Roolvink V, Remkes WS, van der Sluis A, Suryapranata H, Kedhi E. Clinical outcomes of deferred revascularisation using fractional flow reserve in patients with and without diabetes mellitus. *Cardiovasc Diabetol* 2016; **15**: 100 [PMID: 27431395 DOI: 10.1186/s12933-016-0417-2]

3 **Kedhi E**, Berta B, Roleder T, Hermanides RS, Fabris E, IJsselmuiden AJJ, Kauer F, Alfonso F, von Birgelen C, Escaned J, Camaro C, Kennedy MW, Pereira B, Magro M, Nef H, Reith S, Al Nooryani A, Rivero F, Malinowski K, De Luca G, Garcia Garcia H, Granada JF, Wojakowski W. Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial. *Eur Heart J* 2021; **42**: 4671-4679 [PMID: 34345911 DOI: 10.1093/eurheartj/ehab433]

4 **Clerc OF**, Fuchs TA, Stehli J, Benz DC, Gräni C, Messerli M, Giannopoulos AA, Buechel RR, Lüscher TF, Pazhenkottil AP, Kaufmann PA, Gaemperli O. Non-invasive screening for coronary artery disease in asymptomatic diabetic patients: a systematic review and meta-analysis of randomised controlled trials. *Eur Heart J Cardiovasc Imaging* 2018; **19**: 838-846 [PMID: 29452348 DOI: 10.1093/ehjci/jey014]

5 **Marx N**, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, Christodorescu RM, Crawford C, Di Angelantonio E, Eliasson B, Espinola-Klein C, Fauchier L, Halle M, Herrington WG, Kautzky-Willer A, Lambrinou E, Lesiak M, Lettino M, McGuire DK, Mullens W, Rocca B, Sattar N; ESC Scientific Document Group. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J* 2023; **44**: 4043-4140 [PMID: 37622663 DOI: 10.1093/eurheartj/ehad192]

6 **Cortigiani L**, Bigi R, Sicari R, Rigo F, Bovenzi F, Picano E. Comparison of prognostic value of pharmacologic stress echocardiography in chest pain patients with versus without diabetes mellitus and positive exercise electrocardiography. *Am J Cardiol* 2007; **100**: 1744-1749 [PMID: 18082519 DOI: 10.1016/j.amjcard.2007.07.026]

7 **Cortigiani L**, Rigo F, Gherardi S, Sicari R, Galderisi M, Bovenzi F, Picano E. Additional prognostic value of coronary flow reserve in diabetic and nondiabetic patients with negative dipyridamole stress echocardiography by wall motion criteria. *J Am Coll Cardiol* 2007; **50**: 1354-1361 [PMID: 17903635 DOI: 10.1016/j.jacc.2007.06.027]

8 **Murthy VL**, Naya M, Foster CR, Gaber M, Hainer J, Klein J, Dorbala S, Blankstein R, Di Carli MF. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. *Circulation* 2012; **126**: 1858-1868 [PMID: 22919001 DOI: 10.1161/CIRCULATIONAHA.112.120402]

9 **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]

10 **Domínguez-Franco AJ**, Jiménez-Navarro MF, Muñoz-García AJ, Alonso-Briales JH, Hernández-García JM, de Teresa Galván E. [Long-term prognosis in diabetic patients in whom revascularization is deferred following fractional flow reserve assessment]. *Rev Esp Cardiol* 2008; **61**: 352-359 [PMID: 18405515]

11 **Al-Lamee R**, Mintz GS. What are the PROSPECTs and clinical implications of vulnerable plaque? *Eur Heart J* 2021; **42**: 4680-4682 [PMID: 34370846 DOI: 10.1093/eurheartj/ehab521]

12 **Nissen SE**, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006; **295**: 1556-1565 [PMID: 16533939 DOI: 10.1001/jama.295.13.jpc60002]

13 **Mygind ND**, Michelsen MM, Pena A, Frestad D, Dose N, Aziz A, Faber R, Høst N, Gustafsson I, Hansen PR, Hansen HS, Bairey Merz CN, Kastrup J, Prescott E. Coronary Microvascular Function and Cardiovascular Risk Factors in Women With Angina Pectoris and No Obstructive Coronary Artery Disease: The iPOWER Study. *J Am Heart Assoc* 2016; **5**: e003064 [PMID: 27068634 DOI: 10.1161/JAHA.115.003064]

14 **Radico F**, Zimarino M, Fulgenzi F, Ricci F, Di Nicola M, Jespersen L, Chang SM, Humphries KH, Marzilli M, De Caterina R. Determinants of long-term clinical outcomes in patients with angina but without obstructive coronary artery disease: a systematic review and meta-analysis. *Eur Heart J* 2018; **39**: 2135-2146 [PMID: 29688324 DOI: 10.1093/eurheartj/ehy185]

15 **Kunadian V**, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, Prescott E, Karam N, Appelman Y, Fraccaro C, Buchanan GL, Manzo-Silberman S, Al-Lamee R, Regar E, Lansky A, Abbott JD, Badimon L, Duncker DJ, Mehran R, Capodanno D, Baumbach A. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *EuroIntervention* 2021; **16**: 1049-1069 [PMID: 32624456 DOI: 10.4244/EIJY20M07_01]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2275-2280

DOI: 10.12998/wjcc.v12.i13.2275

ISSN 2307-8960 (online)

CASE REPORT

Thymic carcinoid with multiple bone metastases: A case report

Chun-Qiao Chen, Ming-Yue Huang, Min Pan, Qiu-Qiu Chen, Fei-Fei Wei, Hui Huang

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: Mallin MM, United States

Received: December 23, 2023
Peer-review started: December 23, 2023
First decision: January 30, 2024
Revised: February 9, 2024
Accepted: March 28, 2024
Article in press: March 28, 2024
Published online: May 6, 2024

Chun-Qiao Chen, Ming-Yue Huang, Min Pan, Qiu-Qiu Chen, Fei-Fei Wei, Hui Huang, Department of Oncology, People's Hospital of Guilin, Guilin 541000, Guangxi Zhuang Autonomous Region, China

Corresponding author: Hui Huang, MD, Doctor, Department of Oncology, People's Hospital of Guilin, No. 12 Wenming Road, Guilin 541000, Guangxi Zhuang Autonomous Region, China. huanghui25002@163.com

Abstract

BACKGROUND

Thymic carcinoid (TC) is a rare entity among anterior mediastinal malignancies. TCs are neuroendocrine carcinomas that constitute approximately 2%–5% of all thymic epithelial tumors.

CASE SUMMARY

The study reported a rare TC with multiple bone metastases. A 77-year-old man presented with a 2-month history of lower back pain and weight loss of 5 kg. Magnetic resonance imaging scans revealed damage to the lumbar spine, sacrocaudal vertebrae and iliac crest, suggesting bone metastasis; computed tomography (CT) scan of the thorax showed a calcified anterior mediastinal mass; positron emission tomography-CT demonstrated multiple abnormal bone signals; and laboratory work-up showed no endocrine abnormalities. Fine-needle aspiration biopsy revealed predominantly single small, round to oval cells with scant cytoplasm and some loose clusters, suggesting endocrine manifestations. The pathological diagnosis was atypical carcinoid, which tend to originate from the thymus and was classified as intermediate-highly invasive. The patient underwent anlotinib-targeted therapy. Anlotinib (12 mg) was administered daily for 2 wk, after which the patient was allowed to rest for 21 d. Follow-up CT after one year demonstrated that the tumor had shrunk by approximately 29% after therapy. Treatment has a long stable disease benefit of more than 2.5 years.

CONCLUSION

These findings demonstrated that anlotinib is a promising treatment regimen for patients with TC and multiple bone metastases.

Key Words: Thymic carcinoid; Anlotinib; Multitargeted tyrosine kinase inhibitor; Bone metastasis; Case report

Core Tip: Here, we report a 77-year-old man diagnosed with thymic carcinoid (TC) with multiple bone metastases, and the study reports the rapid contraction of thymoid carcinoma after therapy with the multitargeted tyrosine kinase inhibitor anlotinib. The treatment has shown good efficacy, with a long stable disease benefit of more than 2.5 years (until March 2022). These findings demonstrated that anlotinib is a promising treatment regimen for TC tumors with multiple bone metastases.

Citation: Chen CQ, Huang MY, Pan M, Chen QQ, Wei FF, Huang H. Thymic carcinoid with multiple bone metastases: A case report. *World J Clin Cases* 2024; 12(13): 2275-2280
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2275.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2275

INTRODUCTION

Thymic carcinoid (TC) tumors are malignant and clinically rare tumors originating from thymic neuroendocrine cells. These tumors are different from thymomas and thymic carcinomas and have their own clinical and pathological characteristics. These tumors were first described as separate entities by Rosai and Higa[1] in 1972 and were named TC tumors. The latest World Health Organization classification from 2015 grouped lung and thymic neuroendocrine tumors within one unique group[2]. TC tumors, also known as highly differentiated neuroendocrine tumors, are divided into typical carcinoid tumors and atypical carcinoid tumors according to their morphology, among which atypical carcinoid tumors have a greater degree of malignancy and invasion. There is a lack of understanding of thymic carcinogenesis and no clear standardized diagnosis or treatment strategies due to the rarity of this disease; therefore, further knowledge is required for its clinical diagnosis and treatment. This report describes a 77-year-old man diagnosed with TC with multiple bone metastases, and the study reports the rapid contraction of thymoid carcinoma after therapy with the multitargeted tyrosine kinase inhibitor anlotinib.

