ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 March 16; 11(8): 1669-1887

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 11 Number 8 March 16, 2023

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

Prospective Study

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 8 March 16, 2023

Contents

CASE REPORT

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 8 March 16, 2023

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Zaza Demetrashvili, FACS, FICS, MD, PhD, Professor, Department of Surgery, Tbilisi State Medical University, Tbilisi 0177, Georgia. zdemetr@yahoo.com

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, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJCC* as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The *WJCC*'s CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Hua-Ge Yu*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

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

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

PUBLICATION DATE
March 16, 2023

COPYRIGHT
© 2023 Baishideng Publishing Group Inc

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

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

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

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

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

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

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

ONLINE SUBMISSION
https://www.f6publishing.com

© 2023 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1669-1683

DOI: 10.12998/wjcc.v11.i8.1669

ISSN 2307-8960 (online)

REVIEW

Understanding the multifaceted etiopathogenesis of foot complications in individuals with diabetes

Tatjana Matijević, Jasminka Talapko, Tomislav Meštrović, Marijan Matijević, Suzana Erić, Ivan Erić, Ivana Škrlec

Specialty type: Medicine, general and internal

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Corvino A, Italy; Rastogi A, India

Received: December 7, 2022
Peer-review started: December 7, 2022
First decision: January 17, 2023
Revised: February 1, 2023
Accepted: February 17, 2023
Article in press: February 17, 2023
Published online: March 16, 2023

Tatjana Matijević, Department of Dermatology and Venereology, University Hospital Center Osijek, Osijek 31000, Croatia

Jasminka Talapko, Ivana Škrlec, Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek 31000, Croatia

Tomislav Meštrović, University Centre Varaždin, University North, Varaždin 42000, Croatia

Tomislav Meštrović, Institute for Health Metrics and Evaluation and the Department for Health Metrics Sciences, University of Washington School of Medicine, Seattle, WA 98195, United States

Marijan Matijević, Department of Surgery, National Memorial Hospital Vukovar, Vukovar 32000, Croatia

Suzana Erić, Ivan Erić, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek 31000, Croatia

Suzana Erić, Department of Radiotherapy and Oncology, Clinical Hospital Center Osijek, Osijek 31000, Croatia

Ivan Erić, Department of Surgery, Osijek University Hospital Centre, Osijek 31000, Croatia

Corresponding author: Ivana Škrlec, MSc, PhD, Assistant Professor, Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Crkvena 21, Osijek 31000, Croatia. iskrlec@fdmz.hr

Abstract

Diabetes mellitus, a chronic disease of metabolism, is characterized by a disordered production or cellular utilization of insulin. Diabetic foot disease, which comprises the spectrum of infection, ulceration, and gangrene, is one of the most severe complications of diabetes and is the most common cause of hospitalization in diabetic patients. The aim of this study is to provide an evidence-based overview of diabetic foot complications. Due to neuropathy, diabetic foot infections can occur in the form of ulcers and minor skin lesions. In patients with diabetic foot ulcers, ischemia and infection are the main causes of non-healing ulcers and amputations. Hyperglycemia compromises the immune system of individuals with diabetes, leading to persistent inflammation and delayed wound healing. In

addition, the treatment of diabetic foot infections is challenging due to difficulty in accurate identification of pathogenic microorganisms and the widespread issue of antimicrobial resistance. As a further complicating factor, the warning signs and symptoms of diabetic foot problems can easily be overlooked. Issues associated with diabetic foot complications include peripheral arterial disease and osteomyelitis; accordingly, the risk of these complications in people with diabetes should be assessed annually. Although antimicrobial agents represent the mainstay of treatment for diabetic foot infections, if peripheral arterial disease is present, revascularization should be considered to prevent limb amputation. A multidisciplinary approach to the prevention, diagnosis, and treatment of diabetic patients, including those with foot ulcers, is of the utmost importance to reduce the cost of treatment and avoid major adverse consequences such as amputation.

Key Words: Diabetic foot; Diabetes mellitus; Foot ulcer; Infection; Peripheral arterial disease

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Diabetic foot disease is a common and debilitating consequence of diabetes mellitus. Unfortunately, the recurrence rate of diabetic foot ulcers is exceptionally high, even after effective wound healing. Risk factors for foot ulcers in diabetes include peripheral neuropathy, peripheral arterial disease, mild or recurrent foot trauma, infection, foot abnormalities, history of diabetic foot ulcers or amputations, and Charcot osteoarthropathy. However, poor wound healing is thought to be the major cause of long-term diabetic wounds, while the presence of polymicrobial infections may further compound this issue. Additional studies are needed to understand the underlying mechanisms and fill the knowledge gaps that would ultimately lead to successful treatment.

Citation: Matijević T, Talapko J, Meštrović T, Matijević M, Erić S, Erić I, Škrlec I. Understanding the multifaceted etiopathogenesis of foot complications in individuals with diabetes. *World J Clin Cases* 2023; 11(8): 1669-1683
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1669.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1669

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by insufficient insulin production or cellular insulin use, currently affecting around 537 million people worldwide. This number is forecasted to grow to 693 million by 2045 if adequate preventive measures are not implemented[1,2]. The projected increase in prevalence is higher in developing countries compared to developed, high-income countries [3]. Diabetes mellitus types 1 and 2, despite having different pathogenic mechanisms, tend to have similar associated complications[4]. One of the most severe complications of diabetes and the most common cause of hospitalization in diabetic patients is diabetic foot disease, which is a term that includes infections, diabetic foot ulcers (DFU), and gangrene[5,6]. The risk of developing DFU in diabetic patients is 25%, and is similar for patients with DM type 1 or type 2[6,7]. Consequently, diabetes is one of the leading causes of limb amputation worldwide, as it accounts for more than 60% of non-traumatic lower extremity amputation, with approximately 80%-85% being preceded by DFU[8,9]. This statistic implies that annually, more than 1 million people with diabetes suffer limb loss. To put this staggering number into perspective, every 20 s, there is a need for amputation somewhere in the world due to diabetes[8,9]. People with diabetes and diabetic foot complications have a higher mortality rate than those without foot complications[10,11]. Furthermore, individuals with diabetes have increased mortality after incidence of DFU compared to people of the same age and duration of diabetes without DFU[12]. This mortality is further increased in diabetic patients with foot disease necessitating amputation[11]. Ischemic heart disease is a significant cause of premature mortality in patients with DFU, and those with neuropathic DFU have even higher mortality[12,13]. Thus, it is evident that diabetes represents a substantial public health and economic burden; more specifically, financial costs related to the treatment of diabetes reach up to 673 million dollars (USD) annually, and 20%-40% of the healthcare budget spent on diabetes is related to foot complications[5,14,15]. Apart from financial burden, diabetic foot disease (particularly DFU) is a major personal tragedy with a significant impact on quality of life for patients and their families, and can represent a major burden for health care professionals and institutions as well. Despite the generally accepted need for a multidisciplinary approach in the prevention, diagnosis, and management of individuals with diabetes, including patients with DFU, data related to financial cost and the sequelae of diabetic foot complications (especially major

amputations) is still insufficient[9]. Although guidelines related to diabetic foot management are available, there is only limited high-quality evidence to address remaining critical questions. Therefore, a better understanding of diabetic foot complications is fundamental for further improvement in the care of this group of patients.

PATHOPHYSIOLOGY

Foot ulcers in individuals with diabetes arise *via* a specific given pathophysiologic mechanism, which can affect clinical presentation and management. Ischemia and neuropathy are two key pathological components that can lead to diabetic foot complications, while infection usually arises as a secondary phenomenon. Nevertheless, all three components often have a synergistic role in the etiologic triad[6]. Peripheral neuropathy is present in around 50% of diabetic patients, who often gradually develop "high-pressure" zones on foot with decreased protective sensation, a phenomenon considered the leading cause of DFU[16]. Although it seems changes are arising with respect to the accepted etiopathology, ischemia has an increasingly prominent role. Recent large-scale studies have shown that in high-income countries, almost half of DFUs are neuroischemic or ischemic in origin, and patients presenting with manifest peripheral arterial disease (PAD) and frank neuropathic ulcers are still more prevalent in low-income countries[3,17-22].

The pathogenesis of diabetic neuropathy is still not fully understood, but it is known that diabetes and associated aberrant glucose metabolism can affect sensory, motor, and autonomic fibers[14]. Two accepted potential mechanisms include ischemic injury to the nerve due to changes to vasa nervorum and oxidative stress in the nerve caused by increased activity of the sorbitol pathway[6]. Sensory neuropathy causes decreased pain and pressure sensation, vibratory perception, proprioception, and altered temperature sensation. Motor neuropathy causes atrophy of foot muscles with secondary foot deformity and impaired gait, leading to high plantar pressure and elevated mechanical stress[23]. Finally, autonomic neuropathy causes anhidrosis, which makes dry skin susceptible to minor fissures and causes impaired microcirculation through arteriovenous shunts[6,24,25].

Microvascular dysfunction in patients with diabetes is also caused by structural and functional changes in endothelial cells, resulting in impaired vasodilatory response, hypercoagulation, and inflammation in the vessel wall[23,26]. Although ischemic complications in diabetes have long been attributed to changes in microcirculation, which mistakenly led to the pervasive opinion that people with diabetes will not benefit from revascularization, today it is known that microvascular dysfunction and PAD are the leading cause of vascular impairment in patients with diabetes[6,27]. Also, PAD and infection impair healing of DFU, and are two main factors leading to amputation in people with diabetes[17,28,29]. PAD in diabetes has some specific charateristics compared to that in the general population. For example, atherosclerotic plaques are usually multisegmental, bilateral, located in infrapopliteal vessels, and involve anterior and posterior tibial arteries with relative sparing of foot arteries. Impaired collateral formation has also been documented[23,27,30].

People with diabetes are more susceptible to infections due to neuropathy, PAD, microcirculation dysfunction, and immunopathy[6,29]. Diabetic foot infections (DFI) can occur in sites of minor skin breaks caused by neuropathy, but most often occur within ulcers[31]. Infection can be uncomplicated and superficial; however, compared to infection in the general population, DFI are more prone to rapid spread to deep structures of the foot, including the fascia, tendons, muscles, joints, and bones. In addition, because of the anatomic compartments of the foot, infection usually spreads along the tendons. At the same time, the ensuing inflammatory response can cause high pressures in these compartments and further impair circulation, leading to a more rapid progression of infection[32-34]. Therefore, DFI can easily become a foot- and life-threatening condition and is a direct cause of amputation in 25%-50% of individuals with diabetes, especially if it arises in the setting of PAD[5,23,31]. Risk factors for developing DFI include neuropathy, limb ischemia, chronic or recurrent deep foot ulcer, traumatic ulcer, chronic renal failure, and poor glycemic control[31,35].

Finally, it should be emphasized that not all patients with diabetes are at risk for DFU[8]. Established neuropathy, foot deformity, and PAD are the main risk factors. Additional risk factors are history of foot ulceration or any limb amputation[36,37]. Patients who develop DFU are usually those with long-standing diabetes (> 10 years), who are male, have poor glycemic control, and have other diabetes-related comorbidities[38]. An incipient trigger for foot ulcer is often a minor injury caused by repetitive trauma while walking in patients with decreased protective sensation, changed biomechanics, and foot deformity with high-pressure zones resulting from neuropathy. Furthermore, the skin of individuals with diabetes is often dry due to autonomic neuropathy and as such is more prone to breakdown and fissure[5,6]. Although foot ischemia as the causative factor in DFU was once underestimated, it is now known that at least half of DFU is neuroischemic or ischemic in origin[17,19]. Ischemia and infection are the main contributing factors in non-healing ulcer and amputation in patients with DFU[17,28].

IMMUNE RESPONSE TO HYPERGLYCEMIA

The immune system regulates inflammation and works to maintain homeostasis[39]. In addition, the innate and adaptive immune systems have an essential function in promoting all stages of wound healing[40]. The innate immune system consists of different types of cells (*e.g.*, macrophages, monocytes, lymphocytes, basophils, natural killer cells, granulocytes, and mast cells)[40]. It is activated quickly, but with limited specificity[40]. On the other hand, the adaptive immune system includes T- and B-lymphocytes and is activated more slowly with long-term memory and high specificity[40].

The immune system of individuals with diabetes is weaker than in those without diabetes, and hyperglycemia increases the number of macrophages and pro-inflammatory cytokines, directly affecting phagocytosis, chemotaxis, and leukocyte activity[40,41]. The imbalance of immune cells leads to the deterioration of the immune environment of the wound, propagating the inflammatory phase and impairing wound healing[39]. This delayed and incomplete wound healing process leads to impaired healing is thought to underlie development of DFU[42]. Acute wounds typically heal with time, while chronic wounds do not due to continuation of the early inflammatory reaction[40]. Non-healing wounds act as entry points for microorganisms implicated in wound infection[43]. Adequate control of hyperglycemia can accelerate wound healing and help to avoid adverse effects on cellular immunity and infection[41].

Dysfunction of immune cells like neutrophils and monocytes can lead to oxidative stress and inflammation during diabetic wound healing[42]. Diabetic wounds are permanently arrested in the inflammatory phase, which promotes wound infection. Deficits in the innate immune response can also contribute to infection[43]. In addition, hyperglycemia can impair the proliferation and migration of fibroblasts and keratinocytes, resulting in unsuccessful epithelization[43].

Neutrophils participate in the early stages of wound healing[42]. At the wound site, there are high levels of neutrophil elastase, which originates from neutrophil extracellular traps (NETs) and contributes to the degradation of the wound matrix, thus delaying wound healing especially in diabetic patients[42].

Macrophages comprise two main types, namely inflammatory macrophages (M1) and wound-healing macrophages (M2)[42]. During the normal wound healing process, there is a predominance of M1 macrophages in the initial stages, followed by polarization of these cells into M2 macrophages[39]. Macrophages initiate the inflammatory phase of diabetic wound healing, while the delayed polarization of macrophages from pro-inflammatory (M1) to the anti-inflammatory (M2) type leads to aberrant wound healing and chronic inflammation[42]. M1 macrophages eliminate pathogenic bacteria, cellular debris, and damaged matrix, promoting inflammation[39]. M2 macrophages are anti-inflammatory and have the ability to suppress the inflammatory response by releasing IL-4 and IL-10[39]. Hyperglycemia prevents the polarization of macrophages from the M1 to the M2 phenotype[39]. This is important, as the polarization from M1 to M2 enables the timely restoration of damaged skin[42]. Furthermore, hyperglycemia and an immunosuppressive environment in individuals with diabetes lead to macrophage dysfunction and reduce phagocytic capacity[42]. The proportion of M1 macrophages in diabetic wounds is increased, and impaired polarization to the M2 phenotype in diabetic wounds is associated with reduced angiogenesis, poor collagen deposition, and decreased wound closure[42]. Depletion of anti-inflammatory M2 macrophages in the wound causes further tissue damage[42].

Diabetic patients, especially those with DFU, have a significantly lower number of naïve T-cells and an increased number of memory and effector T-cells[40,42,44]. In addition, the expression of inflammatory chemokine receptors is significantly reduced in individuals with diabetes[40,44]. The decrease in the diversity of T-cell receptors and the proliferation of effector T-cells can be seen as biomarkers of inflammation due to chronic DFU[42]. A subpopulation of regulatory T-cells (Treg) promotes the repair and regeneration of various tissues, including the skin[40]. Treg plays an essential role in angiogenesis and tissue regeneration in diabetic wounds, and people with diabetes have impaired function of these cells[40,42]. Specifically, diabetes sustains a constant pro-inflammatory environment with elevated levels of IL-1, TNF-α, and IL-6 and regulation of regular T cell expression[42].

In a nutshell, wound healing is a complex process that results in the establishment of normal physiological function[43]. The wound healing process involves several overlapping phases (coagulation, inflammation, proliferation, and remodeling)[40,43]. During the normal wound healing process, there is an initial recruitment of platelets that create a fibrin clot, followed by the recruitment of inflammatory cells (monocytes and neutrophils) that release pro-inflammatory cytokines[40,43]. After the inflammation subsides, a proliferative phase follows, characterized by angiogenesis (*i.e.* the creation of new blood vessels) and the polarization of M1 macrophages into M2 macrophages[43]. M2 macrophages promote the secretion of anti-inflammatory cytokines and angiogenesis, as well as the proliferation of fibroblasts and the formation of extracellular matrix[40]. Consequently, scar tissue formation and remodeling into healed tissue ensues[40].

In diabetic wounds, this process is somewhat different. Diabetic wounds demonstrate impaired recruitment of platelets and increased recruitment of neutrophils and M1 macrophages, resulting in an increased pro-inflammatory response and damage to the surrounding tissue[40]. Due to the increased secretion of inflammatory cytokines, this phase is prolonged in DFU, making it more difficult to progress to the next stage of healing[43]. As the inflammatory phase is prolonged, angiogenesis does not

occur. Poor microcirculation then creates a hypoxic environment, leading to oxidative stress, inflammatory polarization of M1 macrophages, and damage to fibroblasts[40]. Polarization to M2 macrophages is very weak, and as a result damaged cells remain in an inflammatory state and re-epithelialization does not occur, ulceration of the skin occurs, and the wound fails to heal[40,43].

MICROBIOLOGICAL PROFILE OF DIABETIC FOOT INFECTIONS

The microbiological causes of diabetic foot infection, which is a frequent complication of DFU, have been increasingly clarified with the pervasive utilization of both classical microbiological and molecular methods. One of the most important challenges is to delineate microorganisms that are purely incidental from those which are true pathogens, as it is known that the infections of diabetic foot may harbor a plethora of different species[45,46]. There may also be a question of contamination, where the microbiological analysis of the diabetic foot is further hindered by the potential presence of commensal bacteria in clinical samples[46]. On the other hand, conventional culturing methods may also give rise to false negative results, as more than 37% of samples are considered culture-negative[45].

In accordance with the guidelines published by the Infectious Diseases Society of America (IDSA), diabetic foot infections can be classified into three distinct categories: Limited superficial infections presenting with mild symptoms; deeper moderate infections leading to more pronounced symptoms; and severe infections with metabolic changes and true systemic response[47,48]. These various clinical presentations warrant different approaches in treatment, as superficial and moderate infections necessitate the administration of narrow-spectrum antimicrobials orally or intravenously for only a short period of time, whereas severe infections require parenteral administration of broad-spectrum antibiotics[49]. However, the exact characterization of a causative pathogen enables a more targeted treatment approach, as antimicrobial sensitivity testing can be pursued in this scenario[49].

A recent meta-analysis has shown that the most frequent aerobic microorganisms isolated from diabetic foot infection are *Staphylococcus aureus* (23.4%), *Escherichia coli* (11.5%), *Pseudomonas* spp. (11.1%), *Proteus* spp. (8.3%), *Klebsiella* spp. (6.9%) and *Enterococcus* spp. (5.4%)[46]. There was also a high frequency of coagulase-negative staphylococci observed in this study, likely indicating a combination of true pathology and sample contamination when commensals are introduced into damaged and dysfunctional tissues. Among those infections caused by *S. aureus*, a significant prevalence of methicillin-resistant *S. aureus* (MRSA) was observed (18%), which is in line with previous estimates[46,50,51]. Other studies have shown that harbingers of protracted infections and frequent relapses are usually of two bacterial genera: *Acinetobacter* spp. and *Enterococcus* spp.; however, *Citrobacter* spp. predominate in DFU affecting women[49,52,53]. Interestingly, a higher prevalence of Gram-positive microbial isolates in diabetic foot wounds is generally observed in high-income countries when compared to low- and middle-income countries, where Gram-negative isolates predominate. This may reflect differences in hygiene, sanitation, and footwear usage[46,54,55].