CASE PRESENTATION

Chief complaints

A 77-year-old man presented with a complaint of a 2-month history of lower back pain and weight loss of 5 kg.

History of present illness

Initial symptoms included two months of lower back pain and a weight loss of 5 kg.

History of past illness

He had a past medical history of coronary heart disease, hypertension and lacunar cerebral infarction. The patient's past medical history was not significant for night sweats, fevers, facial flushing, or diarrhea.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

Physical examination revealed marked tenderness to percussion over the lumbar 2 vertebra, an Eastern Cooperative Oncology Group score above 1 and a pain score above 4. His physical examination revealed no signs of adenopathy or organomegaly.

Laboratory examinations

Laboratory tests showed an increase in serum neuron specific enolase (NSE) levels, reaching 32.05 mg/L (normal range < 13 mg/L); alpha-fetoprotein 3.29 ng/mL; alkaline phosphatase 95 U/L; β2-MB 2.15 mg/L.

The original percutaneous needle biopsy of the mediastinal mass revealed predominantly single small, round to oval cells with scant cytoplasm and some loose clusters with a mitotic rate > 2/10 high power fields (Figure 1A). Immunohistochemical staining showed positive for common neuroendocrine markers, such as chromogranin A, cytokeratin-Pan, CD56 and synaptophysin, but negative results for cytokeratin7 and thyroid transcription factor-1. The Ki67 index of the tumor moderately increased.

Imaging examinations

Magnetic resonance imaging of the lumbar region of the spine revealed multifocal metastatic lesions, an L2 vertebral compression fracture, and an L1/2-L5/S1 fusion with degenerative disc disease (Figure 1B and C). On computed tomography (CT), CT with intravenous contrast medium showed enhancement in the periphery of the mass (Figure 1D and

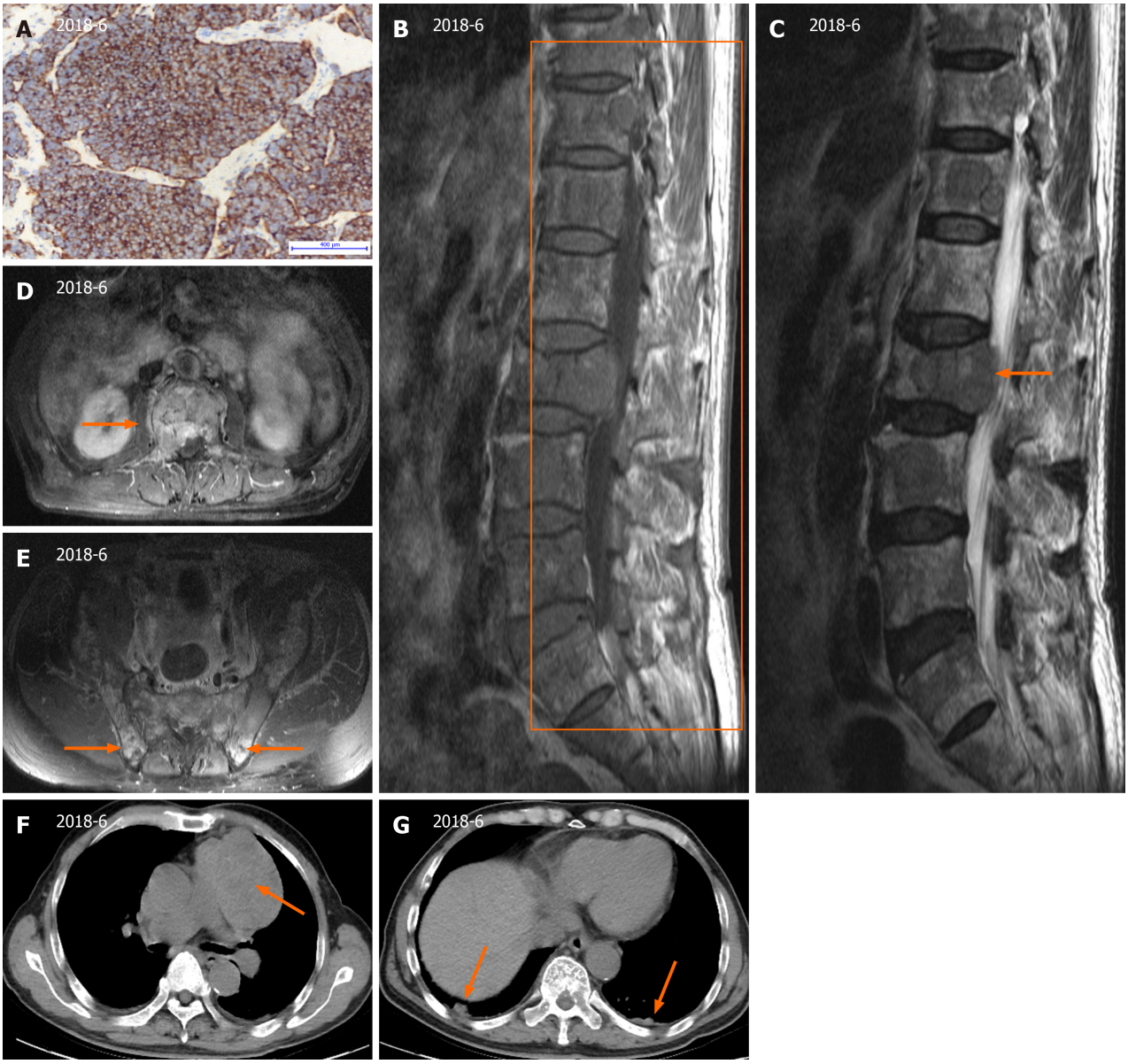

Figure 1 Thymic carcinoid with multiple bone metastases. A: The original percutaneous needle biopsy of the mediastinal mass showed predominantly single small, round to oval cells with scant cytoplasm and some loose clusters (hematoxylin-eosin staining, × 400); B: Magnetic resonance imaging scans of the lumbar spine showed multiple abnormal signals to the lumbar spine, sacrocaudal vertebrae and iliac crest, indicating bone metastasis; C: L2 vertebral compression fracture and L1/2-L5/S1 with degenerative disc disease; D and E: Lumbar vertebrae axial computed tomography (CT) scan showing bone erosion of the T1 vertebra; F and G: CT scan of the thorax showing a calcified anterior mediastinal mass and a nodular shadow in the subpleural area of both lungs.

E). And there was a round, heterogeneous, anterosuperior mediastinal mass measuring 8.1 cm × 7.9 cm × 6.1 cm (Figure 1F), Patchy nodular opacities were also observed in both lungs (Figure 1G). OctreoScan imaging revealed a large focus of increased tracer uptake in the chest corresponding to the mediastinal mass as well as the cervical, lumbar, rib, sternum, and iliac crest regions noted on positron emission tomography CT.

FINAL DIAGNOSIS

In summary, the patient was diagnosed with moderately differentiated neuroendocrine carcinoma (atypical carcinoid).

TREATMENT

Tumor cells extensively invade the lung and various bones and cannot be removed surgically. The patient was administered anlotinib (12 mg) on June 6, 2018, which was administered orally daily before breakfast for 2 weeks with a week of rest in every cycle of 21 d.