In any case, the monomicrobial vantage point is rather narrow. The use of molecular techniques in recent studies have corroborated the assumption of a polymicrobial nature of chronic wounds including diabetic foot ulcers[56-58]. More specifically, bacteria and other organisms found in foot infections may demonstrate specific non-random polymicrobial patterns that can correlate with clinical factors and wound chronicity[59,60]. This could have direct clinical implications for the optimization of antimicrobial treatment (particularly if the aim is to cover all potential organisms pertinent for such processes) and understanding further evolution of polymicrobial diabetic foot infections (from the perspective of interactions that could have a synergistic or alleviating effect on microbial burden, expression of genes, or pathogenicity)[61-63].

A recent study by Barshes *et al*[63] suggested three species co-occurrence patterns: (1) The most pervasive *S. aureus*-dominant pattern (characterized by the absence of *Staphylococcus epidermidis* and other coagulase-negative or nonspeciated staphylococci); (2) A coagulase-negative staphylococci dominate pattern (*i.e.* the inverse of the *S. aureus*-dominant pattern with the absence of *S. aureus*); and (3) A so-called "pattern C," characterized by the absence of *Bacteroides* spp. and *Corynebacterium* spp. and the presence of two or more of alpha-hemolytic streptococci, *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., or *Enterococcus faecalis*. Simply put, these co-occurrence patterns show that *S. aureus* is rarely seen with coagulase-negative staphylococci, while Proteobacteria can be seen with enterococci and alpha-hemolytic streptococci, but not with corynebacteria. In addition, patients that have a polymicrobial diabetic foot infection belonging to the aforementioned "pattern C" group have substantially higher rates of treatment-resistant osteomyelitis[63].

Similar patterns have been reported in other studies. Gardner *et al*[59] discerned a *Staphylococcus*-dominated pattern, a streptococci-dominated pattern, and a high-diversity pattern, the latter typically including members of the phylum Proteobacteria. This means that diabetic foot infections are more commonly polymicrobial in nature when compared to bone and soft tissue infections in other locations, and that the spectrum of microorganisms isolated from foot bone and soft tissue can be comparable among different individuals but distinct from that isolated from other locations in the body[63,64]. This is not simply an academic exercise, as the recognition of specific microbial profiles and patterns has

important clinical implications. For example, recognizing either polymicrobial "pattern C" or isolating *P. aeruginosa* can be considered high risk for treatment failure, and a recent study showed that 15% of patients with infection caused by *P. aeruginosa* ultimately required amputation[49]. Understanding these nuanced interactions might prompt specific intervention; for example, probiotics may be used to fill the niche with beneficial bacteria and eliminate hazardous ones[65,66].

Finally, the frequency of antimicrobial resistance is becoming a true public health concern and is essential to consider in the treatment of diabetic foot infections[67,68]. Even studies published 10 years ago have demonstrated a high prevalence (up to 33%) of resistant bacteria present in diabetic ulcers[69, 70]. The fact that diabetic patients are prone to developing foot infections and that PAD and cigarette smoking may increase the risk of diabetic foot infection[47,49,53], the control of these infections may become increasingly difficult with the continued rise of resistant microorganisms. As a result, there will likely be many negative downstream effects for the healthcare system.

Bacterial biofilm formation also plays a major role in the development of chronic DFU. Biofilms form when commensal and pathogenic bacteria symbiotically merge, perpetuating chronic infection[71]. The presence of biofilms often necessitates complex treatment, which contributes to antibiotic resistance[71]. The most common reason for unsuccessful treatment of biofilm infections with conventional antibiotics is the inability of drugs to pass through the exopolysaccharide matrix formed by sessile cells[72,73]. The seriousness of such infections is demonstrated by the fact that 80% of lower limb amputations in patients with diabetes and foot ulceration are caused by biofilm-forming species. Overall, biofilm is present in 60% of chronic wounds and 6% of acute wounds associated with DFU[74]. For the detection of biofilm in deep tissues, the appropriate sample is a tissue biopsy. Techniques for quantifying biofilm in biopsy specimens include fluorescence in situ hybridization, scanning electron microscopy, and confocal laser scanning microscopy[75-79]. Due to the presence of biofilm, treatment of DFU with conventional antibiotics is problematic, as resistance to these drugs quickly develops[14,71]. Accordingly, new strategies must be developed to solve this problem. Phage, silver nanoparticle, and antimicrobial peptide therapies are being introduced as alternatives to antibiotic drugs[72,80-82].

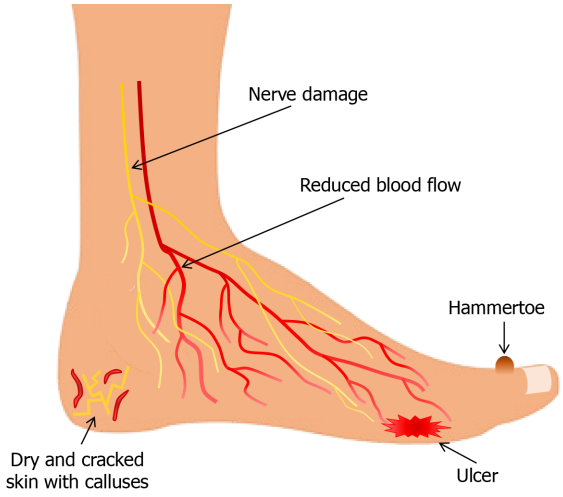
Fungal pathogens may also compound the issue of diabetic foot infection. Their prevalence varies between 5% and 27%, with *Candida* spp. being the most frequently isolated organisms[83-85]. Mold infections are much less prevalent, but can be more menacing in comparison to infections in which only *Candida* is implicated. However, there are just a handful of case reports documenting infections with *Aspergillus ochraceus* or species of the genera *Blastomyces* or *Fusarium*, with skin and nails being the main entry portals[84,86,87]. In any case, consideration of fungal or mold infection must be included in the approach to diabetic foot infection in order obtain a full microbiological profile to guide treatment.

CLINICAL PRESENTATION

The diabetic foot at first glance may have a seemingly normal appearance, and symptoms and signs of complications can easily be missed. However, the clinical presentation of the diabetic foot has some specific characteristics that are important for every clinician to recognize, especially those actively caring for the diabetic patient population.

Due to atrophy of lumbrical and interosseus muscles caused by motor neuropathy, the anatomy of the diabetic foot changes such that the arch and toes are pulled in a "claw" position with prominent metatarsal heads, hammertoe contracture of digits, and other bony prominences. These deformations can create focal areas of high pressure at which susceptibility for ulcer development is increased. Charcot neuroarthropathy (CN) is a severe diabetic foot complication that significantly increases morbidity and mortality, and primarily is seen in patients with concomitant DFU. Patients with CN have a life expectancy reduced by an average of 14 years. CN is characterized by bone and joint destruction, and can be asymptomatic or can mimic other more common conditions such as cellulitis, osteomyelitis, deep vein thrombosis, inflammatory arthritis, or ankle sprain. Due to variability in the presence of symptoms and the variety of potential mimickers, CN is often overlooked in the evaluation of the diabetic foot. In the acute phase, this condition presents as a warm, swollen red joint, often in the absence of pain. In the early stages of CN, there are no clinical signs of bone fracture, but radiological examination usually shows microfractures. Up to 58% of patients with CN also have DFU on initial presentation. Additionally, CN can lead to mid-foot collapse, rocker-bottom foot (collapse and inversion of the plantar arch), acute fracture, and joint dislocation if left untreated[6,23]. With or without extreme deformities such as those seen in CN, the skin of the diabetic foot is usually dry and cracked and often has calluses indicative of increased pressure. In addition, pre-ulcerative signs such as localized redness, blisters, fissures, or hemorrhage may be present[36,37] (Figure 1).

If concomitant with PAD, the diabetic foot appears pale and cold. However, in an ischemic setting, the foot may conversely be warm and pink due to the presence of arteriovenous shunts, the early stages of CN, or fracture. Moreover, tissue ischemia can manifest as pain at rest, claudication, gangrene, or ulceration. However, classical signs and symptoms of PAD may not always be present in diabetic patients with PAD[20]. Therefore, the assessment of vascularization in diabetes should not be performed by clinical examination only. Moreover, clinical signs and symptoms of DFI are often



DOI: 10.12998/wjcc.v11.i8.1669 **Copyright** ©The Author(s) 2023.

Figure 1 Clinical presentation of the diabetic foot.

diminished due to PAD, neuropathy, and immunopathy[31]. These signs and symptoms include redness, warmth, swelling, pain, and purulent secretion. Furthermore, even in the presence of deep infection, usual systemic signs of infection (*e.g.*, fever, elevated white blood cell count) may or may not be apparent. C-reactive protein (CRP) concentrations can be absent or diminished, also contributing to delayed diagnosis. If CRP levels are elevated, this could indicate severe infection, potentially limb- or life-threatening[5,31,88]. Sometimes, the only sign of infection in the setting of DFU can be unexplained hyperglycemia[6]. If a foot ulcer is present, the most common infection symptom is excessive exudate. However, an accurate clinical assessment of an ulcer can be hampered by the presence of a superficial eschar, which must be removed to reveal possible abscess and involvement of deep structures[6,89,90].

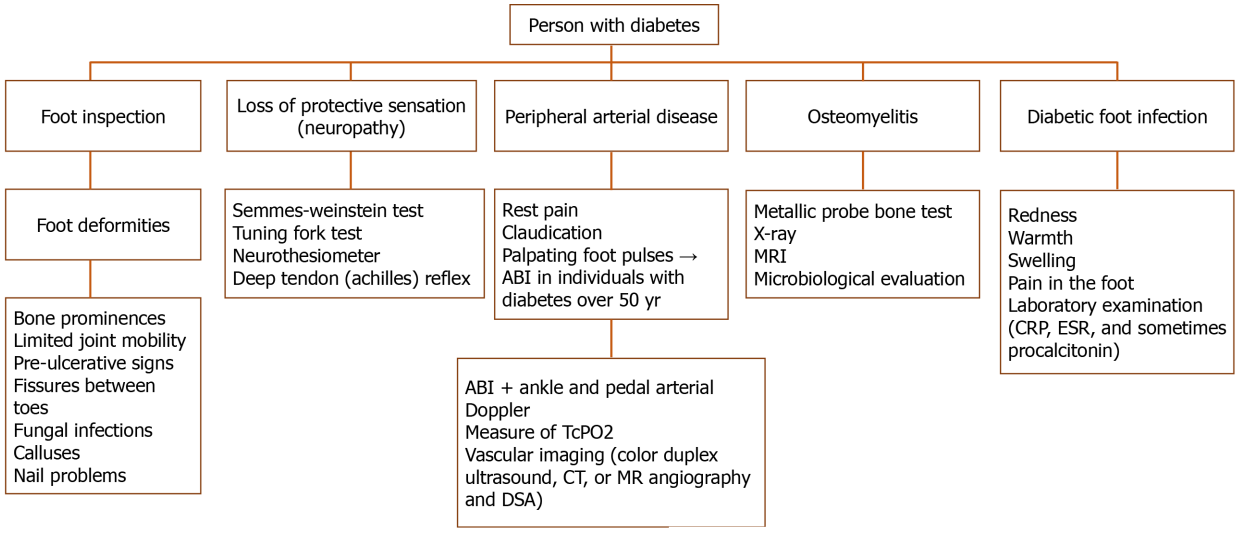
DIAGNOSTIC EVALUATION

All patients with diabetes should be screened annually to assess the risk of foot complications (Figure 2). These patients should be stratified into high-risk and no-risk using the International Working Group on the Diabetic Foot (IWGDF) risk stratification system to establish the necessary frequency of further visits and examinations. This basic evaluation is part of the prevention strategy and includes foot inspection, evaluation of loss of protective sensation (*i.e.* neuropathy), and assessment of PAD. For full risk assessment, the primary evaluation should also include taking of a general medical history as well as a foot-specific history to include instances of previous foot ulceration or amputation. Special attention should be given to assessment of pertinent comorbidities, especially end-stage renal disease[90].

Foot inspection should establish any presence of foot deformities, bony prominences, limited joint mobility, and pre-ulcerative signs. Also, the clinician should actively and thoroughly search for other signs of ulceration or infection, which often can be hidden (*e.g.*, between the toes). The clinician should also inspect for and document any fissures, fungal infections, calluses, or nail problems[90].

Almost all working groups agree that the Semmes-Weinstein test is the most important in the evaluation of neuropathy, as studies have shown that it has high sensitivity for identifying patients at risk and is predictive of foot ulceration[5,9,91]. This test is performed by applying pressure stimulation to defined areas on the foot with nylon monofilaments[6,9]. Other tests (*e.g.*, tuning fork and neurothesiometer tests) can also assess for the presence of neuropathy, but studies have shown that these are less predictive of foot ulceration[6]. The deep tendon (Achilles) reflex should be also examined [5,23].

In all patients with diabetes, vascularization should be assessed annually by taking the relevant history (*i.e.* rest pain, claudication) and palpating foot pulses. The most valuable noninvasive diagnostic method for diagnosing PAD is the ankle-brachial index (ABI)[20]. ABI should be performed in all individuals with diabetes aged 50 or older, regardless of the presence of other risk factors. If other risk factors are present, this test should be performed annually. This approach should also be used for all patients with diabetic foot ulcers[9], as it will not only aid in the diagnosis of PAD but also in evaluating the potential for ulcer healing, the need for revascularization, and the risk for limb amputation[92]. ABI is usually combined with ankle and pedal arterial Doppler assessment[20]. Because of frequent advanced arterial calcification in people with diabetes, ABI can be falsely elevated. Therefore, it is often recommended to measure toe or transcutaneous oxygen pressure, both of which have been shown to be good predictors of ulcer healing potential or the need for revascularization[5,20]. If the ulcer is not



DOI: 10.12998/wjcc.v11.i8.1669 **Copyright** ©The Author(s) 2023.

Figure 2 Flow diagram for screening for foot complications in persons with diabetes. ABI: Ankle-brachial index; CRP: C-reactive protein; DSA: Digital subtraction angiography; ESR: Erythrocyte sedimentation rate; TcPO2: Transcutaneous oxygen pressure.

healing, when considering revascularization or when critical ABI is present, vascular imaging should be ordered. Useful imaging modalities include color duplex ultrasound, computed tomography, methicillin-resistant angiography and, in some instances, digital subtraction angiography[20].

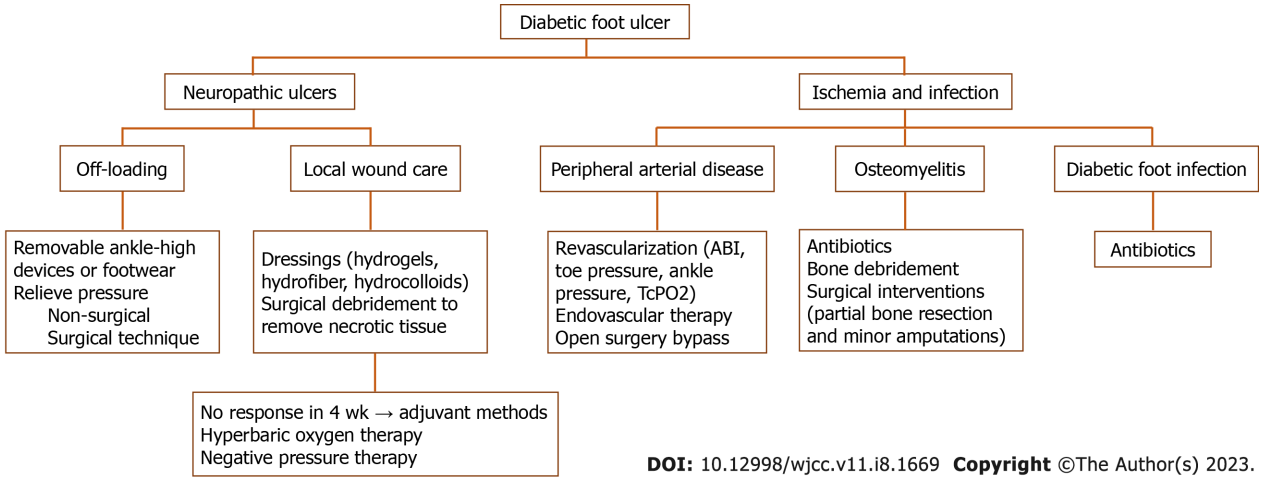
For the diagnosis of diabetic foot infection, including infection of DFU, it is recommended to start with appraising classical clinical signs of infection such as redness, warmth, swelling, pain in the foot, and possible entry of pathogens through minor skin fissures[31]. Additionally, the most common sign of an infected ulcer is increased exudate. However, the severity of infection should be assessed after wound debridement and evaluation of the extent and depth of infection with consideration of any masking superficial eschar[5,88]. If clinical findings are unclear, laboratory examination with CRP, ESR, and sometimes procalcitonin should be performed. However, diagnosis of infection in individuals with diabetes can be challenging as signs and symptoms are often subtle.

Further difficulties include diagnosing deep tissue infection, osteomyelitis, and CN, which can mimic infection. If osteomyelitis is suspected, a metallic probe bone test should be performed[31]. If a sterile probe hits the bone, the diagnosis of osteomyelitis is highly likely, with a positive predictive value of 89%[93]. A positive probe test, elevated CRP or procalcitonin, and plain X-ray findings compatible with osteomyelitis are sufficient for diagnosis. However, further diagnostic procedures should be performed in the case of equivocal findings. The plain X-ray has low sensitivity and specificity for osteomyelitis. Still, it should always be performed in patients with new DFI to detect possible foreign bodies, soft tissue gas, bone destruction, fracture, or deformity[9,94]. To diagnose osteomyelitis, it is better to perform two X-ray studies with an interval of at least 2 wk to detect changes in radiologic appearance [48]. At the moment, magnetic resonance is considered the best imaging modality, with 90% sensitivity and 79% specificity for osteomyelitis[94]. It is rarely necessary to obtain a bone specimen by debridement or biopsy for diagnosis. Still, an appropriate sample of the infected wound should always be collected for culture and microbiological evaluation before starting empirical therapy. Wound swabs should be avoided; the preferred method for sample collection is curettage or biopsy of the ulcer[31].

If a DFU is present, not only potential limb ischemia and infection should be assessed, but the characteristics of the ulcer should also be described. The most significant are the localization, size, and depth of the ulcer, as well as any presence of gangrene. Following reduction in the size of the ulcer, it is possible to predict treatment outcomes[95,96].

MANAGEMENT

In consideration of the complexity of diabetic foot pathophysiology, the necessity of a multidisciplinary approach to treating its complications is very evident (Figure 3). Studies have shown that adequate glycemic control with a glycosylated hemoglobin (HbA1c) goal of less than 6.5%-7% is important in preventing DFU and other complications, and can also significantly decrease the risk of amputation and improve the rate of wound healing[9,97,98]. Management should be directed towards all established contributing etiological factors to achieve adequate healing of the DFU. In the case of purely neuropathic ulcers, offloading and local wound care is most likely sufficient. Still, in the case of concomitant ischemia and infection, treatment may be more complicated.



DOI: 10.12998/wjcc.v11.i8.1669 **Copyright** ©The Author(s) 2023.

Figure 3 Algorithm for management of diabetic foot ulcer. ABI: Ankle-brachial index; TcPO2: Transcutaneous oxygen pressure.

Offloading strategies aim to relieve pressure on the extremity and prevent high-pressure focal zones, the most common site of ulcer development. A simple debridement of nonviable tissue or callus around the ulcer is often the best starting point for distributing the pressure. There are many offloading techniques available. If non-surgical offloading fails to promote healing of the ulcer, even with appropriate standard wound care, surgical offloading must be considered. The site of the ulcer determines the selection of the appropriate offloading device. For example, if the ulcer is located on the plantar side of the foot, a non-removable knee-high device like a total contact cast or non-removable knee-high walker are usually recommended. Removable knee- or ankle-high devices are recommended in case of contraindication or patient intolerance. Additionally, the offloading strategy should be determined accordingly if moderate or severe infection or ischemia are present[16]. Plantar heel ulcers are less prevalent than plantar forefoot or mid-foot ulcers. These ulcers are characterized by higher pressures, longer healing time, and more cumbersome pressure decrease *via* offloading[16,17,99]. If the ulcer is localized on the dorsal foot, removable ankle-high devices or footwear modifications, orthoses, or toe spacers can be used. It is extremely important to address patient compliance, as patients frequently forgo wearing recommended offloading devices[9,100]. Surgical techniques can help offload pressure from the ulcer and promote healing in selected patients. In patients with plantar metatarsal head ulcer, Achilles tendon lengthening, metatarsal head resection, or joint arthroplasty, surgery should be considered. Moreover, in patients with apex or digital plantar ulcers, digital flexor tenotomy can help decrease pressure to the ulcer site[16]. Also, surgical correction should be considered if there are foot deformities that cannot be managed with therapeutic footwear[5].