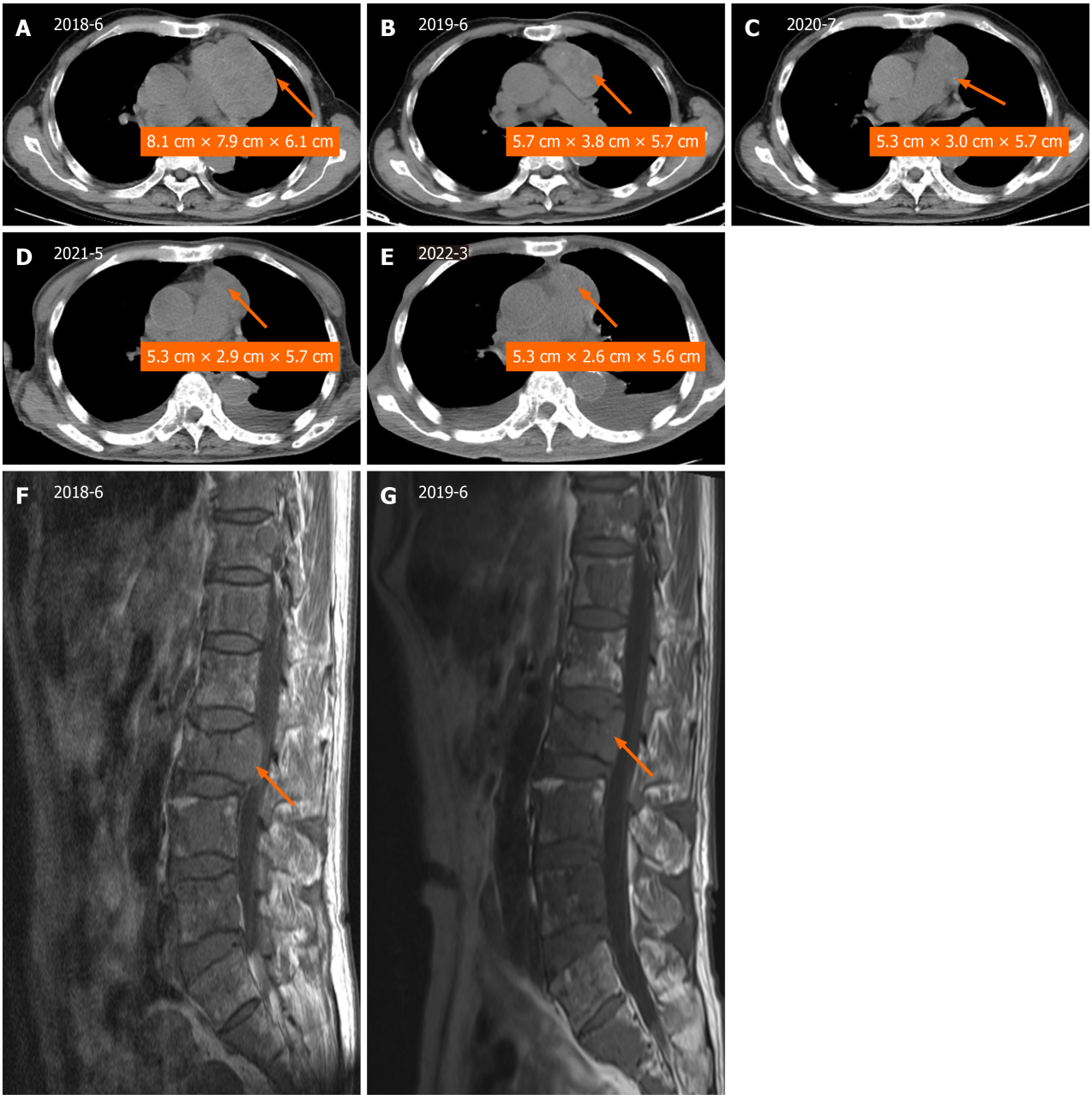

Figure 2 Tumor shrinkage before and after therapy. A-E: Heterogenous, mediastinal, soft tissue mass observed *via* computed tomography scan. The mass was measured at the level of branching of the main pulmonary artery; F and G: The vertebral compression fractures improved significantly.

OUTCOME AND FOLLOW-UP

Treatment has shown good efficacy, with a long stable disease (SD) benefit of more than 2.5 years (until March 2022) (Figure 2). During the year of anlotinib-targeted therapy, a follow-up CT scan of the chest taken in June 2019 demonstrated that the tumor measured approximately 5.7 cm × 3.8 cm × 5.7 cm (Figure 2B), and the tumor had shrunk by approximately 29% after therapy. The patient reported significant relief of lower back pain (Figure 2F and G). His pain score was reduced to above 1. There was no evidence of disease progression after treatment, and the NSE index continued to decrease (Table 1). The patient died on May 10, 2022 due to respiratory and circulatory failure.

DISCUSSION

TCs are uncommon lesions. The clinical characteristics of TC tumors are male predominance, difficult diagnosis, high malignancy, frequent recurrence and extrathoracic metastasis over a long period of time[3]. In fact, TC tumors are amine precursor uptake and decarboxylation tumors and thus can exhibit endocrine function. TCs associated with Cushing's syndrome are more common than other types of carcinoids and account for 29% to 38% of all TCs[4]. In addition, TCs are usually slow-growing tumors that cause symptoms only when they begin to exert pressure on adjacent structures. Some

Table 1 Neuron specific enolase indicators

Date	2018-06	2018-08	2019-06	2020-07	2021-05	2022-03
NSE (ng/mL)	32.05	111.6	51.6	35.83	41.51	25.34

NSE: Neuron specific enolase.

patients have no clinical symptoms at all, and only thymic masses are found at physical examination. Symptoms can vary greatly, as in our case, in which the disease was acutely manifested as lumbar pain caused by lumbar metastasis compression and nerve root stimulation. Such cases have not been previously reported.

TC tumors have a greater rate of metastatic disease than carcinoid tumors in other locations. The 5-year survival rate of TCs is 60%, and recurrence is common[3]. The prognosis of these tumors is poor, even in patients whose tumors appear favorable in terms of resectability and histology. With the development of molecular pharmacology, targeted therapy has gradually become possible[5]. In fact, in this case, the patient was assessed as inoperable due to tumor invasion into the mediastinum and multiple bone metastases from thymic cancer, and a new adjuvant strategy was adopted to induce tumor response and improve quality of life.

Anlotinib, a multiple tyrosine kinase receptor, is a potent anti-angiogenic and anti-tumor drug that inhibits signal transduction vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptors, fibroblast growth factor receptor, and c-KIT[6]. Anlotinib has been shown to inhibit the osteosarcoma cell lines by affecting cell proliferation and the protein levels of the VEGFR2 and MET signaling pathways[7]. Additionally, anlotinib inhibits cell viability and induces apoptosis in lung cancer cells, which in turn enhances the cytotoxicity of anlotinib and amplifies its antiangiogenic effect through Janus kinase 2/signal transducer and activator of transcription 3/vascular endothelial growth factor A signaling[8]. In human trials, Han *et al*[9] and Zhang *et al*[10] reported that, compared with placebo, anlotinib is well tolerated and significantly improves progression-free survival (PFS) and overall survival. Additionally, anlotinib is a promising treatment option for patients with relapsed small-cell lung cancer who have experienced treatment failure with two lines of chemotherapy[11]. The use of anlotinib in previously treated, recurrent or metastatic esophageal squamous cell carcinoma patients significantly improved PFS and the disease control rate compared with those of patients treated with a placebo[12].

However, in our patient, anlotinib therapy was administered with the neoadjuvant intent of increasing the disease control rate and quality of life. The patient was started on anlotinib (12 mg) on June 6, 2018, which was administered orally daily for 2 wk with a week of rest in every cycle of 21 d. The follow-up included CT imaging. One year after treatment, a CT scan indicated that the tumor was approximately 5.7 cm × 3.8 cm × 5.7 cm, and approximately 29% of the tumors had shrunk before and after therapy. The patient was discharged in good clinical condition and did not receive further radiation and chemotherapy treatment. There were no signs of disease progression after treatment with anlotinib. After receiving long-term anlotinib therapy, his pain score decreased from 4 to above 1, and his SD reached 2.5 years (until March 2022), indicating the effectiveness of anlotinib treatment.

CONCLUSION

This report demonstrates that anlotinib is a promising treatment regimen for TC tumors with multiple bone metastases.

FOOTNOTES

Co-first authors: Chun-Qiao Chen and Ming-Yue Huang.

Author contributions: Chen CQ and Huang H designed the research; Chen CQ, Huang MY, Pan M and Chen QQ performed the research; Wei FF analyzed the data; Chen CQ, Huang MY and Huang H wrote the paper; Chen CQ and Huang MY contributed equally to the manuscript.

Supported by Guangxi Guilin Science and Technology Fund, No. 20190218-7-6.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest to disclose.

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: Chun-Qiao Chen 0009-0004-6614-3933; Hui Huang 0000-0002-4232-9416.