In patients with DFU and PAD, revascularization should always be considered, especially in those with a severe degree of ischemia as established by one or more appropriate test (*i.e.* ABI, toe pressure, ankle pressure, TcPO2) or in patients with non-healing ulcer and PAD regardless of test results. An ABI of 0.9-1.3 suggests that PAD is less likely, and an ABI less than 0.8 is associated with an increased risk of limb amputation[92]. Usually, it is recommended to use wound, ischemia, and foot infection classification to predict which patients with diabetes and PAD are more likely to require and benefit from revascularization[9,20]. There are two approaches to revascularization: Endovascular therapy and open surgical bypass. Randomized clinical trials providing evidence favoring one technique over the other are lacking[5,101]. However, there has been significant progress in endovascular medicine, and there are emerging endovascular techniques such as drug-eluting technologies for PAD management. Nevertheless, high-quality randomized studies to evaluate the efficacy of these techniques in diabetic foot patients are still lacking[102]. Furthermore, recent reports suggest an innovative treatment alternative for patients without endovascular or surgical options. Intravascular ultrasound (IVUS), a guided percutaneous deep vein arterialization with the creation of an arteriovenous fistula between the posterior tibial artery and its satellite deep vein, has shown promising results in such patients with critical limb ischemia[103]. Special consideration should be given to patients with DFU and PAD who are candidates for revascularization but have invasive foot infections, as they are at exceptionally high risk of amputation. In that case, the infection should be controlled before revascularization is pursued to avoid sepsis. Appropriate and aggressive therapy (*i.e.* surgical interventions and antibiotics) usually takes a few days to stabilize the patient. After stabilization, prompt revascularization should be considered to help resolve infection and improve circulation to avoid limb amputation[20].

Antibiotics are key to treating DFI, but they are often insufficient in controlling the infection, especially in the presence of polymicrobial infection, as described above. Hence, surgical treatment in managing DFI is often required due to the special features of DFI. Indications for surgical interventions include the involvement of deep tissues (especially bone), abscess formation, the presence of necrotic

tissue, compartment syndrome, and extensive gangrene. In such cases, prompt surgical incision allowing abscess drainage and debridement of necrotic tissue must be performed. Uncomplicated osteomyelitis can be initially treated with antibiotics for no longer than 6 wk. However, his strategy has limited long-term results in controlling infection[104,105]. Thus, surgical intervention such as partial bone resection or minor amputation is often necessary to manage infection. Selection, duration, and the route of antibiotic administration in treating DFI should be based on the likely causative pathogen and the clinical severity of infection. It is always preferable to prove a causative pathogen by tissue culture [31]. Using IDSA/IWGDF infection classification is also recommended to guide the management of DFI [9,106]. Finally, amputation below the knee may be necessary if minor amputation is insufficient to control infection or in the case of extensive tissue loss or severe tissue ischemia after failed revascularization[5,107]. Generally, surgeons should try to preserve the knee joint if possible as ambulation is significant in successful rehabilitation[6].

Finally, appropriate standards of local wound care should be followed to promote DFU healing. This involves frequent clinical evaluation with irrigation and debridement and use of modern dressings. There are different debridement methods available, but sharp surgical debridement is usually recommended to remove necrotic tissue in DFU[9,108]. Other possible techniques are hydrogels, occlusive dressings, larval therapy, enzymes, ultrasound, and hydrotherapy, but studies have yet to prove that any method is better than the others[109]. Dressings should provide optimal conditions for wound healing, including maintenance of a moist wound bed, exudate control with prevention of maceration of the surrounding skin, prevention of infection, and promotion of granulation tissue. They should also be comfortable for the patients and enable atraumatic dressing changes. Modern (advanced) non-adherent dressings usually meet these requirements. The most commonly used dressings are hydrogels, hydrofiber dressings, hydrocolloids, foam dressings, and alginates. Still, studies showed that none of these is superior to the others in promoting wound healing, and the choice is usually made based on the assessment of wound characteristics, comfort, and cost[9,108].

If improvement in DFU healing is not seen after a minimum of 4 wk of treatment with the standard of care, adjuvant methods should be considered. Hyperbaric oxygen therapy and negative pressure therapy are most often recommended[110]. However, before any other treatment modality is used, reevaluation of vascular status, the presence of infection, and high-pressure zones should be pursued[9, 108].

CONCLUSION

Although knowledge of diabetic foot problems has grown tremendously in recent years, there are still unmet therapeutic needs. DFU, often associated with infection or ischemia, is thought to precede the majority of diabetes-related lower extremity amputations and is the leading cause of non-traumatic lower extremity amputation worldwide. In patients with peripheral neuropathy or PAD, DFUs mainly result from mild or recurrent trauma to the foot. The pathophysiology of diabetic wound healing is complex, multidimensional, and remains to be fully understood. In addition, more than half of DFUs become infected, which impairs wound healing and increases the likelihood of foot amputation. The management of the diabetic foot is complex for any healthcare provider; however, as the number of people with diabetes increases, so does the need for DFU treatment. Hence, more targeted research endeavors are needed for establishment of an evidence-based approach to diabetic wound healing and improving patient quality of life.

FOOTNOTES

Author contributions: Matijević T performed the literature review and drafted the article; Talapko J conceived and designed the article, aided in interpretation of relevant literature, and assisted in drafting the article with significant contributions from Meštrović T, Matijević M, Erić S, and Erić I contributed to the interpretation of relevant literature and article drafting; Škrlec I coordinated the literature search and article and figure preparation and critically revised the manuscript. All authors have read and approved the final version of the manuscript.

Conflict-of-interest statement: All authors declare that they have no conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Croatia

ORCID number: Tatjana Matijević 0000-0002-3316-1391; Jasminka Talapko 0000-0001-5957-0807; Tomislav Meštrović 0000-

0002-8751-8149; Marijan Matijević 0000-0002-3615-5413; Suzana Erić 0000-0002-3060-3748; Ivan Erić 0000-0002-5511-6436; Ivana Škrlec 0000-0003-1842-930X.

S-Editor: Wang LL
L-Editor: Filipodia
P-Editor: Wang LL

REFERENCES

1 **Lin X**, Xu Y, Pan X, Xu J, Ding Y, Sun X, Song X, Ren Y, Shan PF. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Sci Rep* 2020; **10**: 14790 [PMID: 32901098 DOI: 10.1038/s41598-020-71908-9]
2 **International Diabetes Federation**. IDF Diabetes Atlas. 10th ed. Brussels; Belgium, 2021
3 **World Health Organization**. Global Report on Diabetes. Geneva, Switzerland: 2016 [cited 2022 Nov 12]. Available from: http://www.who.int/about/Licensing/copyright_form/index.html%0A
4 **Banday MZ**, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. *Avicenna J Med* 2020; **10**: 174-188 [PMID: 33437689 DOI: 10.4103/ajm.ajm_53_20]
5 **Lepäntalo M**, Apelqvist J, Setacci C, Ricco JB, de Donato G, Becker F, Robert-Ebadi H, Cao P, Eckstein HH, De Rango P, Diehm N, Schmidli J, Teraa M, Moll FL, Dick F, Davies AH. Chapter V: Diabetic foot. *Eur J Vasc Endovasc Surg* 2011; **42** Suppl 2: S60-S74 [PMID: 22172474 DOI: 10.1016/S1078-5884(11)60012-9]
6 **Kalish J**, Hamdan A. Management of diabetic foot problems. *J Vasc Surg* 2010; **51**: 476-486 [PMID: 19853400 DOI: 10.1016/j.jvs.2009.08.043]
7 **Armstrong DG**, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. *N Engl J Med* 2017; **376**: 2367-2375 [PMID: 28614678 DOI: 10.1056/NEJMra1615439]
8 **Schaper NC**, Apelqvist J, Bakker K. The international consensus and practical guidelines on the management and prevention of the diabetic foot. *Curr Diab Rep* 2003; **3**: 475-479 [PMID: 14611743 DOI: 10.1007/S11892-003-0010-4]
9 **Hingorani A**, LaMuraglia GM, Henke P, Meissner MH, Loretz L, Zinszer KM, Driver VR, Frykberg R, Carman TL, Marston W, Mills JL Sr, Murad MH. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *J Vasc Surg* 2016; **63**: 3S-21S [PMID: 26804367 DOI: 10.1016/j.jvs.2015.10.003]
10 **Walsh JW**, Hoffstad OJ, Sullivan MO, Margolis DJ. Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. *Diabet Med* 2016; **33**: 1493-1498 [PMID: 26666583 DOI: 10.1111/dme.13054]
11 **Al-Rubeaan K**, Almashouq MK, Youssef AM, Al-Qumaidi H, Al Derwish M, Ouizi S, Al-Shehri K, Masoodi SN. All-cause mortality among diabetic foot patients and related risk factors in Saudi Arabia. *PLoS One* 2017; **12**: e0188097 [PMID: 29176889 DOI: 10.1371/journal.pone.0188097]
12 **Rastogi A**, Goyal G, Kesavan R, Bal A, Kumar H, Mangalanadanam, Kamath P, Jude EB, Armstrong DG, Bhansali A. Long term outcomes after incident diabetic foot ulcer: Multicenter large cohort prospective study (EDI-FOCUS investigators) epidemiology of diabetic foot complications study: Epidemiology of diabetic foot complications study. *Diabetes Res Clin Pract* 2020; **162**: 108113 [PMID: 32165163 DOI: 10.1016/j.diabres.2020.108113]
13 **Chammas NK**, Hill RL, Edmonds ME. Increased Mortality in Diabetic Foot Ulcer Patients: The Significance of Ulcer Type. *J Diabetes Res* 2016; **2016**: 2879809 [PMID: 27213157 DOI: 10.1155/2016/2879809]
14 **Baig MS**, Banu A, Zehravi M, Rana R, Burle SS, Khan SL, Islam F, Siddiqui FA, Massoud EES, Rahman MH, Cavalu S. An Overview of Diabetic Foot Ulcers and Associated Problems with Special Emphasis on Treatments with Antimicrobials. *Life (Basel)* 2022; **12** [PMID: 35888142 DOI: 10.3390/life12071054]
15 **Poretsky L**. Principles of Diabetes Mellitus. Berlin/Heidelberg, Germany: Springer Science & Business Media, 2010 [DOI: 10.1007/978-0-387-09841-8]
16 **Bus SA**, Armstrong DG, Gooday C, Jarl G, Caravaggi C, Viswanathan V, Lazzarini PA; International Working Group on the Diabetic Foot (IWGDF). Guidelines on offloading foot ulcers in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev* 2020; **36** Suppl 1: e3274 [PMID: 32176441 DOI: 10.1002/dmrr.3274]
17 **Prompers L**, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, Edmonds M, Holstein P, Jirkovska A, Mauricio D, Ragnarson Tennvall G, Reike H, Spraul M, Uccioli L, Urbancic V, Van Acker K, van Baal J, van Merode F, Schaper N. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia* 2007; **50**: 18-25 [PMID: 17093942 DOI: 10.1007/S00125-006-0491-1]
18 **Morbach S**, Furchert H, Gröblinghoff U, Hoffmeier H, Kersten K, Klauke GT, Klemp U, Roden T, Icks A, Haastert B, Rümenapf G, Abbas ZG, Bharara M, Armstrong DG. Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. *Diabetes Care* 2012; **35**: 2021-2027 [PMID: 22815299 DOI: 10.2337/DC12-0200]
19 **Gershater MA**, Löndahl M, Nyberg P, Larsson J, Thörne J, Eneroth M, Apelqvist J. Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. *Diabetologia* 2009; **52**: 398-407 [PMID: 19037626 DOI: 10.1007/s00125-008-1226-2]
20 **Chuter V**, Quigley F, Tosenovsky P, Ritter JC, Charles J, Cheney J, Fitridge R; Australian Diabetes-related Foot Disease Guidelines & Pathways Project. Australian guideline on diagnosis and management of peripheral artery disease: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *J Foot Ankle Res* 2022; **15**: 51 [PMID: 35787293 DOI: 10.1186/s13047-022-00550-7]
21 **Monteiro-Soares M**, Russell D, Boyko EJ, Jeffcoate W, Mills JL, Morbach S, Game F; International Working Group on the Diabetic Foot (IWGDF). Guidelines on the classification of diabetic foot ulcers (IWGDF 2019). *Diabetes Metab Res*

Rev 2020; **36** Suppl 1: e3273 [PMID: 32176445 DOI: 10.1002/dmrr.3273]
22 **Hinchliffe RJ**, Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, Katsanos K, Mills JL, Nikol S, Reekers J, Venermo M, Zierler RE, Schaper NC; International Working Group on the Diabetic Foot (IWGDF). Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev* 2020; **36** Suppl 1: e3276 [PMID: 31958217 DOI: 10.1002/dmrr.3276]
23 **Bandyk DF**. The diabetic foot: Pathophysiology, evaluation, and treatment. *Semin Vasc Surg* 2018; **31**: 43-48 [PMID: 30876640 DOI: 10.1053/j.semvascsurg.2019.02.001]
24 **Steed DL**, Attinger C, Colaizzi T, Crossland M, Franz M, Harkless L, Johnson A, Moosa H, Robson M, Serena T, Sheehan P, Veves A, Wiersma-Bryant L. Guidelines for the treatment of diabetic ulcers. *Wound Repair Regen* 2006; **14**: 680-692 [PMID: 17199833 DOI: 10.1111/J.1524-475X.2006.00176.X]
25 **Ward JD**, Boulton AJ, Simms JM, Sandler DA, Knight G. Venous distension in the diabetic neuropathic foot (physical sign of arteriovenous shunting). *J R Soc Med* 1983; **76**: 1011-1014 [PMID: 6672192 DOI: 10.1177/014107688307601206]
26 **Esteghamati A**, Aflatoonian M, Rad MV, Mazaheri T, Mousavizadeh M, Nakhjavani M, Noshad S. Association of osteoprotegerin with peripheral artery disease in patients with type 2 diabetes. *Arch Cardiovasc Dis* 2015; **108**: 412-419 [PMID: 26184866 DOI: 10.1016/j.acvd.2015.01.015]
27 **LoGerfo FW**, Coffman JD. Current concepts. Vascular and microvascular disease of the foot in diabetes. Implications for foot care. *N Engl J Med* 1984; **311**: 1615-1619 [PMID: 6390204 DOI: 10.1056/NEJM198412203112506]
28 **Meloni M**, Izzo V, Giurato L, Lázaro-Martínez JL, Uccioli L. Prevalence, Clinical Aspects and Outcomes in a Large Cohort of Persons with Diabetic Foot Disease: Comparison between Neuropathic and Ischemic Ulcers. *J Clin Med* 2020; **9** [PMID: 32521700 DOI: 10.3390/jcm9061780]
29 **Apelqvist J**. Diabetic foot ulcers: Evidence, cost and management. *Diabet foot J* 2007; **10**: 1-8 [cited 20 September 2022]. Available from: https://www.woundsinternational.com/resources/details/diabetic-foot
30 **Graziani L**, Silvestro A, Bertone V, Manara E, Andreini R, Sigala A, Mingardi R, De Giglio R. Vascular involvement in diabetic subjects with ischemic foot ulcer: a new morphologic categorization of disease severity. *Eur J Vasc Endovasc Surg* 2007; **33**: 453-460 [PMID: 17196848 DOI: 10.1016/J.EJVS.2006.11.022]
31 **Lipsky BA**, Senneville É, Abbas ZG, Aragón-Sánchez J, Diggle M, Embil JM, Kono S, Lavery LA, Malone M, van Asten SA, Urbančič-Rovan V, Peters EJG; International Working Group on the Diabetic Foot (IWGDF). Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev* 2020; **36** Suppl 1: e3280 [PMID: 32176444 DOI: 10.1002/dmrr.3280]
32 **Aragón-Sánchez J**, Lázaro-Martínez JL, Pulido-Duque J, Maynar M. From the diabetic foot ulcer and beyond: how do foot infections spread in patients with diabetes? *Diabet Foot Ankle* 2012; **3** [PMID: 23050067 DOI: 10.3402/dfa.v3I0.18693]
33 **Bridges RM Jr**, Deitch EA. Diabetic foot infections. Pathophysiology and treatment. *Surg Clin North Am* 1994; **74**: 537-555 [PMID: 8197529]
34 **Maharaj D**, Bahadursingh S, Shah D, Chang BB, Darling RC 3rd. Sepsis and the scalpel: anatomic compartments and the diabetic foot. *Vasc Endovascular Surg* 2005; **39**: 421-423 [PMID: 16193214 DOI: 10.1177/153857440503900506]
35 **Spiliopoulos S**, Festas G, Paraskevopoulos I, Mariappan M, Brountzos E. Overcoming ischemia in the diabetic foot: Minimally invasive treatment options. *World J Diabetes* 2021; **12**: 2011-2026 [PMID: 35047116 DOI: 10.4239/wjd.v12.I12.2011]
36 **Naemi R**, Chockalingam N, Lutale JK, Abbas ZG. Predicting the risk of future diabetic foot ulcer occurrence: a prospective cohort study of patients with diabetes in Tanzania. *BMJ Open Diabetes Res Care* 2020; **8** [PMID: 32371531 DOI: 10.1136/bmjdrc-2019-001122]
37 **Crawford F**, Cezard G, Chappell FM, Murray GD, Price JF, Sheikh A, Simpson CR, Stansby GP, Young MJ. A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). *Health Technol Assess* 2015; **19**: 1-210 [PMID: 26211920 DOI: 10.3310/hta19570]
38 **Mayfield JA**, Reiber GE, Sanders LJ, Janisse D, Pogach LM; American Diabetes Association. Preventive foot care in diabetes. *Diabetes Care* 2004; **27** Suppl 1: S63-S64 [PMID: 14693928 DOI: 10.2337/DIACARE.27.2007.S63]
39 **Song J**, Hu L, Liu B, Jiang N, Huang H, Luo J, Wang L, Zeng J, Huang F, Huang M, Cai L, Tang L, Chen S, Chen Y, Wu A, Zheng S, Chen Q. The Emerging Role of Immune Cells and Targeted Therapeutic Strategies in Diabetic Wounds Healing. *J Inflamm Res* 2022; **15**: 4119-4138 [PMID: 35898820 DOI: 10.2147/JIR.S371939]
40 **Rehak L**, Giurato L, Meloni M, Panunzi A, Manti GM, Uccioli L. The Immune-Centric Revolution in the Diabetic Foot: Monocytes and Lymphocytes Role in Wound Healing and Tissue Regeneration-A Narrative Review. *J Clin Med* 2022; **11** [PMID: 35160339 DOI: 10.3390/jcm11030889]
41 **Ansari P**, Akther S, Khan JT, Islam SS, Masud MSR, Rahman A, Seidel V, Abdel-Wahab YHA. Hyperglycaemia-Linked Diabetic Foot Complications and Their Management Using Conventional and Alternative Therapies. Appl Sci [Internet], 2022. [cited 20 September 2022]. Available from: https://www.mdpi.com/2076-3417/12/22/11777/htm
42 **Lin S**, Wang Q, Huang X, Feng J, Wang Y, Shao T, Deng X, Cao Y, Chen X, Zhou M, Zhao C. Wounds under diabetic milieu: The role of immune cellar components and signaling pathways. *Biomed Pharmacother* 2023; **157**: 114052 [PMID: 36462313 DOI: 10.1016/j.biopha.2022.114052]
43 **Rodríguez-Rodríguez N**, Martínez-Jiménez I, García-Ojalvo A, Mendoza-Mari Y, Guillén-Nieto G, Armstrong DG, Berlanga-Acosta J. Wound Chronicity, Impaired Immunity and Infection in Diabetic Patients. *MEDICC Rev* 2022; **24**: 44-58 [PMID: 34653116 DOI: 10.37757/MR2021.V23.N3.8]
44 **Moura J**, Rodrigues J, Gonçalves M, Amaral C, Lima M, Carvalho E. Impaired T-cell differentiation in diabetic foot ulceration. *Cell Mol Immunol* 2017; **14**: 758-769 [PMID: 26996067 DOI: 10.1038/cmi.2015.116]
45 **Smith K**, Collier A, Townsend EM, O'Donnell LE, Bal AM, Butcher J, Mackay WG, Ramage G, Williams C. One step closer to understanding the role of bacteria in diabetic foot ulcers: characterising the microbiome of ulcers. *BMC Microbiol* 2016; **16**: 54 [PMID: 27005417 DOI: 10.1186/s12866-016-0665-Z]