S-Editor: Che XX
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Rosai J**, Higa E. Mediastinal endocrine neoplasm, of probable thymic origin, related to carcinoid tumor. Clinicopathologic study of 8 cases. *Cancer* 1972; **29**: 1061-1074 [PMID: 4111691 DOI: 10.1002/1097-0142(197204)29:4<1061::aid-cncr2820290456>3.0.co;2-3]
2 **Marx A**, Chan JK, Coindre JM, Detterbeck F, Girard N, Harris NL, Jaffe ES, Kurrer MO, Marom EM, Moreira AL, Mukai K, Orazi A, Ströbel P. The 2015 World Health Organization Classification of Tumors of the Thymus: Continuity and Changes. *J Thorac Oncol* 2015; **10**: 1383-1395 [PMID: 26295375 DOI: 10.1097/JTO.0000000000000654]
3 **Bakhos CT**, Salami AC, Kaiser LR, Petrov RV, Abbas AE. Thymic Neuroendocrine Tumors and Thymic Carcinoma: Demographics, Treatment, and Survival. *Innovations (Phila)* 2020; **15**: 468-474 [PMID: 32938293 DOI: 10.1177/1556984520949287]
4 **Filosso PL**, Ruffini E, Solidoro P, Roffinella M, Lausi PO, Lyberis P, Oliaro A, Guerrera F. Neuroendocrine tumors of the thymus. *J Thorac Dis* 2017; **9**: S1484-S1490 [PMID: 29201451 DOI: 10.21037/jtd.2017.10.83]
5 **Liang Y**, Ji S, Yu X, Chen J. [Updates on medical treatment for neuroendocrine neoplasm]. *Zhongguo Aizheng Zazhi* 2022; **32**: 757-764 [DOI: 10.19401/j.cnki.1007-3639.2022.09.001]
6 **Shen G**, Zheng F, Ren D, Du F, Dong Q, Wang Z, Zhao F, Ahmad R, Zhao J. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. *J Hematol Oncol* 2018; **11**: 120 [PMID: 30231931 DOI: 10.1186/s13045-018-0664-7]
7 **Wang G**, Sun M, Jiang Y, Zhang T, Sun W, Wang H, Yin F, Wang Z, Sang W, Xu J, Mao M, Zuo D, Zhou Z, Wang C, Fu Z, Duan Z, Hua Y, Cai Z. Anlotinib, a novel small molecular tyrosine kinase inhibitor, suppresses growth and metastasis *via* dual blockade of VEGFR2 and MET in osteosarcoma. *Int J Cancer* 2019; **145**: 979-993 [PMID: 30719715 DOI: 10.1002/ijc.32180]
8 **Liang L**, Hui K, Hu C, Wen Y, Yang S, Zhu P, Wang L, Xia Y, Qiao Y, Sun W, Fei J, Chen T, Zhao F, Yang B, Jiang X. Autophagy inhibition potentiates the anti-angiogenic property of multikinase inhibitor anlotinib through JAK2/STAT3/VEGFA signaling in non-small cell lung cancer cells. *J Exp Clin Cancer Res* 2019; **38**: 71 [PMID: 30755242 DOI: 10.1186/s13046-019-1093-3]
9 **Han B**, Li K, Wang Q, Zhang L, Shi J, Wang Z, Cheng Y, He J, Shi Y, Zhao Y, Yu H, Chen W, Luo Y, Wu L, Wang X, Pirker R, Nan K, Jin F, Dong J, Li B, Sun Y. Effect of Anlotinib as a Third-Line or Further Treatment on Overall Survival of Patients With Advanced Non-Small Cell Lung Cancer: The ALTER 0303 Phase 3 Randomized Clinical Trial. *JAMA Oncol* 2018; **4**: 1569-1575 [PMID: 30098152 DOI: 10.1001/jamaoncol.2018.3039]
10 **Zhang RS**, Liu J, Deng YT, Wu X, Jiang Y. The real-world clinical outcomes and treatment patterns of patients with unresectable locally advanced or metastatic soft tissue sarcoma treated with anlotinib in the post-ALTER0203 trial era. *Cancer Med* 2022; **11**: 2271-2283 [PMID: 35191609 DOI: 10.1002/cam4.4613]
11 **Cheng Y**, Wang Q, Li K, Shi J, Liu Y, Wu L, Han B, Chen G, He J, Wang J, Lou D, Yu H, Qin H, Li XL. Overall survival (OS) update in ALTER 1202: Anlotinib as third-line or further-line treatment in relapsed small-cell lung cancer (SCLC). *Ann Oncol* 2019; **30**: v711 [DOI: 10.1093/annonc/mdz264]
12 **Huang J**, Xiao J, Fang W, Lu P, Fan Q, Shu Y, Feng J, Zhang S, Ba Y, Zhao Y, Liu Y, Bai C, Bai Y, Tang Y, Song Y, He J. Anlotinib for previously treated advanced or metastatic esophageal squamous cell carcinoma: A double-blind randomized phase 2 trial. *Cancer Med* 2021; **10**: 1681-1689 [PMID: 33586360 DOI: 10.1002/cam4.3771]

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2281-2285

DOI: 10.12998/wjcc.v12.i13.2281

ISSN 2307-8960 (online)

CASE REPORT

Atypical presentation of a posterior fossa tumour: A case report

Alisha Narotam, Mikara Archary, Poobalan Naidoo, Yeshkhir Naidoo, Vanesha Naidu

Specialty type: Medicine, general and internal

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: Alsawy MF, Egypt

Received: January 5, 2024
Peer-review started: January 5, 2024
First decision: January 30, 2024
Revised: February 19, 2024
Accepted: March 21, 2024
Article in press: March 21, 2024
Published online: May 6, 2024

Alisha Narotam, Mikara Archary, Department of Internal Medicine, King Edward VIII Hospital - University of Kwazulu-Natal, Durban 4001, Kwa-Zulu Natal, South Africa

Poobalan Naidoo, Department of Internal Medicine, Nelson R Mandela, School of Medicine, University of Kwa-Zulu Natal, Durban 4001, Kwa-Zulu Natal, South Africa

Yeshkhir Naidoo, Vanesha Naidu, Department of Radiology, King Edward VIII Hospital - University of Kwazulu-Natal, Durban 4001, Kwazulu-Natal, South Africa

Corresponding author: Alisha Narotam, MBChB, Doctor, Department of Internal Medicine, King Edward VIII Hospital - University of Kwazulu-Natal, 719 Umbilo Road Umbilo, Durban 4001, Kwa-Zulu Natal, South Africa. alisha296@gmail.com

Abstract

BACKGROUND

We described a case of a patient with a meningioma in the posterior fossa presenting atypically with an isolated unilateral vocal cord palsy causing severe respiratory distress. This is of interest as the patient had no other symptomatology, especially given the size of the mass, which would typically cause a pressure effect leading to neurological and auditory symptoms.

CASE SUMMARY

This case report described a 48-year-old male who was married with two children and employed as a car guard. He had a medical history of asthma for the past 10 years controlled with an as-needed beta 2 agonist metered dose inhaler. He initially presented to our facility with severe respiratory distress. He reported a 1-wk history of shortness of breath and wheezing that was not relieved by his bronchodilator. He had no constitutional symptoms or impairment of hearing. On clinical examination, the patient's chest was "silent." Our initial assessment was status asthmaticus with type 2 respiratory failure, based on the history of asthma, a "silent chest," and the arterial blood gas results.

CONCLUSION

A posterior fossa meningioma of such a large size and with extensive infiltration rarely presents with an isolated unilateral vocal cord palsy. The patient's chief presenting feature was severe respiratory distress, which combined with his background medical history of asthma, was misleading. Clinicians should thus consider meningioma as a differential diagnosis for a unilateral vocal cord palsy even without audiology involvement.

Key Words: Respiratory distress; Meningioma; Unilateral vocal cord palsy; Posterior fossa

tumour; Neurosurgery; Neurology; Radiology; Case report

Core Tip: This case report described an atypical presentation for a posterior fossa tumour. Initially, the patient was assessed as severe respiratory distress after a background history of asthma. However, after further investigation and management the patient had an upper airway obstruction secondary to a unilateral vocal cord palsy. This was found to be a complication of a cerebellar-pontine tumour. Upon further research, no cases have been presented recently where a patient had unilateral vocal cord palsy subsequent to the tumour. This presentation may be explained secondary to the effacement and displacement of the surrounding structures from the tumour.

Citation: Narotam A, Archary M, Naidoo P, Naidoo Y, Naidu V. Atypical presentation of a posterior fossa tumour: A case report. *World J Clin Cases* 2024; 12(13): 2281-2285
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2281.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2281

INTRODUCTION

We described a rare case of unilateral vocal cord palsy secondary to a posterior fossa tumour presenting atypically with severe respiratory distress. The patient had a background history of asthma, and initial assessment was that of status asthmaticus based on history of asthma, severe respiratory distress, and a "silent chest." He was intubated and ventilated due to respiratory failure. In retrospect, we assessed him as having upper airway obstruction secondary to unilateral vocal cord paralysis based on stridor immediately after extubation and as evidenced by direct laryngoscopy. To identify the underlying cause of the unilateral vocal cord palsy, we undertook imaging of the head, neck, and chest, which revealed a large cerebellar-pontine tumour with abutment of adjacent structures. Debulking neurosurgery with excision biopsy demonstrated a psammomatous meningioma. At the time of publication, the patient was awaiting radiotherapy.

CASE PRESENTATION

Chief complaints

A 48-year-old man presented to the Acute Medical Unit with sudden onset shortness of breath.

History of present illness

This was the first episode of the patient presenting in acute respiratory distress with an otherwise healthy background. The patient reported a 1-wk history of feeling short of breath that was not relieved after using his inhaler.

History of past illness

The patient was diagnosed with asthma 10 years prior to presentation. It was controlled with a beta-2 agonist metered dose inhalers. No auditory fallouts were reported.

Personal and family history

The patient had no constitutional symptoms, and there was no family history reported for meningiomas either.

Physical examination

On examination, the patient required the use of accessory muscles during respiration and was significantly short of breath. On auscultation of the chest, no air entry bilaterally was heard.

Laboratory examinations

An arterial blood gas analysis was performed. It demonstrated a type 2 respiratory failure requiring intubation. During his stay in the intensive care unit, the patient had persistent respiratory acidosis with subsequent *Klebsiella pneumonia* and *Ciprobacter koseri* cultured on the endotracheal aspirate as well as a positive blood culture for *Acinitobacter baumanii.*

Imaging examinations

After extubation, the unilateral vocal cord palsy was identified through examination under anaesthesia. As part of the diagnostic workup, the patient underwent a contrasted computed tomography scan of his head, neck, and chest. The scan identified a large, densely calcified, extra-axial right posterior fossa mass measuring 4 cm × 4 cm × 4 cm that extended into the internal auditory meatus, jugular fossa, and hypoglossal canal with inferior extension into the upper spinal canal

via the foramen magnum. This also demonstrated a resultant right supratentorial hydrocephalus. A subsequent magnetic resonance imaging (MRI) revealed a large right cerebellar pontine angle mass with associated expansion of the internal acoustic meatus and extension into the upper cervical canal, jugular fossa, and right paravertebral region (Figure 1).

FINAL DIAGNOSIS

A biopsy of the posterior fossa mass was sent for further investigation. The histology came back as a psammomatous meningioma.

TREATMENT

The patient initially received continuous nebulization, intravenous hydrocortisone, and intravenous magnesium sulphate. While still being ineffective, the patient was intubated for respiratory support. After extubation, there was a persistent stridor, and subsequently a vocal cord palsy was identified. The patient underwent a tracheostomy and was weaned off the ventilator. Once the posterior fossa mass was visualized on the computed tomography and MRI, debulking neurosurgery with excision biopsy followed by radiotherapy was performed.

OUTCOME AND FOLLOW-UP

The patient was transferred to a quaternary level facility.

DISCUSSION

Isolated left-sided vocal cord palsy with respiratory failure is a rare presentation of a tumour in the posterior fossa. In this patient, the tumour resulted in a mass effect with resultant effacement and displacement of the pons and medulla to the left. This may have explained the left-sided vocal cord paralysis. An excision biopsy demonstrated a psammomatous meningioma.

Unilateral vocal cord paralysis can be asymptomatic or can present with hoarse voice, dysphonia, dysphagia, aspiration, and coughing[1,2]. Patients may recover spontaneously in some instances, or the contralateral cord may compensate for its dysfunctional counterpart[1]. The most commonly affected side for an isolated vocal cord paralysis is the left side, as was the case in our patient[1]. This is due to the longer course of the left recurrent laryngeal nerve compared to the right side making it more vulnerable to damage, especially in the mediastinum. Most patients present in the fifth or sixth decade of life, on average at age 53 years[2]. Diagnosis of a vocal cord paralysis is dependent on confirmation during indirect laryngoscopy or laryngeal endoscopy[2], as confirmed in our patient.

The underlying cause of vocal cord palsy varies based on geographic location. Malignancy contributes to 34% of cases of vocal cord palsy[2]. Primary malignancy only accounts for 7.5%, while secondary pressure effects and nerve damage accounts for 85.0% of these cases presenting with cord paralysis[3]. If not laryngeal in origin, abnormalities of the thyroid gland, oesophagus, mediastinum, and lung are the most common causes for this presentation. An otolaryngological assessment includes otoscopy to exclude a cholesteatoma. Flexible nasolaryngoscopy or rigid laryngoscopy can also be performed to exclude infiltration of the primary lesion[4]. Radiological investigation, namely a computed tomography scan from the base of the skull to the upper mediastinum, is needed to identify the possible cause of unilateral vocal cord palsy. This is the approach that we followed.

Senior *et al*[4] reported a case involving a 78-year-old female who presented with progressive dysphonia and dysphagia. She also had further neurological fallout, which included progressive left-sided hearing loss with normal otoscopic examination. Flexible nasoendoscopy showed a unilateral vocal cord palsy. MRI revealed a primary cerebellar pontine angle meningioma arising from the jugular foramen. Another case report described a 34-year-old man who presented with dysphagia, loss of taste, and dysarthria. Laryngoscopy showed a unilateral left vocal cord palsy. Electrodiagnostic study confirmed paralysis of the lower cranial nerves (IX to XII). Further imaging with brain MRI revealed a left cerebellar pontine angle meningioma. This patient was subsequently diagnosed with Collet-Sicard syndrome (unilateral lower cranial nerve paralysis) secondary to the cerebellar pontine angle mass[5].

Our patient differed from the aforementioned cases in that he had vocal cord palsy with respiratory failure, eventually requiring a tracheostomy. The late presentation may have accounted for the severe respiratory distress that, to the best of our knowledge, has not been reported with other cases of meningioma. One may speculate that his asthma may have also contributed to his severe respiratory distress.

CONCLUSION

A meningioma in the posterior fossa of such size and infiltration as described in this case rarely presents asymptomat-

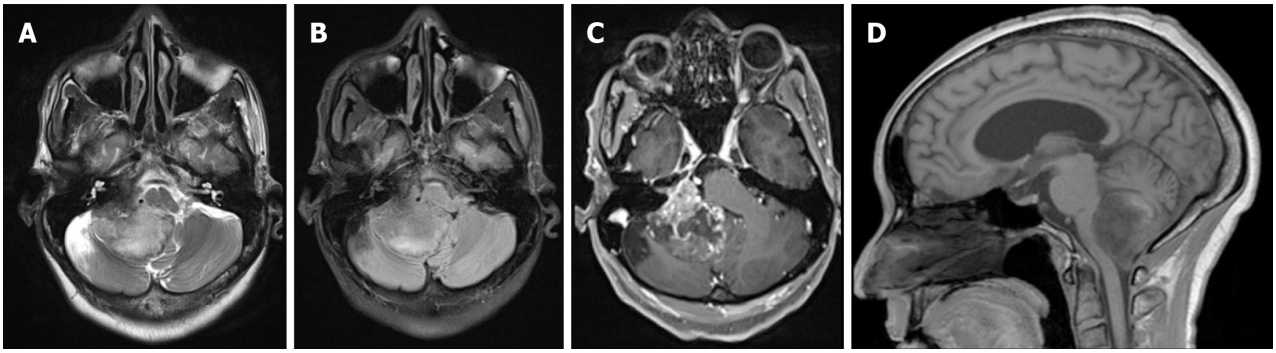

Figure 1 Right cerebellar poutine angle tumour with inferior extension to the craniocervical junction, anterior effacement, and compression of the cervical cord. A: T2-weighted axial image; B: Fluid-attenuated inversion recovery axial image; C: T1-weighted fat suppression gadolinium axial image; D: T1-weighted sagittal image.

ically or with a unilateral vocal cord palsy. Larger meningiomas are mostly symptomatic due to tissue compression and subsequent oedema. Despite this patient having both findings, the symptoms were limited. Cases described previously in the literature presented with audiological and vocal cord involvement, but the presentation of vocal cord involvement in isolation is a rare finding. Early recognition in such cases would lead to a better prognosis, especially with the possibility of resection. Imaging, histopathology, and then prompt referral to oncology is required for management planning. Clinicians should thus consider meningioma as a differential diagnosis for a unilateral vocal cord palsy, even without audiology involvement. In this case, the diagnosis in a male with isolated unilateral vocal cord palsy and respiratory failure was confounded by the history of asthma.

FOOTNOTES

Author contributions: Narotam A was the corresponding author and submitted the manuscript; Archary M, Narotam A, and Naidoo P wrote, edited, and reviewed the manuscript; Naidoo Y and Naidu V analysed and reported the radiological images.

Informed consent statement: Written informed consent was obtained from the patient.

Conflict-of-interest statement: All the authors declare that they have no conflicts of interest.

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 Africa

ORCID number: Alisha Narotam 0000-0002-1103-5378; Mikara Archary 0000-0001-5654-4064; Poobalan Naidoo 0000-0002-5950-1585; Yeshkhir Naidoo 0000-0002-3877-2597.

S-Editor: Liu JH
L-Editor: Filipodia
P-Editor: Zhao S

REFERENCES

1 **Gandhi S**, Rai S, Bhowmick N. Etiological profile of unilateral vocal cord paralysis: A single institutional experience over 10 years. *J Laryngol Voice* 2014; **4**: 58-62 [DOI: 10.4103/2230-9748.157471]
2 **Gupta J**, Varshney S, Bist SS, Bhagat S. Clinico-etiolological study of vocal cord paralysis. *Indian J Otolaryngol Head Neck Surg* 2013; **65**: 16-19 [PMID: 24381912 DOI: 10.1007/s12070-012-0574-x]
3 **Al-Khtoum N**, Shawakfeh N, Al-Safadi E, Al-Momani O, Hamasha K. Acquired unilateral vocal fold paralysis: retrospective analysis of a single institutional experience. *N Am J Med Sci* 2013; **5**: 699-702 [PMID: 24404552 DOI: 10.4103/1947-2714.123254]
4 **Senior A**, Douglas JA, Thompson S. Unilateral vocal cord palsy and dysphagia: an unusual presentation of cerebellopontine angle meningioma. *J Surg Case Rep* 2015; **2015** [PMID: 26486157 DOI: 10.1093/jscr/rjv129]

5 **Lee S**, Yang HS, Chun MH. Collet-Sicard Syndrome with Dysphagia due to Cerebellopontine Angle Meningioma: A case report. *J Korean Acad Rehabil Med* 2006; **30**: 402-405

World Journal of Clinical Cases

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

World J Clin Cases 2024 May 6; 12(13): 2286-2292

DOI: 10.12998/wjcc.v12.i13.2286

ISSN 2307-8960 (online)

CASE REPORT

Refractory autoimmune hemolytic anemia in a patient with systemic lupus erythematosus and ulcerative colitis: A case report

Dai-Xing Chen, Yue Wu, Sui-Feng Zhang, Xiao-Jun 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): 0
Grade E (Poor): 0

P-Reviewer: Dauyey K, Kazakhstan

Received: January 23, 2024
Peer-review started: January 23, 2024
First decision: January 31, 2024
Revised: February 6, 2024
Accepted: March 27, 2024
Article in press: March 27, 2024
Published online: May 6, 2024

Dai-Xing Chen, Yue Wu, Sui-Feng Zhang, Xiao-Jun Yang, Department of Digestive System, Chongqing Traditional Chinese Medicine Hospital, Chongqing 400021, China

Corresponding author: Xiao-Jun Yang, MD, PhD, Chief Doctor, Department of Digestive System, Chongqing Traditional Chinese Medicine Hospital, No. 6 Panxi 7 Branch Road, Jiangbei District, Chongqing 400021, China. yangxj88@126.com

Abstract

BACKGROUND

Ulcerative colitis (UC) and systemic lupus erythematosus (SLE) are both systemic immunoreactive diseases, and their pathogenesis depends on the interaction between genes and environmental factors. There are no reports of UC with SLE in China, but six cases of SLE with UC have been reported in China. The combination of these two diseases has distinct effects on the pathogenesis of both diseases.