46 **Macdonald KE**, Boeckh S, Stacey HJ, Jones JD. The microbiology of diabetic foot infections: a meta-analysis. *BMC Infect Dis* 2021; **21**: 770 [PMID: 34372789 DOI: 10.1186/s12879-021-06516-7]

47 **Bader MS**. Diabetic foot infection. *Am Fam Physician* 2008; **78**: 71-79 [PMID: 18649613]

48 **Lipsky BA**, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, Deery HG, Embil JM, Joseph WS, Karchmer AW, Pinzur MS, Senneville E; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 2012; **54**: e132-e173 [PMID: 22619242 DOI: 10.1093/cid/cis346]

49 **Chai W**, Wang Y, Zheng H, Yue S, Liu Y, Wu Y, Li X. The Profile of Microbiological Pathogens in Diabetic Foot Ulcers. *Front Med (Lausanne)* 2021; **8**: 656467 [PMID: 34621756 DOI: 10.3389/fmed.2021.656467]

50 **Eleftheriadou I**, Tentolouris N, Argiana V, Jude E, Boulton AJ. Methicillin-resistant Staphylococcus aureus in diabetic foot infections. *Drugs* 2010; **70**: 1785-1797 [PMID: 20836573 DOI: 10.2165/11538070-000000000-00000]

51 **Stacey HJ**, Clements CS, Welburn SC, Jones JD. The prevalence of methicillin-resistant Staphylococcus aureus among diabetic patients: a meta-analysis. *Acta Diabetol* 2019; **56**: 907-921 [PMID: 30955124 DOI: 10.1007/s00592-019-01301-0]

52 **Shanmugam P**, M J, Susan S L. The bacteriology of diabetic foot ulcers, with a special reference to multidrug resistant strains. *J Clin Diagn Res* 2013; **7**: 441-445 [PMID: 23634392 DOI: 10.7860/JCDR/2013/5091.2794]

53 **Li T**, Li Z, Huang L, Tang J, Ding Z, Zeng Z, Liu Y, Liu J. Cigarette Smoking and Peripheral Vascular Disease are Associated with Increasing Risk of ESKAPE Pathogen Infection in Diabetic Foot Ulcers. *Diabetes Metab Syndr Obes* 2022; **15**: 3271-3283 [PMID: 36311916 DOI: 10.2147/DMSO.S383701]

54 **Ramakant P**, Verma AK, Misra R, Prasad KN, Chand G, Mishra A, Agarwal G, Agarwal A, Mishra SK. Changing microbiological profile of pathogenic bacteria in diabetic foot infections: time for a rethink on which empirical therapy to choose? *Diabetologia* 2011; **54**: 58-64 [PMID: 20835702 DOI: 10.1007/s00125-010-1893-7]

55 **Mishra SC**, Chhatbar KC, Kashikar A, Mehndiratta A. Diabetic foot. *BMJ* 2017; **359**: j5064 [PMID: 29146579 DOI: 10.1136/bmj.j5064]

56 **van Asten SA**, La Fontaine J, Peters EJ, Bhavan K, Kim PJ, Lavery LA. The microbiome of diabetic foot osteomyelitis. *Eur J Clin Microbiol Infect Dis* 2016; **35**: 293-298 [PMID: 26670675 DOI: 10.1007/s10096-015-2544-1]

57 **Zou M**, Cai Y, Hu P, Cao Y, Luo X, Fan X, Zhang B, Wu X, Jiang N, Lin Q, Zhou H, Xue Y, Gao F. Analysis of the Composition and Functions of the Microbiome in Diabetic Foot Osteomyelitis Based on 16S rRNA and Metagenome Sequencing Technology. *Diabetes* 2020; **69**: 2423-2439 [PMID: 32801139 DOI: 10.2337/db20-0503]

58 **Moon J**, Kim N, Lee HS, Lee ST, Jung KH, Park KI, Lee SK, Lee DO, Lee DY, Chu K. Nanopore 16S Amplicon Sequencing Enhances the Understanding of Pathogens in Medically Intractable Diabetic Foot Infections. *Diabetes* 2021; **70**: 1357-1371 [PMID: 34162681 DOI: 10.2337/db20-0907]

59 **Gardner SE**, Hillis SL, Heilmann K, Segre JA, Grice EA. The neuropathic diabetic foot ulcer microbiome is associated with clinical factors. *Diabetes* 2013; **62**: 923-930 [PMID: 23139351 DOI: 10.2337/db12-0771]

60 **Malone M**, Johani K, Jensen SO, Gosbell IB, Dickson HG, Hu H, Vickery K. Next Generation DNA Sequencing of Tissues from Infected Diabetic Foot Ulcers. *EBioMedicine* 2017; **21**: 142-149 [PMID: 28669650 DOI: 10.1016/j.ebiom.2017.06.026]

61 **Ramsey MM**, Freire MO, Gabrilska RA, Rumbaugh KP, Lemon KP. Staphylococcus aureus Shifts toward Commensalism in Response to Corynebacterium Species. *Front Microbiol* 2016; **7**: 1230 [PMID: 27582729 DOI: 10.3389/fmicb.2016.01230]

62 **Hardy BL**, Dickey SW, Plaut RD, Riggins DP, Stibitz S, Otto M, Merrell DS. Corynebacterium pseudodiphtheriticum Exploits Staphylococcus aureus Virulence Components in a Novel Polymicrobial Defense Strategy. *mBio* 2019; **10** [PMID: 30622190 DOI: 10.1128/mBio.02491-18]

63 **Barshes NR**, Clark NJ, Bidare D, Dudenhoeffer JH, Mindru C, Rodriguez-Barradas MC. Polymicrobial Foot Infection Patterns Are Common and Associated With Treatment Failure. *Open Forum Infect Dis* 2022; **9**: ofac475 [PMID: 36267251 DOI: 10.1093/ofid/ofac475]

64 **Lipsky BA**, Armstrong DG, Citron DM, Tice AD, Morgenstern DE, Abramson MA. Ertapenem *vs* piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial. *Lancet* 2005; **366**: 1695-1703 [PMID: 16291062 DOI: 10.1016/S0140-6736(05)67694-5]

65 **Xu Z**, Hsia HC. The Impact of Microbial Communities on Wound Healing: A Review. *Ann Plast Surg* 2018; **81**: 113-123 [PMID: 29746280 DOI: 10.1097/SAP.0000000000001450]

66 **Knackstedt R**, Knackstedt T, Gatherwright J. The role of topical probiotics on wound healing: A review of animal and human studies. *Int Wound J* 2020; **17**: 1687-1694 [PMID: 32869480 DOI: 10.1111/iwj.13451]

67 **European Antimicrobial Resistance Collaborators**. The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis. *Lancet Public Health* 2022; **7**: e897-e913 [PMID: 36244350 DOI: 10.1016/s2468-2667(22)00225-0]

68 **Ahmad S**, Khan MSA, Shah MH, Khan A, Bano R, Qazi M. Microbial Profile and Antimicrobial Susceptibility Pattern in Diabetic Foot Ulcer Patients Attending a Tertiary Care Hospital. *Cureus* 2022; **14**: e29770 [PMID: 36324354 DOI: 10.7759/cureus.29770]

69 **Ertugrul BM**, Oncul O, Tulek N, Willke A, Sacar S, Tunccan OG, Yilmaz E, Kaya O, Ozturk B, Turhan O, Yapar N, Ture M, Akin F. A prospective, multi-center study: factors related to the management of diabetic foot infections. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 2345-2352 [PMID: 22354524 DOI: 10.1007/s10096-012-1574-1]

70 **Rastogi A**, Sukumar S, Hajela A, Mukherjee S, Dutta P, Bhadada SK, Bhansali A. The microbiology of diabetic foot infections in patients recently treated with antibiotic therapy: A prospective study from India. *J Diabetes Complications* 2017; **31**: 407-412 [PMID: 27894749 DOI: 10.1016/j.jdiacomp.2016.11.001]

71 **Afonso AC**, Oliveira D, Saavedra MJ, Borges A, Simões M. Biofilms in Diabetic Foot Ulcers: Impact, Risk Factors and Control Strategies. *Int J Mol Sci* 2021; **22** [PMID: 34361044 DOI: 10.3390/ijmsS22158278]

72 **Talapko J**, Škrlec I. The Principles, Mechanisms, and Benefits of Unconventional Agents in the Treatment of Biofilm Infection. *Pharmaceuticals (Basel)* 2020; **13** [PMID: 33050521 DOI: 10.3390/ph13100299]

73 **Singh S**, Datta S, Narayanan KB, Rajnish KN. Bacterial exo-polysaccharides in biofilms: role in antimicrobial resistance and treatments. *J Genet Eng Biotechnol* 2021; **19**: 140 [PMID: 34557983 DOI: 10.1186/s43141-021-00242-y]

74 **Pouget C**, Dunyach-Remy C, Pantel A, Schuldiner S, Sotto A, Lavigne JP. Biofilms in Diabetic Foot Ulcers: Significance and Clinical Relevance. *Microorganisms* 2020; **8** [PMID: 33066595 DOI: 10.3390/microorganisms8101580]

75 **Sousa R**, Carvalho A, Santos AC, Abreu MA. Optimal microbiological sampling for the diagnosis of osteoarticular infection. *EFORT Open Rev* 2021; **6**: 390-398 [PMID: 34267930 DOI: 10.1302/2058-5241.6.210011]

76 **Boulton AJM**, Armstrong DG, Hardman MJ, Malone M, Embil JM, Attinger CE, Lipsky BA, Aragón-Sánchez J, Li HK, Schultz G, Kirsner RS. Diagnosis and Management of Diabetic Foot Infections. Arlington (VA): American Diabetes Association; 2020 Jan. [PMID: 32105420 DOI: 10.2337/DB2020-01]

77 **Li S**, Renick P, Senkowsky J, Nair A, Tang L. Diagnostics for Wound Infections. *Adv Wound Care (New Rochelle)* 2021; **10**: 317-327 [PMID: 32496977 DOI: 10.1089/wound.2019.1103]

78 **Esteban J**, Gómez-Barrena E. An update about molecular biology techniques to detect orthopaedic implant-related infections. *EFORT Open Rev* 2021; **6**: 93-100 [PMID: 33828851 DOI: 10.1302/2058-5241.6.200118]

79 **Kvich L**, Burmølle M, Bjarnsholt T, Lichtenberg M. Do Mixed-Species Biofilms Dominate in Chronic Infections? *Front Cell Infect Microbiol* 2020; **10**: 396 [PMID: 32850494 DOI: 10.3389/fcimb.2020.00396]

80 **Talapko J**, Škrlec I, Alebić T, Bekić S, Včev A. From Bacteriophage to Antibiotics and Back. Coll Antropol 2018; 42: 131-138 [cited 20 September 2022]. Available from: https://hrcak.srce.hr/index.php?show=clanak&id_clanak_jezik=302435

81 **Talapko J**, Matijević T, Juzbašić M, Antolović-Požgain A, Škrlec I. Antibacterial Activity of Silver and Its Application in Dentistry, Cardiology and Dermatology. Microorganisms 2020;8:1400 [PMID: 32932967 DOI: 10.3390/microorganisms8091400]

82 **Talapko J**, Meštrović T, Juzbašić M, Tomas M, Erić S, Horvat Aleksijević L, Bekić S, Schwarz D, Matić S, Neuberg M, Škrlec I. Antimicrobial Peptides-Mechanisms of Action, Antimicrobial Effects and Clinical Applications. *Antibiotics (Basel)* 2022; **11** [PMID: 36290075 DOI: 10.3390/antibiotics11101417]

83 **Chellan G**, Neethu K, Varma AK, Mangalanandan TS, Shashikala S, Dinesh KR, Sundaram KR, Varma N, Jayakumar RV, Bal A, Kumar H. Targeted treatment of invasive fungal infections accelerates healing of foot wounds in patients with Type 2 diabetes. *Diabet Med* 2012; **29**: e255-e262 [PMID: 22248392 DOI: 10.1111/j.1464-5491.2012.03574.x]

84 **Öztürk AM**, Taşbakan M, Metin DY, Yener C, Uysal S, Yıldırım Şımşır I, Ertam İ, Pullukçu H, Arda B, Çetinkalp Ş. A neglected causative agent in diabetic foot infection: a retrospective evaluation of 13 patients with fungal etiology. *Turk J Med Sci* 2019; **49**: 81-86 [PMID: 30761877 DOI: 10.3906/sag-1809-74]

85 **Talapko J**, Juzbašić M, Matijević T, Pustijanac E, Bekić S, Kotris I, Škrlec I. Candida albicans-The Virulence Factors and Clinical Manifestations of Infection. J Fungi 2021;7:79 PMID: 33499276 [DOI: 10.3390/jof7020079]

86 **Babamahmoodi F**, Shokohi T, Ahangarkani F, Nabili M, Afzalian Ashkezari E, Alinezhad S. Rare Case of Aspergillus ochraceus Osteomyelitis of Calcaneus Bone in a Patient with Diabetic Foot Ulcers. *Case Rep Med* 2015; **2015**: 509827 [PMID: 26064128 DOI: 10.1155/2015/509827]

87 **Federer AE**, Haughom BD, Levy DM, Riff AJ, Nho SJ. Blastomyces Tenosynovitis of the Foot and Ankle: A Case Report and Review of the Literature. *J Foot Ankle Surg* 2015; **54**: 1183-1187 [PMID: 26215556 DOI: 10.1053/j.jfas.2015.04.014]

88 **Eneroth M**, Larsson J, Apelqvist J. Deep foot infections in patients with diabetes and foot ulcer: an entity with different characteristics, treatments, and prognosis. *J Diabetes Complications* 1999; **13**: 254-263 [PMID: 10764999 DOI: 10.1016/S1056-8727(99)00065-3]

89 **Eneroth M**, Apelqvist J, Stenström A. Clinical characteristics and outcome in 223 diabetic patients with deep foot infections. *Foot Ankle Int* 1997; **18**: 716-722 [PMID: 9391817 DOI: 10.1177/107110079701801107]

90 **Bus SA**, Lavery LA, Monteiro-Soares M, Rasmussen A, Raspovic A, Sacco ICN, van Netten JJ; International Working Group on the Diabetic Foot. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev* 2020; **36** Suppl 1: e3269 [PMID: 32176451 DOI: 10.1002/dmrr.3269]

91 **Singh N**, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA* 2005; **293**: 217-228 [PMID: 15644549 DOI: 10.1001/JAMA.293.2.217]

92 **Armstrong DG**, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. *Diabetes Care* 1998; **21**: 855-859 [PMID: 9589255 DOI: 10.2337/DIACARE.21.5.855]

93 **Grayson ML**, Gibbons GW, Balogh K, Levin E, Karchmer AW. Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. *JAMA* 1995; **273**: 721-723 [PMID: 7853630]

94 **Dinh T**, Snyder G, Veves A. Current techniques to detect foot infection in the diabetic patient. *Int J Low Extrem Wounds* 2010; **9**: 24-30 [PMID: 20207620 DOI: 10.1177/1534734610363004]

95 **Borys S**, Hohendorff J, Koblik T, Witek P, Ludwig-Slomczynska AH, Frankfurter C, Kiec-Wilk B, Malecki MT. Negative-pressure wound therapy for management of chronic neuropathic noninfected diabetic foot ulcerations - short-term efficacy and long-term outcomes. *Endocrine* 2018; **62**: 611-616 [PMID: 30099674 DOI: 10.1007/s12020-018-1707-0]

96 **Snyder RJ**, Cardinal M, Dauphinée DM, Stavosky J. A post-hoc analysis of reduction in diabetic foot ulcer size at 4 wk as a predictor of healing by 12 wk. *Ostomy Wound Manage* 2010; **56**: 44-50 [PMID: 20368673]

97 **Hasan R**, Firwana B, Elraiyah T, Domecq JP, Prutsky G, Nabhan M, Prokop LJ, Henke P, Tsapas A, Montori VM, Murad MH. A systematic review and meta-analysis of glycemic control for the prevention of diabetic foot syndrome. *J Vasc Surg* 2016; **63**: 22S-28S.e1 [PMID: 26804364 DOI: 10.1016/j.jvs.2015.10.005]

98 **Christman AL**, Selvin E, Margolis DJ, Lazarus GS, Garza LA. Hemoglobin A1c predicts healing rate in diabetic wounds. *J Invest Dermatol* 2011; **131**: 2121-2127 [PMID: 21697890 DOI: 10.1038/jid.2011.176]

99 **Cavanagh PR**, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. *Plast Reconstr Surg* 2011; **127** Suppl 1: 248S-256S [PMID: 21200298 DOI: 10.1097/PRS.0b013e3182024864]

100 **Chang MC**, Choo YJ, Park IS, Park MW, Kim DH. Orthotic approach to prevention and management of diabetic foot: A

narrative review. *World J Diabetes* 2022; **13**: 912-920 [PMID: 36437865 DOI: 10.4239/wjd.V13.I11.912]

101 **Meloni M**, Morosetti D, Giurato L, Stefanini M, Loreni G, Doddi M, Panunzi A, Bellia A, Gandini R, Brocco E, Lazaro-Martinez JL, Lauro D, Uccioli L. Foot Revascularization Avoids Major Amputation in Persons with Diabetes and Ischaemic Foot Ulcers. *J Clin Med* 2021; **10** [PMID: 34501432 DOI: 10.3390/jcm10173977]

102 **Reekers JA**. The Role of Interventional Radiology in the Treatment of Arterial Diabetic Foot Disease. *Cardiovasc Intervent Radiol* 2016; **39**: 1369-1371 [PMID: 27435578 DOI: 10.1007/s00270-016-1337-y]

103 **Cangiano G**, Corvino F, Giurazza F, De Feo EM, Fico F, Palumbo V, Amodio F, Silvestre M, Corvino A, Niola R. Percutaneous Deep Foot Vein Arterialization IVUS-Guided in No-Option Critical Limb Ischemia Diabetic Patients. *Vasc Endovascular Surg* 2021; **55**: 58-63 [PMID: 33256561 DOI: 10.1177/1538574420965743]

104 **Tice AD**, Hoaglund PA, Shoultz DA. Outcomes of osteomyelitis among patients treated with outpatient parenteral antimicrobial therapy. *Am J Med* 2003; **114**: 723-728 [PMID: 12829198 DOI: 10.1016/S0002-9343(03)00231-6]

105 **Pittet D**, Wyssa B, Herter-Clavel C, Kursteiner K, Vaucher J, Lew PD. Outcome of diabetic foot infections treated conservatively: a retrospective cohort study with long-term follow-up. *Arch Intern Med* 1999; **159**: 851-856 [PMID: 10219931 DOI: 10.1001/ARCHINTE.159.8.851]