CASE SUMMARY

A female patient (30 years old) came to our hospital due to dull umbilical pain, diarrhea and mucous bloody stool in August 2018 and was diagnosed with UC. The symptoms were relieved after oral administration of mesalazine (1 g po tid) or folic acid (5 mg po qd), and the patient were fed a control diet. On June 24, 2019, the patient was admitted for treatment due to anemia and tinnitus. During hospitalization, the patient had repeated low-grade fever and a progressively decreased Hb level. Blood tests revealed positive antinuclear antibody test, positive anti-dsDNA antibody, 0.24 g/L C3 (0.9-1.8 g/L), 0.04 g/L C4 (0.1-0.4 g/L), 32.37 g/L immunoglobulin (8-17 g/L), and 31568.1 mg/24 h total 24-h urine protein (0-150 mg/24 h). The patient was diagnosed with SLE involving the joints, kidneys and blood system. Previously reported cases of SLE were retrieved from PubMed to characterize clinicopathological features and identify prognostic factors for SLE.

CONCLUSION

The patient was discharged in remission after a series of treatments, such as intravenous methylprednisolone sodium succinate, intravenous human immunoglobulin, cyclophosphamide injection, and plasma exchange. After discharge, the patient took oral prednisone acetate tablets, cyclosporine capsules, hydroxychloroquine sulfate tablets and other treatments for symptoms and was followed up regularly for 1 month, after which the patient's condition continued to improve

and stabilize.

Key Words: Plasma exchange; Autoimmune hemolytic anemia; Systemic lupus erythematosus; Ulcerative colitis; Case report

Core Tip: The association between ulcerative colitis (UC) and systemic lupus erythematosus (SLE) is a rare phenomenon. We first diagnosed a patient with coexisting UC and SLE with refractory autoimmune hemolytic anemia. Combined with the analysis of the cases indexed in PubMed, plasma exchange (PE) has been reported as a promising strategy for treating refractory autoimmune hemolytic anemia. The patient was successfully treated and maintained stable conditions through PE and continuous treatment with cyclophosphamide and hydroxychloroquine. Therefore, personalized treatment is currently the best approach.

Citation: Chen DX, Wu Y, Zhang SF, Yang XJ. Refractory autoimmune hemolytic anemia in a patient with systemic lupus erythematosus and ulcerative colitis: A case report. *World J Clin Cases* 2024; 12(13): 2286-2292
URL: https://www.wjgnet.com/2307-8960/full/v12/i13/2286.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i13.2286

INTRODUCTION

Considerable overlap occurs between various autoimmune rheumatic diseases, either from the beginning of the illness or at any point during the disease course. This may pose a considerable diagnostic challenge. Systemic lupus erythematosus (SLE) is a chronic, potentially severe, frequently disabling autoimmune disease with multiorgan involvement and typically a waxing and waning course. SLE is an immune complex-mediated disorder common in women of reproductive age group and is often considered the prototypical autoimmune disease. SLE can affect virtually every organ, including the gastrointestinal system, but most commonly, patients present with skin rashes, arthritis, oral ulcers, photosensitivity, renal, serositis, neurologic and hematologic disorders[1]. In contrast to other autoimmune diseases, such as inflammatory bowel disease (IBD), is a chronic idiopathic gastrointestinal disorder that includes ulcerative colitis (UC) and Crohn's disease (CD). Almost one fourth of IBD patients suffer from extra-intestinal manifestations, including sacroilitis or spondylitis, non-deforming peripheral arthritis, erythema nodosum, episcleritis, pyoderma gangrenosum, sclerosing cholangitis and thromboembolic events. The coexistence of the IBD and SLE is rare. The coexistence of clinical features of both diseases in a patient represents a diagnostic challenge.

Autoimmune hemolytic anemia (AIHA) is an autoimmune disorder characterized by the production of autoantibodies against erythrocytes and can be attributed to several factors, such as infections, medications, certain malignancies and autoimmune diseases[2]. Steroid or steroid combination with immunoglobulin (IG) is the mainstay of AIHA treatment [3]. Moreover, plasma exchange (PE), such as steroid-resistant or steroid-dependent AIHA, has been reported as a promising strategy for treating refractory AIHA[4,5]. However, the effect of PE on refractory AIHA in patients with multiple coexisting autoimmune diseases has not been evaluated. Here, we report refractory steroid-resistant AIHA in a patient with coexisting UC and SLE who was successfully treated with PE.

CASE PRESENTATION

Chief complaints

A 30-year-old Chinese woman presented to the gastroenterology department with a complaint of fatigue and tinnitus for 1 wk.

History of present illness

Symptoms started 1 wk before presentation with recurrent fatigue and tinnitus, without systemic joint pain or fever.

History of past illness

A 30-year-old female came to our hospital on August 26, 2018, due to "dull pain around the umbilicus complicated with viscous bloody stools", and underwent electronic colonoscopy, which suggested "diffuse erosion and multiple superficial ulcers of the rectum, sigmoid colon and descending colon mucosa" (Figure 1). Pathology revealed "diffuse lymphocytic infiltration of (sigmoid colon) mucosa, visible cryptitis, cryptal abscess, irregular surface epithelium, and distortion of cryptal structure" (Figure 2), and UC (type E2) was diagnosed. Routine blood tests revealed a hemoglobin level of 69 g/L and a serum iron concentration of 2.9 μmol/L, and the stool sample was "white blood cell (WBC) 2 +/HP, red blood cell (RBC) 2-5/HP, OB +, pus cell 2 +/HP", and antinuclear antibody-negative or anti-Sm negative. After admission, the patient was given mesalazine sustained-release granules (1 g, po, tid), enteral nutrition powder, iron saccharate and other

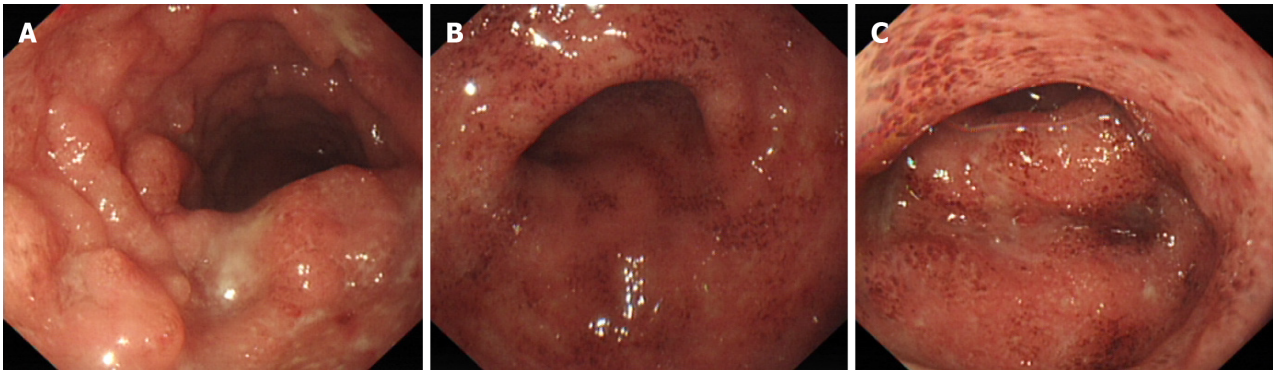

Figure 1 Findings of colonoscopy. A: Descending colon show multiple superficial ulcers and nodular hyperplasia; B: Sigmoid colon show scattered diffuse erosion of the colonic mucosa; C: Rectal mucosa show scattered diffuse erosion of the colonic mucosa.

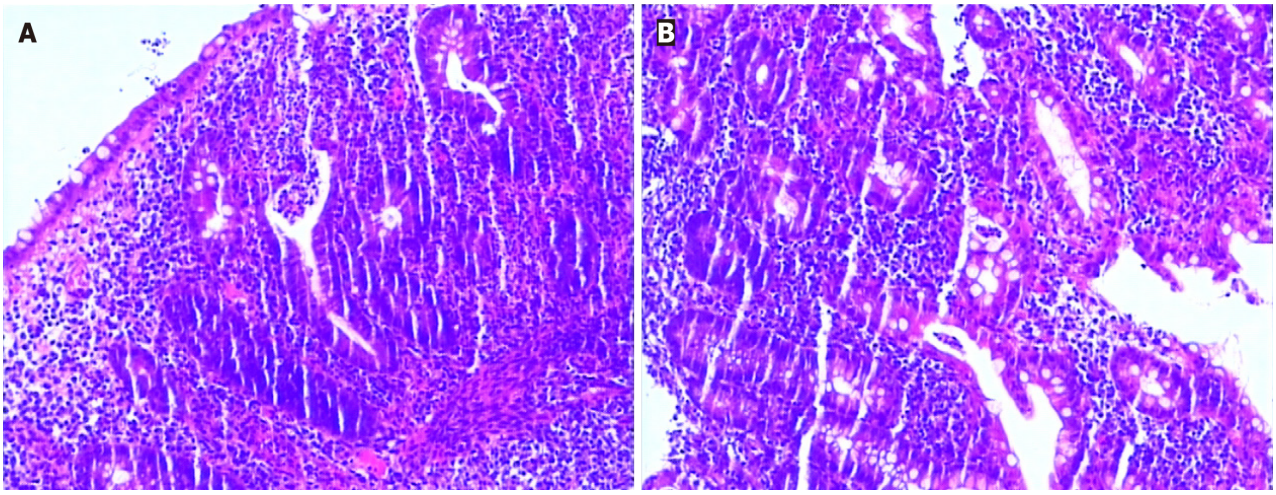

Figure 2 Findings of sigmoid colon biopsy specimens. A: Histopathological findings of specimens [hematoxylin and eosin (HE), × 40)] with diffuse lymphocytic infiltration, irregular surface epithelium; B: Histopathological findings of specimens (HE, × 40) with diffuse lymphocytic infiltration, visible cryptitis, a crypt abscess, and distorted crypt structure.

symptomatic treatment, after which the disease condition improved; after discharge, the patient was orally administered mesalazine sustained-release granules (0.5 g, po, tid) and folic acid tablets to control the disease condition and had 1-2 stools/d, without mucus or purulent bloody stool; on January 14, 2019, routine blood tests showed a hemoglobin level of 122 g/L. The drug was stopped spontaneously in February 2019 without recurrence of the disease.

Personal and family history
The patient denied any family history of disease involving the immune system.

Physical examination
On physical examination, the vital signs were as follows: Body temperature, 36.7 °C; blood pressure, 102/62 mmHg; heart rate, 92 beats/min; and respiratory rate, 19 breaths/min. Furthermore, the patient's face, skin and eyelid membrane were pale, without malar erythema.

Laboratory examinations
Relevant laboratory data can be displayed in the diagnosis and treatment process.

Imaging examinations
Combined with the patient's medical history, the patient was diagnosed with SLE involving the joints, kidneys and blood system.

FINAL DIAGNOSIS

Combined with the patient's medical history, the patient was diagnosed with SLE involving the joints, kidneys and blood system.

TREATMENT

In June 2019, the patient was readmitted to our medical center because she presented with fatigue and tinnitus for 1 wk. When she was presented to our hospital, she had no abdominal or digestive symptoms, such as abdominal pain, diarrhea or bloody stool, and she was experiencing only fatigue and tinnitus. The physical examination was unremarkable, except for a body temperature of 37.7 °C. Laboratory findings revealed a decrease in blood cells (1.67×10^{12}/L, normal range: 3.8-5.6 × 10^{12}/L) and a decrease in hemoglobin (62 g/L), as did the normal WBCs, platelet count, mean corpuscular volume and mean hemoglobin concentration. The fecal occult blood test was negative, and the concentration of serum iron was normal. However, strongly positive direct anti-human globulin and indirect anti-human globulin results were identified. Moreover, abdominal ultrasonography revealed splenomegaly. Therefore, AIHA was considered. Subsequently, the immunological results, including positive antinuclear antibody test results (1:100, 1:320 and 1:1000), positive anti-dsDNA antibody, positive SS-A antibody and decreased complement component C3 (0.24 g/L, normal range 0.9-1.8 g/L) and C4 (0.04 g/L, normal range 0.1-0.4 g/L), were verified. Based on these findings, concomitant SLE was also diagnosed.

The clinical response to therapy is shown in Figure 3. The patient was initially treated with intravenous methylprednisolone (MP) at a dose of 500 mg/d plus intravenous IG at a dose of 20 g/d. Due to the minimal clinical improvement of anemia after high-dose MP in combination with IG therapy, we treated her with intravenous cyclophosphamide (CTX) at a dose of 0.2 g/d after treatment with MP (80 mg/d). Moreover, minimal transfusion of RBCs was performed. Unfortunately, the anemia still did not improve. PE has been used to treat refractory AIHA[3,4]. To improve refractory AIHA, PE was administered on July 24, July 26 and July 29. Hemoglobin was significantly increased following PE therapy. We conclude that PE therapy successfully controlled severe hemolysis. On August 2, 2019, her hemoglobin level was 78 g/L, and the patient was hospital discharged. At the outpatient follow-up, one month after her last session of PE, her hemoglobin and hemolytic marker levels were within the normal range.

OUTCOME AND FOLLOW-UP

Currently, the patient takes cyclosporine capsules (100 mg/d) and hydroxychloroquine sulfate tablets (0.4 g/d), and her condition is stable without related complications. The follow-up laboratory data are shown in the Supplementary Figure.

DISCUSSION

UC and SLE are both systemic immunoreactive diseases, and their pathogenesis depends on the interaction between genes and environmental factors. There are no reports of UC with SLE in China, but six cases of SLE with UC have been reported in China. There are sporadic reports from abroad of preceding SLE with later UC development; there are also cases of preceding UC with later SLE development[6,7]. The combination of these two diseases is likely related to the presence of immune and genetic defects in the pathogenesis of both diseases.

Although the patient's history was nonextensive and the diagnosis was confirmed, the treatment process was extremely difficult, and the selection of PE, which quickly stabilized the patient's condition, was one of the most valuable points of this case report. AIHA is a common feature of SLE. However, AIHA is a relatively rare IBD that develops in 0.2%-1.7% of patients with UC[8]. Notably, to our knowledge, no case of AIHA in patients with coexistent IBD and SLE has been reported. Currently, the confirmation of AIHA is primarily based on the direct antiglobulin test detecting autoantibodies and/or complement agents on the surface of RBCs[9]. Strongly positive results for direct anti-human globulin and indirect anti-human globulin were identified in this patient. Therefore, the diagnosis of AIHA was exact for the patient. The backbone of treatment in AIHA is based on corticosteroid therapy, which induces remission from autoantibody production in approximately 80% of patients[10]. PE therapy is used in many autoimmune disorders, such as amyopathic dermatomyositis, dermatomyositis, SLE during pregnancy and lupus enteritis, to decrease the antibody burden, which contributes to acute crises[11-14]. PE can effectively remove pathogenic substances, such as autoantibodies, immune complexes, and cryoglobulins, from plasma with high molecular weights. The efficacy of PE in treating AIHA has been confirmed by previous studies[15]. In conclusion, our case study is the first to demonstrate the value of PE for the management of refractory AIHA in the setting of coexisting autoimmune diseases such as UC and SLE. Furthermore, our case reports and treatments have at least played a role in the management of these patients.

The pathogenesis of UC is multifactorial and involves genetic predisposition, epithelial barrier defects, dysregulated immune responses, and environmental factors. Extraintestinal manifestations can occur in approximately one-third of patients with UC[16]. Histological findings include distortion of the crypt architecture, crypt shortening, increased lymphocytes and plasma cells in the lamina propria (basal plasmacytosis), mucin depletion, and Paneth cell metaplasia [17,18]. Treatments for UC include 5-aminosalicylic acid drugs, steroids, and immunosuppressants. However, oral ulcers are a cardinal feature of SLE. Studies show that 0.2% to 5.8% of patients with SLE are affected by lupus enteritis[19]. The

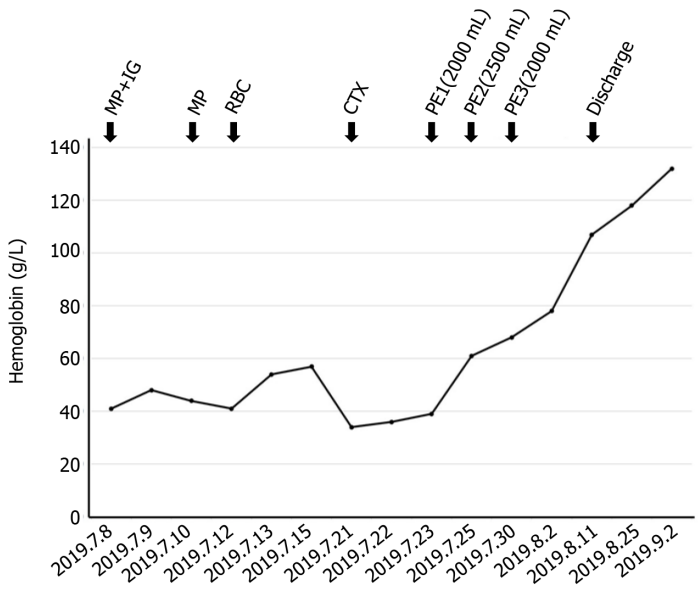

Figure 3 Clinical response to therapies. MP: Methylprednisolone; IG: Immunoglobulin; RBC: Red blood cell; CTX: Cyclophosphamide; PE: Plasma exchange.

median age of onset was 34 years, and symptoms typically appear, on average, 34.3 months after the diagnosis of SLE; 85% of the patients were females. The three principal pathologic and pathophysiologic components of lupus enteritis include lupus mesenteric vasculitis, intestinal pseudo-obstruction, and protein-losing enteropathy. Other observational studies have shown a prevalence of UC in patients with SLE of 0.4%, which is comparable to that of general population controls[20]. Treatments for SLE include steroids, CTX, azathioprine, mycophenolate mofetil, and (less frequently) hydroxychloroquine and immunosuppressants. A meta-analysis revealed a significant association between miRNA-499 gene polymorphisms and autoimmune diseases, such as Behcet's disease, rheumatoid arthritis (RA), SLE and UC[21]. Aynacıoğlu believed that Midkine is involved in the onset and progression of autoimmune rheumatic diseases, including RA, SLE, and Sjögren's syndrome and other autoimmune conditions such as multiple sclerosis[22]. However, a two-sample Mendelian randomization study revealed a negative causal effect of SLE on overall incidence of IBD and UC in European populations but not between SLE and CD[23]. In contrast, there was no causal relationship between SLE and IBD in East Asian populations. We consider these two autoimmune disorders to share certain common features.