106 **Hamilton EJ**, Scheepers J, Ryan H, Perrin BM, Charles J, Cheney J, Twigg SM; Australian Diabetes-related Foot Disease Guidelines & Pathways Project. Australian guideline on wound classification of diabetes-related foot ulcers: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *J Foot Ankle Res* 2021; **14**: 60 [PMID: 34861898 DOI: 10.1186/s13047-021-00503-6]

107 **Abou-Zamzam AM Jr**, Gomez NR, Molkara A, Banta JE, Teruya TH, Killeen JD, Bianchi C. A prospective analysis of critical limb ischemia: factors leading to major primary amputation *vs* revascularization. *Ann Vasc Surg* 2007; **21**: 458-463 [PMID: 17499967 DOI: 10.1016/J.AVSG.2006.12.006]

108 **Chen P**, Carville K, Swanson T, Lazzarini PA, Charles J, Cheney J, Prentice J; Australian Diabetes-related Foot Disease Guidelines & Pathways Project. Australian guideline on wound healing interventions to enhance healing of foot ulcers: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *J Foot Ankle Res* 2022; **15**: 40 [PMID: 35610723 DOI: 10.1186/s13047-022-00544-5]

109 **Edwards J**, Stapley S. Debridement of diabetic foot ulcers. *Cochrane Database Syst Rev* 2010; **2010**: CD003556 [PMID: 20091547 DOI: 10.1002/14651858.CD003556.pub2]

110 **Meloni M**, Izzo V, Vainieri E, Giurato L, Ruotolo V, Uccioli L. Management of negative pressure wound therapy in the treatment of diabetic foot ulcers. *World J Orthop* 2015; **6**: 387-393 [PMID: 25992316 DOI: 10.5312/wjo.v6.i4.387]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1684-1693

DOI: 10.12998/wjcc.v11.i8.1684

ISSN 2307-8960 (online)

MINIREVIEWS

Diabetic foot ulcer: A comprehensive review of pathophysiology and management modalities

Joel M Raja, Miguel A Maturana, Sharif Kayali, Amir Khouzam, Nephertiti Efeovbokhan

Specialty type: Medicine, general and internal

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Liao Z, Singapore; Moreno-Gómez-Toledano R, Spain; Shalaby MN, Egypt; Sutkowska E, Poland

Received: October 22, 2022
Peer-review started: October 22, 2022
First decision: December 26, 2022
Revised: January 8, 2023
Accepted: February 17, 2023
Article in press: February 17, 2023
Published online: March 16, 2023

Joel M Raja, Miguel A Maturana, Sharif Kayali, Amir Khouzam, Department of Internal Medicine, University of Tennessee Health Science Center, Memphis, TN 38119, United States

Nephertiti Efeovbokhan, Department of Cardiology, NEA Baptist Jonesboro, Jonesboro, AR 72401, United States

Corresponding author: Joel M Raja, MD, Postdoctoral Fellow, Department of Internal Medicine, University of Tennessee Health Science Center, 2750 Mcvay Road, Memphis, TN 38119, United States. jraja@uthsc.edu

Abstract

Diabetic foot ulcer (DFU) is a debilitating and severe manifestation of uncontrolled and prolonged diabetes that presents as ulceration, usually located on the plantar aspect of the foot. Approximately 15% of individuals with diabetes will eventually develop DFU, and 14%-24% of them will require amputation of the ulcerated foot due to bone infection or other ulcer-related complications. The pathologic mechanisms underlying DFU are comprise a triad: Neuropathy, vascular insufficiency, and secondary infection due to trauma of the foot. Standard local and invasive care along with novel approaches like stem cell therapy pave the way to reduce morbidity, decrease amputations, and prevent mortality from DFU. In this manuscript, we review the current literature with focus on the pathophysiology, preventive options, and definitive management of DFU.

Key Words: Diabetes; Ulcer; Foot; Antibiotics; Revascularization; Cell therapy

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Diabetic foot ulcer: Pathophysiology: - Neuropathy including sensory and motor - Vascular insufficiency leading to ischemia - Secondary infection with inflammation. Overview of management: (1) Preventive care including self-screening, health care screening, insoles, podiatric care; (2) Noninvasive modalities including wound dressing, human skin equivalent, topical growth factors, shock wave therapy, stem cell therapy, hyperbaric oxygen, negative pressure, shock wave therapy, maggot therapy, antibiotics; and (3) Invasive modalities including debridement, revascularization, skin grafting, amputation.

Citation: Raja JM, Maturana MA, Kayali S, Khouzam A, Efeovbokhan N. Diabetic foot ulcer: A comprehensive review of pathophysiology and management modalities. *World J Clin Cases* 2023; 11(8): 1684-1693
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1684.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1684

INTRODUCTION

Diabetes mellitus affects approximately 422 million people worldwide and is responsible for an estimated 2 million deaths per year[1]. It affects 11.3% of the United States population[2]. Diabetic foot ulcer (DFU) is a debilitating and severe manifestation of uncontrolled and prolonged diabetes that presents as an ulceration, usually located at the plantar aspect of the foot. Approximately 15% of individuals with diabetes will eventually develop one of these ulcers, and out of these individuals, 14%-24% of them will require amputation of the ulcerated foot due to bone infection or other ulcer-related complications[3]. With such a high level of morbidity stemming from debilitating osteomyelitis and amputation in patients with DFU, it is of the utmost importance to properly address and treat the underlying causes of DFU. In this paper, we review the current literature with focus on the pathophysiology, preventive options, and definitive management of DFU.

PATHOPHYSIOLOGY

DFU comprises a full-thickness wound involving the dermis, located in the weight-bearing or exposed area below the ankle. The Wagner system aids in categorizing the severity of the ulcer, ranking it on a scale of 1 to 5 (Table 1). The pathologic mechanisms of DFU are described in terms of a triad. This triad includes neuropathy, vascular insufficiency, and secondary infection due to trauma of the foot[4] (Figure 1).

First, the lack of protective sensation in the feet predisposes patients with diabetes to developing trauma and ulcers. This sensory impairment occurs due to hyperglycemia-induced upregulation of aldose reductase and sorbitol dehydrogenase, which in turn increase the production of fructose and sorbitol. These glucose products accumulate and induce osmotic stress, thereby reducing nerve cell myoinositol synthesis and nerve conduction[5]. Also, from a pathological stance, advanced glycation end-products (AGEs) must be considered. AGEs are non-enzymatic protein, amino acid, and DNA adducts which form from dicarbonyls and glucose. AGE formation is enhanced in diabetes and is associated with the development of diabetic complications[6]. In addition to sensory neuropathy, diabetes can induce neuronal autonomic dysfunction that results in impaired sweat production, leaving the foot susceptible to dryness, skin cracking, and fissuring[7]. Furthermore, motor neuron dysfunction can give rise to muscle wasting and structural abnormalities of the foot[8]. This causes focally elevated pressures at various zones of the plantar foot and increases the risk of ulceration[9].

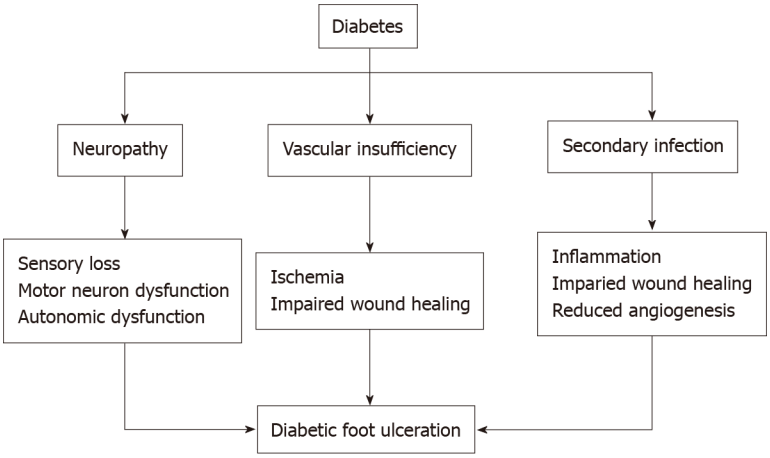
In addition to the triad, impaired wound healing has been established as a key means of DFU progression[10]. Importantly, molecular changes at the site of DFU precede the grossly visualized tissue abnormalities[11]. In fact, the route from hyperglycemia to DFU involves complex molecular dysfunctions in wound healing. Ordinarily, wounds undergo several healing stages involving hemostasis, inflammation, proliferation, and remodeling. Acute wounds advance linearly through these stages; however, chronic nonhealing DFUs stall in 1 or more phases. In the early phases of wound healing, neutrophils normally release granular molecules to kill foreign pathogens in a process known as neutrophil extracellular traps (NETosis)[12]. However, in a diabetic microenvironment, NETosis becomes dysregulated, causing a proinflammatory cascade and overproduction of cytokines and superoxide, which delay wound healing[13,14]. Moreover, hyperglycemia induces formation of AGEs that cause structural and functional changes in key proteins[15]. Specifically, AGEs can bind to the receptor of advanced glycation end-products (RAGE), which is normally minimally expressed in normoglycemic conditions[16]. This in turn activates nuclear factor kappa-B (NF-κB). Ultimately, cytokine release is enhanced with a self-sustaining cascade that prolongs inflammation and favors apoptosis[17]. Overall, hyperglycemia induces a proinflammatory environment largely due to the dysregulation of cytokine release, NETosis, and AGE production.

Along with inflammation, substantial alterations of the extracellular matrix (ECM) also play a significant role in perpetuating the non-healing DFU. In cases of normal wound healing, the production and degradation of ECM proteins such as collagen and fibrin are tightly regulated[18]. Collagen comprises most of the soft tissue ECM, and thus, abnormalities of collagen metabolism have significant consequences on wound healing. Specifically, collagen-degrading enzymes known as matrix metalloproteinases (MMPs) become hyperactive, resulting in a highly-proteolytic environment with reduced collagen content[19,20]. Overall, the ECM becomes disorganized and insufficient to support wound healing. Alongside elevated MMP activity, the accumulation of AGEs results in a reduction of fibroblast

Table 1 Wagner's classification of diabetic foot ulcers

Grade	Characteristic
Wagner grade 1	Partial- or full-thickness ulcer (superficial)
Wagner grade 2	Deep ulcer extending to ligament, tendon, joint capsule, bone, or deep fascia without abscess or OM
Wagner grade 3	Deep abscess, OM, or joint sepsis
Wagner grade 4	Partial-foot gangrene

OM: Osteomyelitis.



DOI: 10.12998/wjcc.v11.i8.1684 **Copyright** ©The Author(s) 2023.

Figure 1 Pathophysiology of diabetic foot ulceration.

growth factor (FGF) and transforming growth factor-beta[21,22]. This has a similar effect of reducing the collagen content *via* the induction of fibroblast apoptosis[23].

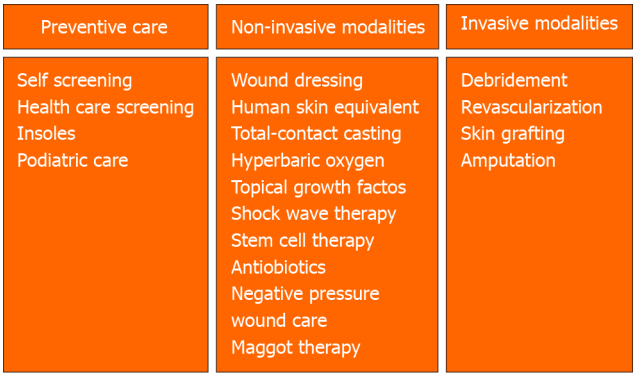
Lastly, impaired angiogenesis plays a key role in the disruption of diabetic wound healing. Angiogenesis ordinarily occurs during the proliferative phase of wound healing, and is responsible for both the formation of granulation tissue and delivery of nutrition and oxygen to the wound[24]. In the case of DFU, there is a reduction of angiogenic growth factors such as vascular endothelial growth factor (VEGF) 20 and FGF-2[25]. Essentially, VEGF initiates angiogenesis and mediates endothelial cell proliferation while FGF-2 facilitates migration of new blood vessels through the ECM[26,27]. When VEGF and FGF-2 expression is compromised, wound healing declines. Furthermore, endothelial progenitor cells (EPCs) have been implicated as expressors of proangiogenic factors and receptors including VEGF and FGF[28]. A deficiency of function and number of EPCs has been demonstrated in patients with type 2 diabetes mellitus, which is attributed to AGE accumulation[29-31]. Overall, the dysfunction of EPCs and circulating growth factors contributes significantly to the development and progression of DFU by way of disrupting angiogenesis.

MANAGEMENT

The management of DFU involves preventative care as well as various treatment modalities, including both noninvasive and invasive measures (Figure 2).

Preventative care

Due to diabetes being a risk factor for the development of underlying peripheral vascular disease, the majority of DFUs are asymptomatic until advanced enough to recognize more severe signs and symptoms. During the diagnosis of DFU, neuropathy may mask ischemia and vice versa. Therefore, the primary preventative strategy is regular diabetic foot screening to allow early identification of DFU, followed by initiation of treatment if appropriate. Ultimately, early detection and management work to avoid further complications such as gangrene and amputation[32]. Screening comprises the patient checking his or her own feet for trauma or ulceration every day and routine screening during health care visits.



DOI: 10.12998/wjcc.v11.i8.1684 **Copyright** ©The Author(s) 2023.

Figure 2 Overview of management of diabetic foot ulceration.

Noninvasive care

The most prevalent management modality for DFU is local care, in which many potential avenues of treatment can be utilized. These include wound dressings, human skin equivalents (HSEs), pressure offloading, total-contact casting (TCC), systemic hyperbaric oxygen, larvae therapy (maggot therapy), and topical growth factors.

Wound dressings

Wound dressings are the most basic and common treatment measure, and although they serve a vital purpose in the management of DFU, other methods have proven vastly more effective in comparison to or in adjunct with wound dressings.

Human skin equivalent

HSE is more effective compared to the standard treatment of saline-moistened gauze in reducing the rates of amputation and infection and in improving the rate of ulcer healing. One randomized controlled trial (RCT) assessed the effectiveness of Graftskin, a living skin equivalent indicated for use in noninfected, nonischemic DFU. In this study, Graftskin was applied weekly for a maximum of 4 wk or until complete healing occurred. The results of the trial highlighted the increased effectiveness of HSE in comparison to the control group, in which ulcers were treated only with saline-moistened gauze. The use of HSE resulted in an 18% increase in complete wound healing when compared to the control group [33]. Despite these impressive results, one limitation to this treatment is that HSE may have limited availability or accessibility.

Offloading, TCC

Pressure offloading serves as one of the primary treatments of DFU, primarily in ulcers accompanied by neuropathy, with many variants being utilized. For ischemic DFUs, however, revascularization is more commonly used. Common methods of offloading include bed rest, wheelchair use, implementation of a crutch-assisted gait, total contact casting, use of felted foam, use of therapeutic shoes, and use of removable cast walkers[34]. The most effective offloading treatment is TCC, in which full casts are applied by an experienced physiotherapist and are changed weekly for 2-3 wk or until healing has occurred. One RCT found that TCC was extremely effective in increasing ulcer healing and reducing infection when compared to traditional dressing changes and other offloading methods. The study reported a 91% rate of healing within the TCC population, compared to a 32% rate of healing in the control group. This rate was reported following a 65 d period. Furthermore, the TCC group reported a 0% incidence of infection, with the same in the control group reported as 26%[35]. Multiple other studies have reported similar results, with TCC being an extremely effective treatment to DFU, particularly when compared to traditional dressing changes. One adverse effect of this treatment, however, is fungal infection, but this was addressed with topical treatment and did not prevent continued casting. Despite the evident success of TCC, one national survey in the United States evaluating 901 foot clinics in 48 states and the District of Columbia indicated that TCCs were used only by 1.7% of centers; this is potentially due to the tedious nature of this treatment option. TCC requires an experienced physiotherapist, and constant replacement and care. The application of the cast is a timely and intricate endeavor, and tends to cause patients discomfort according to the survey. The survey also indicated that the primary treatment across the foot clinics was shoe modifications.

Hyperbaric oxygen therapy

Another treatment for DFU is systemic hyperbaric oxygen therapy (HBOT), which is reserved for advanced cases and aimed at reducing the risk of amputation. This treatment is prevalent particularly in

the treatment of infected DFU, where 1 systematic review identified 6 RCTs that evaluated chronic DFU. Systemic HBOT sessions are usually conducted in 45 to 120 min sessions once or twice daily at pressures between 1.5-3.0 ATA. This method resulted in significantly reduced rates of major amputation compared with usual care of DFU. HBOT is typically used as an adjunctive therapy to normal wound care measures[36]. However, this treatment modality is quite expensive, is still not fully researched, and may warrant further trials.

Larvae therapy (maggot therapy)

Maggot therapy is another well-researched technique with respect to the treatment of chronic wounds in which maggots are placed on the wound area. This treatment method has been shown to significantly facilitate debridement. In one study, maggot therapy also enabled faster development of granulation tissue and more significantly decreased wound surface area compared to other topical treatments such as hydrogel dressings. Maggot therapy also had no effect on disinfection or complete healing rate for the wound[37].

Topical growth factors

Topical growth factors, particularly platelet-derived growth factors, have also proven effective in increasing ulcer healing rates when compared with placebo. Growth factors serve as principal immediate mediators of wound healing, and when applied in the setting of DFU, accelerate ulcer healing. One meta-analysis evaluated 26 RCTs with 2088 participants, and focused on recombinant epidermal growth factor, autologous platelet rich plasma, and recombinant human platelet-derived growth factor. Overall, each of the 3 treatments significantly improved rate of healing when used alongside standard treatment, with recombinant human epidermal growth factor slightly favored when compared to other growth factors[38].

Shock wave therapy

Extracorporeal shockwave therapy (ESWT) has been reported to accelerate the healing of soft tissue wounds when treating DFU. ESWT is utilized to stimulate osteoblasts and in turn facilitate soft tissue healing. There have been promising clinical trial results, indicating that ESWT is more effective in the treatment of DFU when compared to traditional methods. Two multi-national RCTs were conducted to compare the efficacy of ESWT when used adjunctively with standard care and other DFU treatments. The trials both lasted 12 wk and showed reduction of wound volume by more than 50% with the use of ESWT when compared to standard treatment alone[39].

Stem cell therapy

The cornerstone of available treatment options currently includes treatment of infection, surgical debridement, and revascularization[40]. Better understanding of the tissue remodeling process, which comprises inflammation, cell migration, neovascularization, and tissue proliferation, has paved the way for stem cell-based therapy to become viable for the treatment of DFU[41]. Stem cells aid wound healing by secretion of cytokines that play an important role in cell migration, angiogenesis, remodeling of extracellular matrix, and regeneration of nerves[42]. Also, stem cell capacity for differentiation into various cell types, including myofibroblasts and endothelial cells, optimizes wound healing[43].

The stem cell types that have been studied to aid in diabetic foot treatment are mainly adult stem cells (ASCs). Bone marrow-derived mesenchymal stem cells (BM-MSC) are the most extensively studied among the different ASCs; other types include adipose-derived stem cells, umbilical cord-derived mesenchymal stem cells (UC-MSC), and peripheral blood-derived mesenchymal stem cells[44] (Table 2). The use of BM-MSC in the treatment of DFU demonstrated more effective ulcer healing, with improvements in Ankle-Brachial Index (ABI), angiogenesis, and blood flow when compared to local treatment[45-47]. Even functional improvement with a decrease in rest pain and an increase in claudication distance was demonstrated. Decreased amputation when compared to conventional treatment was also seen. Furthermore, combining UC-MSC stem cell therapy with traditional angioplasty resulted in improvements in ABI, claudication distance, and skin temperature[48].