In this case, the initial attack of UC involved only the intestine. After enteral nutrition powder (Ansu) was given to replace the diet at the time of initial treatment, along with mesalazine supplementation, abdominal pain, diarrhea and mucous bloody stool were rapidly relieved. This may be due to the action of environmental factors on the susceptibility gene. With the participation of antigens such as intestinal bacteria or food, the intestinal immune system is initiated, causing the excessive and continuous development of the intestinal immune inflammatory response. Since then, the systemic immune response of patients may be abnormally activated, which causes an immune response in systemic multisystem connective tissue on the basis of possible immune and genetic defects and adverse factors. Many published reports suggest that cyclosporine can also be used for the treatment of some patients with UC to alleviate this condition. This patient received maintenance treatment with cyclosporine and hydroxychloroquine. Cyclosporine has immunosuppressive effects, while hydroxychloroquine has anti-inflammatory and immunomodulatory effects. Therefore, we speculate that this is also the reason why UC and SLE can be relieved in patients without the use of steroid hormones. UC and SLE are both immune system diseases. However, the specific underlying mechanism is unclear and needs to be further explored and studied by rheumatologists.

CONCLUSION

The association between UC and SLE seems to be rare, and it is not fully clear whether this association is due to a common physiopathology. On the other hand, for the first time, we report refractory steroid-resistant AIHA in a patient with coexisting UC and SLE who was successfully treated with PE. Moreover, we provide a reference treatment strategy for similar patients. Doctors should make a positive and accurate diagnosis and provide humane care and treatment because patients have experienced both mental and physical problems.

FOOTNOTES

Author contributions: Chen DX and Wu Y contributed to writing and editing of the manuscript and to collecting the data; Zhang SF contributed to the data analysis; Yang XJ contributed to the conceptualization and supervision. All the authors have read and approved the final manuscript.

Informed consent statement: All participants in the study or their legal guardians 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: Dai-Xing Chen 0000-0002-2998-6606; Yue Wu 0000-0003-1511-8004; Sui-Feng Zhang 0000-0003-2811-0503; Xiao-Jun Yang 0000-0003-4871-8057.

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

REFERENCES

1 **Trapani S**, Rubino C, Simonini G, Indolfi G. Gastrointestinal and hepatic involvement in paediatric systemic lupus erythematosus. *Clin Exp Rheumatol* 2021; **39**: 899-906 [PMID: 33666164 DOI: 10.55563/clinexprheumatol/oebrcq]
2 **Barcellini W**, Fattizzo B. The Changing Landscape of Autoimmune Hemolytic Anemia. *Front Immunol* 2020; **11**: 946 [PMID: 32655543 DOI: 10.3389/fimmu.2020.00946]
3 **Heisel MA**, Ortega JA. Factors influencing prognosis in childhood autoimmune hemolytic anemia. *Am J Pediatr Hematol Oncol* 1983; **5**: 147-152 [PMID: 6193721]
4 **Anani W**, Wucinski J, Baumann Kreuziger L, Gottschall J, Karafin M. Therapeutic plasma exchange in refractory warm autoimmune hemolytic anemia. *Transfusion* 2017; **57**: 1336 [PMID: 28594138 DOI: 10.1111/trf.13932]
5 **Damlaj M**, Séguin C. Refractory autoimmune hemolytic anemia in a patient with DiGeorge syndrome treated successfully with plasma exchange: a case report and review of the literature. *Int J Hematol* 2014; **100**: 494-497 [PMID: 25079091 DOI: 10.1007/s12185-014-1648-1]
6 **Khan BA**, Saleem N, Hassan D, Kiani S, Haneef M. Coexistence of Lupus Nephritis, Ulcerative Colitis, and Communicating Hydrocephalus: A Report of a 21-Year-Old Male. *Case Rep Nephrol* 2022; **2022**: 1079300 [PMID: 35178259 DOI: 10.1155/2022/1079300]
7 **Mansour HE**, Arafa SG, Shehata WA. Systemic lupus erythematosus with inflammatory bowel disease-ulcerative colitis: case report. *Lupus* 2018; **27**: 1198-1201 [PMID: 29320975 DOI: 10.1177/0961203317751857]
8 **Giannadaki E**, Potamianos S, Roussomoustakaki M, Kyriakou D, Fragkiadakis N, Manousos ON. Autoimmune hemolytic anemia and positive Coombs test associated with ulcerative colitis. *Am J Gastroenterol* 1997; **92**: 1872-1874 [PMID: 9382055]
9 **Wheeler CA**, Calhoun L, Blackall DP. Warm reactive autoantibodies: clinical and serologic correlations. *Am J Clin Pathol* 2004; **122**: 680-685 [PMID: 15491963 DOI: 10.1309/CJAW-6N8J-6H0H-R2WM]
10 **Lechner K**, Jäger U. How I treat autoimmune hemolytic anemias in adults. *Blood* 2010; **116**: 1831-1838 [PMID: 20548093 DOI: 10.1182/blood-2010-03-259325]
11 **Yamagata A**, Arita M, Tanaka A, Tokioka F, Yoshida T, Nishimura K, Ishida T. Therapeutic plasma exchange for clinically amyopathic dermatomyositis (CADM) associated with rapidly progressive interstitial pneumonia. *J Clin Apher* 2020; **35**: 435-443 [PMID: 32810902 DOI: 10.1002/jca.21824]
12 **Shirakashi M**, Nakashima R, Tsuji H, Tanizawa K, Handa T, Hosono Y, Akizuki S, Murakami K, Hashimoto M, Yoshifuji H, Ohmura K, Mimori T. Efficacy of plasma exchange in anti-MDA5-positive dermatomyositis with interstitial lung disease under combined immunosuppressive treatment. *Rheumatology (Oxford)* 2020; **59**: 3284-3292 [PMID: 32276271 DOI: 10.1093/rheumatology/keaa123]
13 **Thomas A**, Smithhart C, Chopra M, Jayan A, Ali F, Doughem K, Bhatt A, Scoon J, Larson S. Severe Lupus Enteritis Complicated by Intractable Gastrointestinal Hemorrhage. *ACG Case Rep J* 2023; **10**: e01188 [PMID: 37928230 DOI: 10.14309/crj.0000000000001188]
14 **Zhang F**, Zhang BY, Fan R, Cheng T, Hu XR, Liu YQ, Cen X, Bu YJ, Cao JP, Chen FW, Chen JW. Clinical efficacy of plasma exchange in systemic lupus erythematosus during pregnancy. *Immun Inflamm Dis* 2023; **11**: e1041 [PMID: 37904711 DOI: 10.1002/iid3.1041]
15 **Deng J**, Zhou F, Wong CY, Huang E, Zheng E. Efficacy of therapeutic plasma exchange for treatment of autoimmune hemolytic anemia: A systematic review and meta-analysis of randomized controlled trials. *J Clin Apher* 2020; **35**: 294-306 [PMID: 32384203 DOI: 10.1002/jca.21790]
16 **Vavricka SR**, Brun L, Ballabeni P, Pittet V, Prinz Vavricka BM, Zeitz J, Rogler G, Schoepfer AM. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol* 2011; **106**: 110-119 [PMID: 20808297 DOI: 10.1038/ajg.2010.343]
17 **Kornbluth A**, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; **105**: 501-23; quiz 524 [PMID: 20068560 DOI: 10.1038/ajg.2009.727]
18 **Magro F**, Langner C, Driessen A, Ensari A, Geboes K, Mantzaris GJ, Villanacci V, Becheanu G, Borralho Nunes P, Cathomas G, Fries W, Jouret-Mourin A, Mescoli C, de Petris G, Rubio CA, Shepherd NA, Vieth M, Eliakim R; European Society of Pathology (ESP); European Crohn's and Colitis Organisation (ECCO). European consensus on the histopathology of inflammatory bowel disease. *J Crohns Colitis* 2013; **7**:

827-851 [PMID: 23870728 DOI: 10.1016/j.crohns.2013.06.001]

19 **Koo BS**, Hong S, Kim YJ, Kim YG, Lee CK, Yoo B. Lupus enteritis: clinical characteristics and predictive factors for recurrence. *Lupus* 2015; **24**: 628-632 [PMID: 25391541 DOI: 10.1177/0961203314558858]

20 **Shor DB**, Dahan S, Comaneshter D, Cohen AD, Amital H. Does inflammatory bowel disease coexist with systemic lupus erythematosus? *Autoimmun Rev* 2016; **15**: 1034-1037 [PMID: 27481039 DOI: 10.1016/j.autrev.2016.07.027]

21 **Kong X**, Diao S, Xu H, Sun J, Ma B. Association between miRNA-499 gene polymorphism and autoimmune diseases: A meta-analysis. *PLoS One* 2022; **17**: e0266265 [PMID: 35358276 DOI: 10.1371/journal.pone.0266265]

22 **Aynacıoğlu AŞ**, Bilir A, Tuna MY. Involvement of midkine in autoimmune and autoinflammatory diseases. *Mod Rheumatol* 2019; **29**: 567-571 [PMID: 30217121 DOI: 10.1080/14397595.2018.1523701]

23 **Xie W**, Jiang H, Chen Y, Zhang H, Song Y, Yu Z, Gu H, Xu H, Han S, Li S, Liu N. Association between systemic lupus erythematosus and inflammatory bowel disease in European and East Asian populations: a two-sample Mendelian randomization study. *Front Immunol* 2023; **14**: 1199896 [PMID: 38022503 DOI: 10.3389/fimmu.2023.1199896]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com