Embryonic stem cells (ESCs) are usually derived from blastocysts from the inner cell mass grown *via in vitro* fertilization[49]. The controversial ethics behind obtaining ESC and their inherent high rate of proliferation and the risks of tumor formation or immunological rejection has limited them from widespread research[50]. However, in one study using an animal model, the use of ESCs did not increase chances of tumor formation in rats[51]; however, further clinical studies are required to test the efficacy of ESC treatment in diabetic feet. Stem cell therapy shows promise as a viable therapeutic option in the treatment of DFU. Stem cells can be used alongside conventional therapies like angioplasty to achieve more desirable outcomes.

Systemic and local antibiotics

The use of systemic and local antibiotics serves as a noninvasive treatment in the management of DFU. Antibiotics can be administered topically through sponge applications or through gauze wrapping, as well as with use of a circulator boot. The presence of infection is defined by the presence of more than 2

Table 2 Stem cell therapies available for diabetic foot treatment

Stem cell type	Stem cell sub-types	Administration route
Adult stem cell	(1) Bone marrow-derived mesenchymal stem cells; (2) Adipose-derived stem cells; Human umbilical cord-derived; (3) Mesenchymal stem cells; and (4) Peripheral blood-derived mesenchymal stem cells	Local: Intramuscular and subcutaneous; Systemic: Intravenous and intraarterial
Embryonic stem cell	Cell mass of blastocyst by *in vitro* fertilization	Proposed local or systemic administration

classic findings of inflammation or purulence. There are 3 classifications of infection severity: (1) Mild (superficial and limited in size and depth); (2) moderate (deeper and larger in area); and (3) severe (overexpressed and beginning to affect metabolic perturbations). Most DFUs have a microbial cause, with aerobic Gram-positive cocci and staphylococci being the most common implicated microbes. Wounds that lack signs of infection typically do not require antibiotic therapy. If the wound is infected, a post-debridement specimen must be collected for both aerobic and anaerobic cultures. Following testing and potential imaging (including radiographs and MRI, if necessary), antibiotics may be prescribed[52]. If the infection is mild or moderate, narrow-spectrum oral antibiotics may be administered. If infection severity is moderate, high, or severe, broad-spectrum parenteral antibiotics should be utilized[53].

Negative pressure wound therapy

One of the most recent developments in DFU treatment is the utilization of negative pressure wound therapy (NPWT). NPWT utilizes vacuum pressure to draw fluid from the wound and increase blood flow to the affected area, thus stimulating the healing process. While primarily used in burn patients, NPWT has also recently been used in DFU patients with promising results. NPWT results in 2 primary types of tissue deformation: Macro deformation, which is exemplified by wound contraction; and micro deformation, which occurs on the microscopic level. Both deformations stimulate blood flow and promote a wound healing cascade that includes tissue granulation, vessel proliferation, neoangiogenesis, epithelialization, and excess extracellular fluid removal. NPWT also results in increased anti-inflammatory conditions in the patient. Clinical studies in DFU patients have shown that NPWT is more efficient compared to standard therapy, particularly when observing wound healing and amputation rates, without a rise in adverse events[54].

INVASIVE TREATMENT STRATEGIES

Debridement

Debridement is a major component in the treatment of DFU, particularly due to its ability to alter the environment of the chronic wound through the removal of necrotic and nonviable tissue and foreign debris, which impede the healing process. Debridement may not always lead to complete healing of the DFU, but it serves as an important preliminary step in the treatment. Following debridement, the wound is further analyzed and if necessary, other treatment paths are pursued[55]. Debridement is commonly used in conjunction with other treatment modalities.

Revascularization (angioplasty)

When patients with DFU also have a history of peripheral arterial disease (PAD), delayed healing, higher complication rates, and an increased chance of potential amputation may be observed. Thus, when patients have both DFU and chronic limb ischemia, revascularization can serve as a promising treatment option. According to various studies, the ulcer healing rate following revascularization ranges from 46% to 91%, representing a higher rate of healing compared to PAD patients that do not undergo revascularization[56]. Revascularization options include stenting and surgical bypass if other intervention is not possible. Atherectomy, shockwave treatment for calcified lesions, and balloon revascularization (cutting, drug coated, cryoplasty) can also be used alone or with stenting[57]. In a clinical trial in which 80 patients who underwent foot revascularization procedures, promising results were also shown. All patients in this study underwent an endovascular procedure (balloon angioplasty). The patients were followed for 12 mo after the procedure, and results showed that 56.2% of the patients fully recovered, 58.7% had minor amputations, and only 16.2% required major amputations. Overall, revascularization is an effective treatment for DFU, especially when the patient is at risk of amputation [58]. However, the effectiveness of the vascular procedure differs among patients, and it also does not reduce the risk of death associated with PAD. It is important to consider the role of complex therapy (including medical management) in conjunction with revascularization in the treatment of DFU. This includes close monitoring of glucose, lipids, and blood pressure, and the use of antiplatelet therapy

Table 3 Overview of diabetic foot management strategies

Treatment modality	Level of evidence	Strength of recommendation
Non-invasive modalities		
Wound dressing	High	Strong recommendation
Antibiotics	Low to moderate	Strong recommendation
Total-contact casting and pressure offloading techniques	High	Strong recommendation
Maggot therapy	Low	Weak recommendation
Hyperbaric oxygen	Low	Weak recommendation
Topical growth factors	Moderate	Could be beneficial
Cell therapy	Low (more studies required)	Weak recommendation
Invasive modalities		
Debridement	Moderate to high	Strong recommendation
Skin grafting	Moderate	Could be beneficial
Revascularization	Moderate	Strong recommendation

following the surgical procedure. Compared with initial supervised exercise training (SET) alone, endovascular therapy in combination with SET is associated with significant improvements in total walking distance, ABI, and risk of future revascularization or amputation. On the other hand, endovascular therapy alone was not associated with an improvement in functional capacity[59]. It is also important to note that post-endovascular procedure patients must be started on dual antiplatelet therapy, including aspirin plus clopidogrel or ticagrelor for several months. Statin therapy has also been proven to stabilize any plaques present before and after revascularization.

Skin grafting

Skin grafting may serve as a solution when DFUs become more severe, offering a chance to replace the infected skin and promote the healing process. There are a variety of skin grafting techniques that may be used, including bioengineered or artificial skin, autografts (taken from the patient), allografts (taken from another person), or xenografts (taken from animals). A review article that analyzed 17 RCTs concluded that skin grafting and tissue replacement when used in conjunction with standard treatment led to an increase in the healing rate of DFU and slightly lowered the chance of amputation. However, evidence of long-term effectiveness is uncertain[60].

Amputation

Amputation represents the final management option when treating DFU and is reserved for the most chronic levels of infection or deformity that render the foot nonfunctional. Amputation can be classified as either minor or major, with minor amputation being the removal of a smaller area (*e.g.*, removal of a toe or a part of the foot). Major amputation, however, can be performed above or below a major joint such as the knee or elbow. In a clinical trial, minor amputation was performed for 38.4% and major amputation was performed for 6.8% of patients with DFU[61].

CONCLUSION

DFU results in substantial morbidity and mortality in patients with diabetes. It also often leads to longer hospitalizations and associated increases in health care spending. Thus, prompt diagnosis and catered management is essential to management of this prevalent consequence of diabetes. Standard local and invasive care along with novel approaches like stem cell therapy pave the way to reduce morbidity, decrease the need for amputation, and prevent mortality due to DFU (Table 3). Further research into newer modalities that aid in prompt and effective management will further help alleviate the healthcare burden of DFU.

FOOTNOTES

Author contributions: Raja JM, Khouzam A, Maturana MA, Kayali S, Efeovbokhan N all contributed equally to the manuscript; all authors have read and approve the final manuscript.

Conflict-of-interest statement: The authors state that there are no conflicts of interest to declare.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: United States

ORCID number: Joel M Raja 0000-0001-7240-4694; Nephertiti Efeovbokhan 0000-0001-8262-2003.

S-Editor: Wang DM
L-Editor: Filipodia
P-Editor: Wang DM

REFERENCES

1 **GBD 2019 Diabetes in the Americas Collaborators**. Burden of diabetes and hyperglycaemia in adults in the Americas, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Diabetes Endocrinol* 2022; **10**: 655-667 [PMID: 35850129 DOI: 10.1016/S2213-8587(22)00186-3]
2 **Centers for Disease Control and Prevention**. National Diabetes Statistics Report. Center for Disease Control and Prevention. 2020. [cited 22 October, 2022]. Available from: https://www.cdc.gov/diabetes/data/statistics-report/index.html
3 **University of California San Francisco**. Vascular & Endovascular Surgery - Diabetic Foot Ulcers. [cited 22 October, 2022]. Available from: https://vascularsurgery.ucsf.edu/conditions--procedures/diabetic-foot-ulcers.aspx
4 **Boulton AJ**, Kirsner RS, Vileikyte L. Clinical practice. Neuropathic diabetic foot ulcers. *N Engl J Med* 2004; **351**: 48-55 [PMID: 15229307 DOI: 10.1056/NEJMcp032966]
5 **Ramirez-Acuña JM**, Cardenas-Cadena SA, Marquez-Salas PA, Garza-Veloz I, Perez-Favila A, Cid-Baez MA, Flores-Morales V, Martinez-Fierro ML. Diabetic Foot Ulcers: Current Advances in Antimicrobial Therapies and Emerging Treatments. *Antibiotics (Basel)* 2019; **8** [PMID: 31652990 DOI: 10.3390/antibiotics8040193]
6 **Brings S**, Fleming T, Freichel M, Muckenthaler MU, Herzig S, Nawroth PP. Dicarbonyls and Advanced Glycation End-Products in the Development of Diabetic Complications and Targets for Intervention. *Int J Mol Sci* 2017; **18** [PMID: 28475116 DOI: 10.3390/ijms18050984]
7 **Boyko EJ**, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. *Diabetes Care* 1999; **22**: 1036-1042 [PMID: 10388963 DOI: 10.2337/diacare.22.7.1036]
8 **Tesfaye S**. Recent advances in the management of diabetic distal symmetrical polyneuropathy. *J Diabetes Investig* 2011; **2**: 33-42 [PMID: 24843458 DOI: 10.1111/j.2040-1124.2010.00083.x]
9 **Skopljak A**, Sukalo A, Batic-Mujanovic O, Muftic M, Tiric-Campara M, Zunic L. Assessment of diabetic polyneuropathy and plantar pressure in patients with diabetes mellitus in prevention of diabetic foot. *Med Arch* 2014; **68**: 389-393 [PMID: 25650237 DOI: 10.5455/medarh.2014.68.389-393]
10 **Falanga V**. Wound healing and its impairment in the diabetic foot. *Lancet* 2005; **366**: 1736-1743 [PMID: 16291068 DOI: 10.1016/S0140-6736(05)67700-8]
11 **Rubitschung K**, Sherwood A, Crisologo AP, Bhavan K, Haley RW, Wukich DK, Castellino L, Hwang H, La Fontaine J, Chhabra A, Lavery L, Öz OK. Pathophysiology and Molecular Imaging of Diabetic Foot Infections. *Int J Mol Sci* 2021; **22** [PMID: 34768982 DOI: 10.3390/ijms222111552]
12 **Brinkmann V**, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, Weinrauch Y, Zychlinsky A. Neutrophil extracellular traps kill bacteria. *Science* 2004; **303**: 1532-1535 [PMID: 15001782 DOI: 10.1126/science.1092385]
13 **Karima M**, Kantarci A, Ohira T, Hasturk H, Jones VL, Nam BH, Malabanan A, Trackman PC, Badwey JA, Van Dyke TE. Enhanced superoxide release and elevated protein kinase C activity in neutrophils from diabetic patients: association with periodontitis. *J Leukoc Biol* 2005; **78**: 862-870 [PMID: 16081595 DOI: 10.1189/jlb.1004583]
14 **Menegazzo L**, Ciciliot S, Poncina N, Mazzucato M, Persano M, Bonora B, Albiero M, Vigili de Kreutzenberg S, Avogaro A, Fadini GP. NETosis is induced by high glucose and associated with type 2 diabetes. *Acta Diabetol* 2015; **52**: 497-503 [PMID: 25387570 DOI: 10.1007/s00592-014-0676-x]
15 **Byun K**, Yoo Y, Son M, Lee J, Jeong GB, Park YM, Salekdeh GH, Lee B. Advanced glycation end-products produced systemically and by macrophages: A common contributor to inflammation and degenerative diseases. *Pharmacol Ther* 2017; **177**: 44-55 [PMID: 28223234 DOI: 10.1016/j.pharmthera.2017.02.030]
16 **Schmidt AM**, Yan SD, Yan SF, Stern DM. The multiligand receptor RAGE as a progression factor amplifying immune and inflammatory responses. *J Clin Invest* 2001; **108**: 949-955 [PMID: 11581294 DOI: 10.1172/jci14002]
17 **Mahali S**, Raviprakash N, Raghavendra PB, Manna SK. Advanced glycation end products (AGEs) induce apoptosis *via* a novel pathway: involvement of Ca2+ mediated by interleukin-8 protein. *J Biol Chem* 2011; **286**: 34903-34913 [PMID: 21862577 DOI: 10.1074/jbc.M111.279190]
18 **Apte SS**, Parks WC. Metalloproteinases: A parade of functions in matrix biology and an outlook for the future. *Matrix Biol* 2015; **44-46**: 1-6 [PMID: 25916966 DOI: 10.1016/j.matbio.2015.04.005]
19 **Hopkinson I**. Molecular components of the extracellular matrix. *J Wound Care* 1992; **1**: 52-54 [PMID: 27911189 DOI:

10.12968/jowc.1992.1.1.52]
20 **Ferroni L**, Gardin C, Dalla Paola L, Campo G, Cimaglia P, Bellin G, Pinton P, Zavan B. Characterization of Dermal Stem Cells of Diabetic Patients. *Cells* 2019; **8** [PMID: 31315286 DOI: 10.3390/cells8070729]
21 **Alikhani Z**, Alikhani M, Boyd CM, Nagao K, Trackman PC, Graves DT. Advanced glycation end products enhance expression of pro-apoptotic genes and stimulate fibroblast apoptosis through cytoplasmic and mitochondrial pathways. *J Biol Chem* 2005; **280**: 12087-12095 [PMID: 15590648 DOI: 10.1074/jbc.M406313200]
22 **Patel S**, Srivastava S, Singh MR, Singh D. Mechanistic insight into diabetic wounds: Pathogenesis, molecular targets and treatment strategies to pace wound healing. *Biomed Pharmacother* 2019; **112**: 108615 [PMID: 30784919 DOI: 10.1016/j.biopha.2019.108615]
23 **Li J**, Zhang YP, Kirsner RS. Angiogenesis in wound repair: angiogenic growth factors and the extracellular matrix. *Microsc Res Tech* 2003; **60**: 107-114 [PMID: 12500267 DOI: 10.1002/jemt.10249]
24 **Kulwas A**, Drela E, Jundziłł W, Góralczyk B, Ruszkowska-Ciastek B, Rość D. Circulating endothelial progenitor cells and angiogenic factors in diabetes complicated diabetic foot and without foot complications. *J Diabetes Complications* 2015; **29**: 686-690 [PMID: 25872462 DOI: 10.1016/j.jdiacomp.2015.03.013]
25 **Li X**. The association between MCP-1, VEGF polymorphisms and their serum levels in patients with diabetic foot ulcer. *Medicine (Baltimore)* 2018; **97**: e10959 [PMID: 29901584 DOI: 10.1097/MD.0000000000010959]
26 **Kajdaniuk D**, Marek B, Borgiel-Marek H, Kos-Kudła B. Vascular endothelial growth factor (VEGF) - part 1: in physiology and pathophysiology. *Endokrynol Pol* 2011; **62**: 444-455 [PMID: 22069106]
27 **Mizia-Malarz A**, Sobol G, Woś H. [Proangiogenic factors: vascular-endothelial growth factor (VEGF) and basic fibroblast growth factor--the characteristics and function]. *Przegl Lek* 2008; **65**: 353-357 [PMID: 19004235]
28 **Tecilazich F**, Dinh T, Pradhan-Nabzdyk L, Leal E, Tellechea A, Kafanas A, Gnardellis C, Magargee ML, Dejam A, Toxavidis V, Tigges JC, Carvalho E, Lyons TE, Veves A. Role of endothelial progenitor cells and inflammatory cytokines in healing of diabetic foot ulcers. *PLoS One* 2013; **8**: e83314 [PMID: 24358275 DOI: 10.1371/journal.pone.0083314]
29 **Tepper OM**, Galiano RD, Capla JM, Kalka C, Gagne PJ, Jacobowitz GR, Levine JP, Gurtner GC. Human endothelial progenitor cells from type II diabetics exhibit impaired proliferation, adhesion, and incorporation into vascular structures. *Circulation* 2002; **106**: 2781-2786 [PMID: 12451003 DOI: 10.1161/01.cir.0000039526.42991.93]
30 **Chen MC**, Sheu JJ, Wang PW, Chen CY, Kuo MC, Hsieh CJ, Chen JF, Chang HW. Complications impaired endothelial progenitor cell function in Type 2 diabetic patients with or without critical leg ischaemia: implication for impaired neovascularization in diabetes. *Diabet Med* 2009; **26**: 134-141 [PMID: 19236615 DOI: 10.1111/j.1464-5491.2008.02649.x]
31 **Boström L**, Linder LE, Bergström J. Influence of smoking on the outcome of periodontal surgery. A 5-year follow-up. *J Clin Periodontol* 1998; **25**: 194-201 [PMID: 9543189 DOI: 10.1111/j.1600-051x.1998.tb02428.x]
32 **Lim JZ**, Ng NS, Thomas C. Prevention and treatment of diabetic foot ulcers. *J R Soc Med* 2017; **110**: 104-109 [PMID: 28116957 DOI: 10.1177/0141076816688346]
33 **Veves A**, Falanga V, Armstrong DG, Sabolinski ML; Apligraf Diabetic Foot Ulcer Study. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care* 2001; **24**: 290-295 [PMID: 11213881 DOI: 10.2337/diacare.24.2.290]
34 **Wu SC**, Jensen JL, Weber AK, Robinson DE, Armstrong DG. Use of pressure offloading devices in diabetic foot ulcers: do we practice what we preach? *Diabetes Care* 2008; **31**: 2118-2119 [PMID: 18694976 DOI: 10.2337/dc08-0771]
35 **Mueller MJ**, Diamond JE, Sinacore DR, Delitto A, Blair VP 3rd, Drury DA, Rose SJ. Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial. *Diabetes Care* 1989; **12**: 384-388 [PMID: 2659299 DOI: 10.2337/diacare.12.6.384]
36 **Roeckl-Wiedmann I**, Bennett M, Kranke P. Systematic review of hyperbaric oxygen in the management of chronic wounds. *Br J Surg* 2005; **92**: 24-32 [PMID: 15635604 DOI: 10.1002/bjs.4863]
37 **Mohd Zubir MZ**, Holloway S, Mohd Noor N. Maggot Therapy in Wound Healing: A Systematic Review. *Int J Environ Res Public Health* 2020; **17** [PMID: 32825736 DOI: 10.3390/ijerph17176103]
38 **Sridharan K**, Sivaramakrishnan G. Growth factors for diabetic foot ulcers: Mixed treatment comparison analysis of randomized clinical trials. *Br J Clin Pharmacol* 2018; **84**: 434-444 [PMID: 29148070 DOI: 10.1111/bcp.13470]
39 **Galiano R**, Snyder R, Mayer P, Rogers LC, Alvarez O; Sanuwave Trial Investigators. Focused shockwave therapy in diabetic foot ulcers: secondary endpoints of two multicentre randomised controlled trials. *J Wound Care* 2019; **28**: 383-395 [PMID: 31166864 DOI: 10.12968/jowc.2019.28.6.383]
40 **Baltzis D**, Eleftheriadou I, Veves A. Pathogenesis and treatment of impaired wound healing in diabetes mellitus: new insights. *Adv Ther* 2014; **31**: 817-836 [PMID: 25069580 DOI: 10.1007/s12325-014-0140-x]
41 **Demidova-Rice TN**, Hamblin MR, Herman IM. Acute and impaired wound healing: pathophysiology and current methods for drug delivery, part 1: normal and chronic wounds: biology, causes, and approaches to care. *Adv Skin Wound Care* 2012; **25**: 304-314 [PMID: 22713781 DOI: 10.1097/01.ASW.0000416006.55218.d0]
42 **Lopes L**, Setia O, Aurshina A, Liu S, Hu H, Isaji T, Liu H, Wang T, Ono S, Guo X, Yatsula B, Guo J, Gu Y, Navarro T, Dardik A. Stem cell therapy for diabetic foot ulcers: a review of preclinical and clinical research. *Stem Cell Res Ther* 2018; **9**: 188 [PMID: 29996912 DOI: 10.1186/s13287-018-0938-6]
43 **Sasaki M**, Abe R, Fujita Y, Ando S, Inokuma D, Shimizu H. Mesenchymal stem cells are recruited into wounded skin and contribute to wound repair by transdifferentiation into multiple skin cell type. *J Immunol* 2008; **180**: 2581-2587 [PMID: 18250469 DOI: 10.4049/jimmunol.180.4.2581]
44 **Ding DC**, Shyu WC, Lin SZ. Mesenchymal stem cells. *Cell Transplant* 2011; **20**: 5-14 [PMID: 21396235 DOI: 10.3727/096368910X]
45 **Chiang KJ**, Chiu LC, Kang YN, Chen C. Autologous Stem Cell Therapy for Chronic Lower Extremity Wounds: A Meta-Analysis of Randomized Controlled Trials. *Cells* 2021; **10** [PMID: 34943815 DOI: 10.3390/cells10123307]
46 **Wu Q**, Lei X, Chen L, Zheng Y, Huang H, Qian C, Liang Z. Autologous platelet-rich gel combined with in vitro amplification of bone marrow mesenchymal stem cell transplantation to treat the diabetic foot ulcer: a case report. *Ann Transl Med* 2018; **6**: 307 [PMID: 30211195 DOI: 10.21037/atm.2018.07.12]

47 **Dash NR**, Dash SN, Routray P, Mohapatra S, Mohapatra PC. Targeting nonhealing ulcers of lower extremity in human through autologous bone marrow-derived mesenchymal stem cells. *Rejuvenation Res* 2009; **12**: 359-366 [PMID: 19929258 DOI: 10.1089/rej.2009.0872]

48 **Qin HL**, Zhu XH, Zhang B, Zhou L, Wang WY. Clinical Evaluation of Human Umbilical Cord Mesenchymal Stem Cell Transplantation After Angioplasty for Diabetic Foot. *Exp Clin Endocrinol Diabetes* 2016; **124**: 497-503 [PMID: 27219884 DOI: 10.1055/s-0042-103684]

49 **Hikabe O**, Hamazaki N, Nagamatsu G, Obata Y, Hirao Y, Hamada N, Shimamoto S, Imamura T, Nakashima K, Saitou M, Hayashi K. Reconstitution in vitro of the entire cycle of the mouse female germ line. *Nature* 2016; **539**: 299-303 [PMID: 27750280 DOI: 10.1038/nature20104]

50 **Jiang XY**, Lu DB, Chen B. Progress in stem cell therapy for the diabetic foot. *Diabetes Res Clin Pract* 2012; **97**: 43-50 [PMID: 22221581 DOI: 10.1016/j.diabres.2011.12.011]

51 **Lee KB**, Choi J, Cho SB, Chung JY, Moon ES, Kim NS, Han HJ. Topical embryonic stem cells enhance wound healing in diabetic rats. *J Orthop Res* 2011; **29**: 1554-1562 [PMID: 21469178 DOI: 10.1002/jor.21385]

52 **Lipsky BA**, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, Deery HG, Embil JM, Joseph WS, Karchmer AW, Pinzur MS, Senneville E; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 2012; **54**: e132-e173 [PMID: 22619242 DOI: 10.1093/cid/cis346]

53 **Kwon KT**, Armstrong DG. Microbiology and Antimicrobial Therapy for Diabetic Foot Infections. *Infect Chemother* 2018; **50**: 11-20 [PMID: 29637748 DOI: 10.3947/ic.2018.50.1.11]

54 **Borys S**, Hohendorff J, Frankfurter C, Kiec-Wilk B, Malecki MT. Negative pressure wound therapy use in diabetic foot syndrome-from mechanisms of action to clinical practice. *Eur J Clin Invest* 2019; **49**: e13067 [PMID: 30600541 DOI: 10.1111/eci.13067]

55 **Lebrun E**, Tomic-Canic M, Kirsner RS. The role of surgical debridement in healing of diabetic foot ulcers. *Wound Repair Regen* 2010; **18**: 433-438 [PMID: 20840517 DOI: 10.1111/j.1524-475X.2010.00619.x]

56 **Vouillarmet J**, Bourron O, Gaudric J, Lermusiaux P, Millon A, Hartemann A. Lower-extremity arterial revascularization: Is there any evidence for diabetic foot ulcer-healing? *Diabetes Metab* 2016; **42**: 4-15 [PMID: 26072053 DOI: 10.1016/j.diabet.2015.05.004]

57 **Tepe G**, Brodmann M, Werner M, Bachinsky W, Holden A, Zeller T, Mangalmurti S, Nolte-Ernsting C, Bertolet B, Scheinert D, Gray WA; Disrupt PAD III Investigators. Intravascular Lithotripsy for Peripheral Artery Calcification: 30-Day Outcomes From the Randomized Disrupt PAD III Trial. *JACC Cardiovasc Interv* 2021; **14**: 1352-1361 [PMID: 34167675 DOI: 10.1016/j.jcin.2021.04.010]

58 **Meloni M**, Morosetti D, Giurato L, Stefanini M, Loreni G, Doddi M, Panunzi A, Bellia A, Gandini R, Brocco E, Lazaro-Martinez JL, Lauro D, Uccioli L. Foot Revascularization Avoids Major Amputation in Persons with Diabetes and Ischaemic Foot Ulcers. *J Clin Med* 2021; **10** [PMID: 34501432 DOI: 10.3390/jcm10173977]

59 **Pandey A**, Banerjee S, Ngo C, Mody P, Marso SP, Brilakis ES, Armstrong EJ, Giri J, Bonaca MP, Pradhan A, Bavry AA, Kumbhani DJ. Comparative Efficacy of Endovascular Revascularization Versus Supervised Exercise Training in Patients With Intermittent Claudication: Meta-Analysis of Randomized Controlled Trials. *JACC Cardiovasc Interv* 2017; **10**: 712-724 [PMID: 28385410 DOI: 10.1016/j.jcin.2017.01.027]

60 **Santema TB**, Poyck PP, Ubbink DT. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. *Cochrane Database Syst Rev* 2016; **2**: CD011255 [PMID: 26866804 DOI: 10.1002/14651858.CD011255.pub2]

61 **Kim SY**, Kim TH, Choi JY, Kwon YJ, Choi DH, Kim KC, Kim MJ, Hwang HK, Lee KB. Predictors for Amputation in Patients with Diabetic Foot Wound. *Vasc Specialist Int* 2018; **34**: 109-116 [PMID: 30671420 DOI: 10.5758/vsi.2018.34.4.109]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1694-1701

DOI: 10.12998/wjcc.v11.i8.1694

ISSN 2307-8960 (online)

MINIREVIEWS

Isoperistaltic *vs* antiperistaltic anastomosis after right hemicolectomy: A comprehensive review

Dimitrios Symeonidis, Kostas-Sotirios Karakantas, Labrini Kissa, Athina A Samara, Effrosyni Bompou, Konstantinos Tepetes, Georgios Tzovaras

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Feng B, China; Gad EH, Egypt; Kurtcehajic A, Bosnia and Herzegovina; Luo W, China

Received: November 5, 2022
Peer-review started: November 5, 2022
First decision: January 11, 2023
Revised: January 28, 2023
Accepted: February 21, 2023
Article in press: February 21, 2023
Published online: March 16, 2023

Dimitrios Symeonidis, Kostas-Sotirios Karakantas, Labrini Kissa, Athina A Samara, Effrosyni Bompou, Konstantinos Tepetes, Georgios Tzovaras, Department of Surgery, University Hospital of Larissa, Larissa 41110, Greece

Corresponding author: Athina A Samara, MD, Surgeon, Department of Surgery, University Hospital of Larissa, Mezourlo Hill, Larissa 41110, Greece. at.samara93@gmail.com

Abstract

To optimize the efficiency of ileocolic anastomosis following right hemicolectomy, several variations of the surgical technique have been tested. These include performing the anastomosis intra- or extracorporeally or performing a stapled or hand-sewn anastomosis. Among the least studied is the configuration of the two stumps (*i.e.*, isoperistaltic or antiperistaltic) in the case of a side-to-side anastomosis. The purpose of the present study is to compare the isoperistaltic and antiperistaltic side-to-side anastomotic configuration after right hemicolectomy by reviewing the relevant literature. High-quality literature is scarce, with only three studies directly comparing the two alternatives, and no study has revealed any significant differences in the incidence of anastomosis-related complications such as leakage, stenosis, or bleeding. However, there may be a trend towards an earlier recovery of intestinal function following antiperistaltic anastomosis. Finally, existing data do not identify a certain anastomotic configuration (*i.e.*, isoperistaltic or antiperistaltic) as superior over the other. Thus, the most appropriate approach is to master both anastomotic techniques and select between the two configurations based on each individual case scenario.

Key Words: Isoperistaltic side-to-side anastomosis; Antiperistaltic side-to-side anastomosis; Ileocolic anastomosis; Right hemicolectomy; Scenario

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This review assesses and compares two side-to-side anastomotic configurations (isoperistaltic and antiperistaltic) following right hemicolectomy. Current literature does not identify any anastomotic configuration as superior over the other. Thus, the most appropriate approach is to master both anastomotic techniques and select between the configurations based on each individual case scenario.

Citation: Symeonidis D, Karakantas KS, Kissa L, Samara AA, Bompou E, Tepetes K, Tzovaras G. Isoperistaltic *vs* antiperistaltic anastomosis after right hemicolectomy: A comprehensive review. *World J Clin Cases* 2023; 11(8): 1694-1701
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1694.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1694

INTRODUCTION

Colorectal cancer is one of the most common cancers globally, with an increasing incidence in developing countries and stabilizing trends in highly-developed countries[1]. For right-sided colon cancer, right hemicolectomy is the surgical treatment of choice[2]. Following resection, an anastomosis is performed between the terminal ileus and the transverse colon. For example, an ileocolic anastomosis may be performed to reestablish gastrointestinal tract continuity. Over the past decades, two major advances in the field of colon cancer surgery have been observed: The development of the laparoscopic approach and the concept of complete mesocolic excision (CME). Several studies have demonstrated superior short-term results and similar long-term oncological outcomes with the laparoscopic approach as compared to the traditional open approach[3,4]. Similar to the concept of total mesorectal excision for rectal tumors, Hohenberger *et al*[5] proposed CME for the surgical treatment of colon cancer. A recent meta-analysis has shown that a right hemicolectomy with CME is not inferior in terms of safety. Furthermore, this approach is associated with a greater lymph node yield, as well as better overall and disease-free survival as compared to traditional surgery[6]. Additionally, apart from colon cancer, terminal ileitis seen with Crohn's disease is a common indication for a more limited type of resection (*i.e.*, ileocecal resection) including the affected part of the small bowel, followed by an ileocolic anastomosis[7,8].

Following the resection, the efficiency and functionality of the ileocolic anastomosis influence operative outcomes and patient recovery. In the quest for optimal results, several variations of the surgical technique have been extensively tested, with studies often reporting conflicting results[9-11]. Some of the tested alternatives include conducting the anastomosis intra- or extracorporeally when the laparoscopic approach is followed, using a side-to-side or an end-to-end configuration and performing a stapled or hand-sewn anastomosis[9-11]. Parameters of success in the early postoperative period (*e.g.*, incidence of anastomosis-related complications, time to first flatus, time to recommencing oral feeding) as well as parameters reflecting long-term results (*e.g.*, functional recovery of the gastrointestinal tract, post-resection quality of life scores) have been commonly used as comparison end points. However, among the least-studied surgical technique aspects is the configuration of the stumps in the case of side-to-side anastomosis, (*i.e.*, isoperistaltic or antiperistaltic stump configurations). The purpose of the present article is to assess and compare the isoperistaltic *vs* antiperistaltic side-to-side anastomotic configurations following a right hemicolectomy by reviewing relevant literature.

Factors influencing the healing of the anastomosis

Anastomotic leakage is a clinical manifestation of a failing anastomosis. With a reported prevalence ranging between 1% and 19%, it is considered the most dramatic complication following colorectal surgery[12]. Several factors negatively influencing the physiological healing of the anastomosis have been identified. For prevention and early detection, risk factors for anastomotic leakage have been classified into preoperative, tumor-related, and intraoperative risk factors[13]. Table 1 displays potentially modifiable risk factors for anastomotic leakage, which are of the utmost importance in the preoperative setting[12,13]. From a technical perspective, the three most important factors for mastering a bowel anastomosis include: (1) Meticulous surgical technique, taking extra care to prevent hematoma formation and to achieve optimal seromuscular apposition; and (2) Adequate blood supply of the two bowel stumps; and (3) Elimination of tension at the anastomosis[14-16].

TYPES OF ANASTOMOSES

After right hemicolectomy, a favorable operative outcome depends primarily on the efficiency of the ileocolic anastomosis. A functional, complication-free anastomosis can guarantee an uneventful

Table 1 Risk factors for anastomotic leakage

	Preoperative	Tumor related	Intraoperative
Non- modifiable	Male sex	Distal tumor site	Excessive blood loss
	ASA score > II	Tumor size > 3 cm	Need for transfusion
	Chronic renal disease	Advanced stage disease	Duration > 4 hours
	History of radiotherapy	Non-elective surgery	
		Metastatic disease	
Modifiable	Smoking		
	Obesity		
	Poor nutrition		
	Alcohol abuse		
	Immunosuppressant use		

ASA: American Society of Anesthesiology.

postoperative course and improved quality of life in the long-term. To identify the optimal approach, various anastomotic techniques altering several technical parameters have been proposed. In general, anastomosis can be performed either by the use of sutures (*i.e.*, hand-sewn anastomosis) or by the use of stapling devices (*i.e.*, stapled anastomosis).

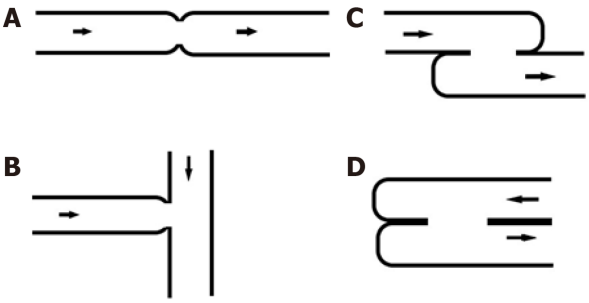
Hand-sewn anastomosis can be performed with the use of various suture materials. Materials such as silk, linen, catgut, and nylon were traditionally utilized for colorectal anastomosis. Generally, the use of absorbable or multi-filament sutures can increase tissue reaction and damage, without the guarantee of uneventful anastomosis healing[17]. Today, most gastrointestinal anastomoses are performed using slowly absorbable monofilament polydioxanone sutures[17]. In earlier decades, a double-layer inverting anastomotic technique was the standard for gastrointestinal anastomosis[18]. However, single-layer anastomosis became popular following favorable results reported by various studies[18,19]. More recent studies have failed to demonstrate a difference between the double- and single-layer techniques[20,21]. However, a single-layer continuous anastomosis costs less and can be constructed in significantly less time, with a similar complication rate as compared to the two-layer technique[22]. The dilemma in choosing between interrupted or continuous sutures arose when single-layer anastomoses became the standard of practice. As existing literature on the subject is limited and does not show obvious trends, a continuous suture may be preferable to interrupted sutures for creating intestinal anastomosis, since it is less time-consuming and technically simpler[23,24].

Conversely, stapled anastomosis can include the use of different types of stapling devices. These include linear, transverse, and circular staplers with two- or three-row stapling line systems. Following the introduction of stapled colorectal anastomosis in the 1980s, both techniques (hand sewn and stapled anastomosis) have become available for the majority of surgeons. Several studies have compared these techniques[25]. A Cochrane review conducted by Choy *et al*[11] concluded that stapled functional end-to-end ileocolic anastomosis after right hemicolectomy is associated with fewer leaks as compared to hand-sewn anastomosis. However, the difference was not considered statistically significant when the clinically significant anastomotic leaks were used as the comparison endpoint[11]. In general, superiority of the stapled over the hand-sewn anastomosis has not been documented in the available literature[26].

Irrespective of the use of sutures or stapling devices, anastomoses can be further classified based on the configuration of the two stumps, (*i.e.*, end-to-end, end-to-side and side-to-side)[15] (Figure 1). Specifically for the side-to-side configuration, an additional distinction is made between isoperistaltic and antiperistaltic anastomoses, depending on the configuration and orientation of the two stumps. In the isoperistaltic variant, the peristaltic flow in both parts is towards the same normal, aboral direction (Figure 1).

DISCUSSION

Several technical parameters influence the final form of an intestinal anastomosis. In the case of a side-to-side anastomosis, one of these parameters is the configuration of the two bowel stumps as isoperistaltic or antiperistaltic. In attempt to identify the optimal configuration, interpretation of the reviewed studies is muddied by the modification of additional technical parameters in addition to the selection of an anastomotic configuration alone. The field becomes even more unclear with increased prevalence of



DOI: 10.12998/wjcc.v11.i8.1694 **Copyright** ©The Author(s) 2023.

Figure 1 Possible anastomotic configurations. A: End-to-end anastomosis; B: End-to-side anastomosis; C: Isoperistaltic side-to-side anastomosis; D: Antiperistaltic side-to-side anastomosis.

laparoscopic surgery and incorporation of CME principles in colorectal cancer surgery, which have notably increased heterogeneity of the comparison groups[3,4,6]. Moreover, the endpoint of functional recovery following colonic resections, time to first flatus, which has been used to compare the two configurations, seems to be influenced by the presence of other confounding factors.

Pros and cons of the different anastomotic configurations

Generally, the ideal intestinal anastomosis is one that can be easily performed from a technical perspective, can be reproduced by surgeons without advanced surgical skills, is associated with low or no rate of complication due to leakage or stenosis, and is aligned with the physiological function of the gastrointestinal tract. To date, no single technique or anastomotic form can guarantee success with respect to these desired characteristics. Traditionally, a hand-sewn end-to-end anastomosis has been considered the standard approach for reestablishing gastrointestinal tract continuity after colonic resection[27]. However, this approach was associated with an increased incidence of anastomosis-related complications, mainly stenosis, particularly if a notable discrepancy occurred in the luminal diameter of the two stumps and in the setting of significant prolongation of operative time[27,28].

After the introduction of stapling devices, a shift in surgical trends was seen from the use of hand-sewn towards stapled anastomosis[29]. A side-to-side stapled anastomosis became the new standard as a rapid and easier alternative, and it allowed surgeons to overcome technical difficulties posed when a significant discrepancy in the luminal diameter of the two stumps was present[30]. Increased safety due to lower anastomotic failure rates was attributed to the stapled approach, at least in early comparative studies[28,29,31-35]. As more colorectal cancer resections are performed laparoscopically, another surgical dilemma has emerged; namely, whether to perform the anastomosis intra- or extracorporeally. In 2003, Casciola *et al*[36] reported the first intracorporeal ileocolic anastomosis after a laparoscopic right hemicolectomy. Generally, performing an intracorporeal anastomosis following laparoscopic right hemicolectomy appears to be associated with quicker recovery of postoperative bowel function, decreased infection rates, and overall postoperative complications when compared to the extracorporeal anastomotic approach[36-38].

Side-to-side anastomoses are considered to have certain advantages over end-to-end anastomoses, including better blood supply and wider diameter. In addition, the detrimental effect of increased intraluminal pressure on the healing process of an anastomosis seems to be more efficiently addressed by the side-to-side configuration[39,40]. A side-to-side ileocolic anastomosis appears to be the preferred anastomotic configuration by the majority of colorectal surgeons[41]. The end-to-side ileocolic configuration following right hemicolectomy has recently gained popularity due to the favorable results reported from retrospective cohort studies comparing end-to-side with side-to-side anastomosis[42-44]. Lower leakage rates and faster recovery at the expense of increased technical difficulty were reported after end-to-side anastomosis as compared to side-to-side anastomosis[42-44]. Several theoretical advantages have been attributed to the end-to-side configuration. This configuration resembles the physiological entry point of the ileum into the cecum lumen, results in less damage to luminal muscle fibers, and has been shown to withstand higher intraluminal pressures than end-to-end anastomosis[45,6]. However, these results were not confirmed in a study by Kim *et al*[47] which is the only available prospective randomized trial in the field, nor by any large retrospective cohort studies.

A side-to-side anastomosis can be performed either with an isoperistaltic or antiperistaltic orientation of the two stumps[48] (Figure 1). In 2005, Tewari *et al*[49] proposed the isoperistaltic, stapled, side-to-side ileocolic anastomosis after right hemicolectomy, rather than the antiperistaltic side-to-side anastomosis which was most common at the time. Despite being the most anatomical anastomotic configuration (as it is consistent with the physiological flow of the intestinal contents), a theoretical limitation of the isoperistaltic side-to-side configuration is that it requires additional mobilization to achieve adequate overlap of the two stumps. Therefore, challenges may arise in cases where the location of the anastomosis precludes such maneuvers, such as in low rectal anastomosis. However, as the

isoperistaltic orientation has already proven valid in other anatomical locations such as the biliary tree, esophagus, and stomach, it could represent the optimal approach to reestablish gastrointestinal tract continuity following colonic resection[48].

Conversely, it has been postulated that the antiperistaltic orientation could reduce the incidence of postoperative ileus, since an ileocolic anastomosis could prevent the mesentery twist seen with the isoperistaltic variant[49]. After the resection of the ileocecal valve in right hemicolectomy, reflux of colonic contents in the terminal ileus may occur. The disruption of the physiological direction of colonic content flow may be associated with secondary bacterial overgrowth in the small bowel lumen[50]. The prolonged small bowel transit times attributable to this increasingly recognized syndrome appear to be more adequately prevented with antiperistaltic anastomosis[50]. This certain anastomotic orientation likely acts through a functional pseudovalvular mechanism, diminishing ileocecal reflux and postoperative ileus[49].

Comparison of isoperistaltic vs antiperistaltic side-to-side ileocolic anastomosis

Few studies have directly compared the two anastomotic orientations. In 2003, Ibáñez *et al*[51] published a narrative review on intracorporeal anastomosis and analyzed the configuration as a possible risk factor for leakage. The authors concluded that there was no difference in anastomotic breakdown when isoperistaltic and antiperistaltic anastomoses were compared. Nevertheless, various studies have utilized different surgical techniques depending on the configuration type (*i.e.*, the isoperistaltic orientation was achieved with stapled and hand-sewn intracorporeal anastomoses, while the antiperistaltic anastomoses were all stapled).

To our knowledge, only three studies have directly compared the isoperistaltic and antiperistaltic orientations for ileocolic anastomoses. The first was a study by Chander Roland *et al*[52] in which the authors conducted a randomized controlled trial comparing isoperistaltic *vs* antiperistaltic stapled side-to-side ileocolic and colocolic anastomoses in colon cancer patients. There were 20 elective resection patients in each study arm. While the antiperistaltic anastomoses were all stapled, the authors used a running suture to close the stapling device entry hole in the isoperistaltic anastomoses to prevent iatrogenic stenosis of the ileum stump. The primary endpoints were rates of anastomotic leakage, hemorrhage, and stenosis. Across all endpoints, no significant differences were observed between the two groups. Specifically, anastomotic leakage was seen in 2 patients from the isoperistaltic group, compared to none from the antiperistaltic group (P = 0.487). One patient from the antiperistaltic group had anastomotic stenosis, while there was no stenosis in the isoperistaltic group (P = 1.000). Median postoperative length of hospital stay was similar between the two groups (P = 0.313). However, the study was suspended due to excess morbidity detected in the isoperistaltic group. While the study did not show any short-term differences between the isoperistaltic and antiperistaltic side-to-side anastomoses, considering that anastomotic leakage occurred only in the isoperistaltic group, study authors suggested that additional modifications to the isoperistaltic technique may be justified. This study had several limitations that must be considered, including small sample size, the different anastomotic types included in the analysis (both ileocolic and colocolic anastomoses), the use of both open and laparoscopic approaches, and the dissimilar technical parameters used between the groups (*i.e.*, the author used additional sutures to reinforce the antiperistaltic anastomosis).

The second study was the ISOVANTI trial published by Tewari *et al*[49]. This was a double-blind, randomized, prospective trial in colon cancer patients undergoing laparoscopic right hemicolectomy and isoperistaltic or antiperistaltic ileocolic anastomosis. A total of 108 patients were randomized either to isoperistaltic or antiperistaltic configuration groups. No differences in surgical time, anastomotic time, or postoperative complication rates (37.0% isoperistaltic *vs* 40.7% antiperistaltic, P = 0.693) were identified. In addition, there were no differences in postoperative ileus or anastomotic leakage rates (3.7% *vs* 5.56%, P = 1.00). However, the antiperistaltic configuration was associated with decreased "time to first flatus" and "time to first deposition" (P = 0.004 and P = 0.017, respectively). In the long-term, there were no differences between the groups at 1, 6 or 12 mo. There was also no difference in the rate of chronic diarrhea rate. The authors concluded that the isoperistaltic and antiperistaltic ileocolic anastomosis configurations present similar results in terms of performance, safety, and functionality.

The third study by Tarta *et al*[53] retrospectively reviewed 214 consecutive patients who underwent laparoscopic right colectomy with gastrointestinal tract continuity reestablished either by an isoperistaltic side-to-side anastomosis or an antiperistaltic side-to-side anastomosis. These anastomotic configurations proved similar in all short-term comparison categories, including operating time, intraoperative bleeding, length of resected intestine, number of harvested lymph nodes, length of incision, time to first flatus, time to first defecation, postoperative complications, and length of hospital stay. Similarly, at a median follow-up time of 35.6 mo, there were no differences in the long-term outcomes. The authors concluded that both configurations are safe, and are associated with similar short- and long-term outcomes. Despite the fact that this study has the larger sample size than the studies discussed above, it is limited by its retrospective nature. However, it is the only study that assessed oncological outcomes following the use of different anastomotic orientations.

Relevant, high-quality data are scarce, making it difficult to draw definite conclusions regarding optimal anastomotic configuration. None of the three aforementioned studies reported any significant differences between the configurations, including no differences in the incidences of anastomosis-

related complications such as leakage, stenosis, and bleeding[49,52-55]. There may be a trend towards shorter intestinal function recovery time following antiperistaltic anastomosis; however, the small sample size and associated lack of statistical significance render any such conclusion unclear. High-quality, prospective randomized trials are needed to fully elucidate the optimal anastomotic configuration after a right hemicolectomy.

CONCLUSION

In conclusion, existing data are insufficient to favor either isoperistaltic or antiperistaltic anastomotic configuration. Thus, the most appropriate approach is to master both anastomotic techniques and select the appropriate configuration based on each individual case scenario.

FOOTNOTES

Author contributions: Symeonidis D, Tzovaras G, Karakantas K-S, Samara AA and Tepetes K wrote the original paper and contributed to study conception and design; Kissa L and Bompou E performed the research; All authors have approved the final version of the manuscript.

Conflict-of-interest statement: All authors declare that they have no conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Greece

ORCID number: Athina A Samara 0000-0002-6177-7281; Effrosyni Bompou 0000-0002-2887-0978; Konstantinos Tepetes 0000-0001-9435-6849; Georgios Tzovaras 0000-0001-5322-8269.

S-Editor: Wang LL
L-Editor: Filipodia
P-Editor: Wang LL

REFERENCES

1 **Arnold M**, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017; **66**: 683-691 [PMID: 26818619 DOI: 10.1136/gutjnl-2015-310912]
2 **Baran B**, Mert Ozupek N, Yerli Tetik N, Acar E, Bekcioglu O, Baskin Y. Difference Between Left-Sided and Right-Sided Colorectal Cancer: A Focused Review of Literature. *Gastroenterology Res* 2018; **11**: 264-273 [PMID: 30116425 DOI: 10.14740/gr1062w]
3 **Guillou PJ**, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM; MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005; **365**: 1718-1726 [PMID: 15894098 DOI: 10.1016/S0140-6736(05)66545-2]
4 **Veldkamp R**, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Påhlman L, Cuesta MA, Msika S, Morino M, Lacy AM; COlon cancer Laparoscopic or Open Resection Study Group (COLOR). Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* 2005; **6**: 477-484 [PMID: 15992696 DOI: 10.1016/S1470-2045(05)70221-7]
5 **Hohenberger W**, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. *Colorectal Dis* 2009; **11**: 354-64; discussion 364 [PMID: 19016817 DOI: 10.1111/j.1463-1318.2008.01735.x]
6 **Anania G**, Davies RJ, Bagolini F, Vettoretto N, Randolph J, Cirocchi R, Donini A. Right hemicolectomy with complete mesocolic excision is safe, leads to an increased lymph node yield and to increased survival: results of a systematic review and meta-analysis. *Tech Coloproctol* 2021; **25**: 1099-1113 [PMID: 34120270 DOI: 10.1007/s10151-021-02471-2]
7 **Chen W**, Zhou J, Chen M, Jiang C, Qian Q, Ding Z. Isoperistaltic side-to-side anastomosis for the surgical treatment of Crohn disease. *Ann Surg Treat Res* 2022; **103**: 53-61 [PMID: 35919111 DOI: 10.4174/astr.2022.103.1.53]
8 **Ng CH**, Chin YH, Lin SY, Koh JWH, Lieske B, Koh FH, Chong CS, Foo FJ. Kono-S anastomosis for Crohn's disease: a systemic review, meta-analysis, and meta-regression. *Surg Today* 2021; **51**: 493-501 [PMID: 32894346 DOI: 10.1007/s00595-020-02130-3]
9 **Ricci C**, Casadei R, Alagna V, Zani E, Taffurelli G, Pacilio CA, Minni F. A critical and comprehensive systematic review and meta-analysis of studies comparing intracorporeal and extracorporeal anastomosis in laparoscopic right hemicolectomy.

Langenbecks Arch Surg 2017; **402**: 417-427 [PMID: 27595589 DOI: 10.1007/s00423-016-1509-x]
10 **Würtz HJ**, Bundgaard L, Rahr HB, Frostberg E. Anastomosis technique and leakage rates in minimally invasive surgery for right-sided colon cancer. A retrospective national cohort study. *Int J Colorectal Dis* 2022; **37**: 701-708 [PMID: 35150297 DOI: 10.1007/s00384-022-04107-9]
11 **Choy PY**, Bissett IP, Docherty JG, Parry BR, Merrie A, Fitzgerald A. Stapled versus handsewn methods for ileocolic anastomoses. *Cochrane Database Syst Rev* 2011; CD004320 [PMID: 21901690 DOI: 10.1002/14651858.CD004320.pub3]
12 **Sciuto A**, Merola G, De Palma GD, Sodo M, Pirozzi F, Bracale UM, Bracale U. Predictive factors for anastomotic leakage after laparoscopic colorectal surgery. *World J Gastroenterol* 2018; **24**: 2247-2260 [PMID: 29881234 DOI: 10.3748/wjg.v24.i21.2247]
13 **McDermott FD**, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. *Br J Surg* 2015; **102**: 462-479 [PMID: 25703524 DOI: 10.1002/bjs.9697]
14 **Kirk RM**, Winslet M. Essential General Surgical Operations. Edinburgh: Churchill Livingstone, 2001 [DOI: 10.1046/j.1365-2168.2002.02093_3.x]
15 **Goulder F**. Bowel anastomoses: The theory, the practice and the evidence base. *World J Gastrointest Surg* 2012; **4**: 208-213 [PMID: 23293735 DOI: 10.4240/wjgs.v4.i9.208]
16 **Scott-Conner CEH**. Chassin's Operative Strategy in General Surgery. Heidelberg: Springer, 2002
17 **Slieker JC**, Daams F, Mulder IM, Jeekel J, Lange JF. Systematic review of the technique of colorectal anastomosis. *JAMA Surg* 2013; **148**: 190-201 [PMID: 23426599 DOI: 10.1001/2013.jamasurg.33]
18 **Gambee LP**. A single-layer open intestinal anastomosis applicable to the small as well as the large intestine. *West J Surg Obstet Gynecol* 1951; **59**: 1-514798834
19 **Gambee LP**, Garnjobst W, Hardwick CE. Ten years' experience with a single layer anastomosis in colon surgery. *Am J Surg* 1956; **92**: 222-227 [PMID: 13340074 DOI: 10.1016/s0002-9610(56)80063-9]
20 **Everett WG**. A comparison of one layer and two layer techniques for colorectal anastomosis. *Br J Surg* 1975; **62**: 135-140 [PMID: 1090318 DOI: 10.1002/bjs.1800620214]
21 **Ceraldi CM**, Rypins EB, Monahan M, Chang B, Sarfeh IJ. Comparison of continuous single layer polypropylene anastomosis with double layer and stapled anastomoses in elective colon resections. *Am Surg* 1993; **59**: 168-171 [PMID: 8476155]
22 **Burch JM**, Franciose RJ, Moore EE, Biffl WL, Offner PJ. Single-layer continuous versus two-layer interrupted intestinal anastomosis: a prospective randomized trial. *Ann Surg* 2000; **231**: 832-837 [PMID: 10816626 DOI: 10.1097/00000658-200006000-00007]
23 **Deen KI**, Smart PJ. Prospective evaluation of sutured, continuous, and interrupted single layer colonic anastomoses. *Eur J Surg* 1995; **161**: 751-753 [PMID: 8555343]
24 **AhChong AK**, Chiu KM, Law IC, Chu MK, Yip AW. Single-layer continuous anastomosis in gastrointestinal surgery: a prospective audit. *Aust N Z J Surg* 1996; **66**: 34-36 [PMID: 8629977 DOI: 10.1111/j.1445-2197.1996.tb00697.x]
25 **MacRae HM**, McLeod RS. Handsewn vs. stapled anastomoses in colon and rectal surgery: a meta-analysis. *Dis Colon Rectum* 1998; **41**: 180-189 [PMID: 9556242 DOI: 10.1007/BF02238246]
26 **Steger J**, Jell A, Ficht S, Ostler D, Eblenkamp M, Mela P, Wilhelm D. Systematic Review and Meta-Analysis on Colorectal Anastomotic Techniques. *Ther Clin Risk Manag* 2022; **18**: 523-539 [PMID: 35548666 DOI: 10.2147/TCRM.S335102]
27 **Ruggiero R**, Sparavigna L, Docimo G, Gubitosi A, Agresti M, Procaccini E, Docimo L. Post-operative peritonitis due to anastomotic dehiscence after colonic resection. Multicentric experience, retrospective analysis of risk factors and review of the literature. *Ann Ital Chir* 2011; **82**: 369-375 [PMID: 21988044]
28 **Golda T**, Lazzara C, Zerpa C, Sobrino L, Fico V, Kreisler E, Biondo S. Risk factors for ileocolic anastomosis dehiscence; a cohort study. *Am J Surg* 2020; **220**: 170-177 [PMID: 31759455 DOI: 10.1016/j.amjsurg.2019.11.020]
29 **Kracht M**, Hay JM, Fagniez PL, Fingerhut A. Ileocolonic anastomosis after right hemicolectomy for carcinoma: stapled or hand-sewn? *Int J Colorectal Dis* 1993; **8**: 29-33 [PMID: 8492040 DOI: 10.1007/BF00341273]
30 **Kyzer S**, Gordon PH. The stapled functional end-to-end anastomosis following colonic resection. *Int J Colorectal Dis* 1992; **7**: 125-131 [PMID: 1402308 DOI: 10.1007/BF00360351]
31 **Steichen FM**. The use staplers in anatomical side-to-side and functional end-to-end enteroanastomosis. *Surgery* 1968; **64**: 948
32 **Hashemi M**, Novell JR, Lewis AA. Side-to-side stapled anastomosis may delay recurrence in Crohn's disease. *Dis Colon Rectum* 1998; **41**: 1293-1296 [PMID: 9788394 DOI: 10.1007/BF02258231]
33 **Muñoz-Juárez M**, Yamamoto T, Wolff BG, Keighley MR. Wide-lumen stapled anastomosis vs. conventional end-to-end anastomosis in the treatment of Crohn's disease. *Dis Colon Rectum* 2001; **44**: 20-5; discussion 25 [PMID: 11805559 DOI: 10.1007/BF02234814]
34 **Resegotti A**, Astegiano M, Farina EC, Ciccone G, Avagnina G, Giustetto A, Campra D, Fronda GR. Side-to-side stapled anastomosis strongly reduces anastomotic leak rates in Crohn's disease surgery. *Dis Colon Rectum* 2005; **48**: 464-468 [PMID: 15719193 DOI: 10.1007/s10350-004-0786-6]
35 **Yamamoto T**, Keighley MR. Stapled functional end-to-end anastomosis in Crohn's disease. *Surg Today* 1999; **29**: 679-681 [PMID: 10452253 DOI: 10.1007/BF02483001]
36 **Casciola L**, Ceccarelli G, Di Zitti L, Valeri R, Bellochi R, Bartoli A, Barbieri F, Spaziani A, D'Ajello M. [Laparoscopic right hemicolectomy with intracorporeal anastomosis. Technical aspects and personal experience]. *Minerva Chir* 2003; **58**: 621-627 [PMID: 14603179 DOI: 10.17797/fdschc17au]
37 **Zhang H**, Sun N, Fu Y, Zhao C. Intracorporeal versus extracorporeal anastomosis in laparoscopic right colectomy: updated meta-analysis of randomized controlled trials. *BJS Open* 2021; **5** [PMID: 34964826 DOI: 10.1093/bjsopen/zrab133]
38 **Cheek FE**, Tomarchio T, Burtle V, Moss H, McConnell D. A behavior modification training program for staff working with drug addicts. *Int J Addict* 1975; **10**: 1073-1101 [PMID: 338 DOI: 10.1089/Lap.2019.0693]
39 **Małczak P**, Wysocki M, Pisarska-Adamczyk M, Major P, Pędziwiatr M. Bowel function after laparoscopic right

hemicolectomy: a randomized controlled trial comparing intracorporeal anastomosis and extracorporeal anastomosis. *Surg Endosc* 2022; **36**: 4977-4982 [PMID: 34734306 DOI: 10.1007/s00464-021-08854-8]

40 Soluble CD4: another therapeutic option in HIV infection. *Lancet* 1990; **335**: 1128-1130 [PMID: 1971867 DOI: 10.1007/BF02173451]

41 **Hallböök O**, Johansson K, Sjödahl R. Laser Doppler blood flow measurement in rectal resection for carcinoma--comparison between the straight and colonic J pouch reconstruction. *Br J Surg* 1996; **83**: 389-392 [PMID: 8665202 DOI: 10.1002/bjs.1800830330]

42 **Allaix ME**, Degiuli M, Bonino MA, Arezzo A, Mistrangelo M, Passera R, Morino M. Intracorporeal or Extracorporeal Ileocolic Anastomosis After Laparoscopic Right Colectomy: A Double-blinded Randomized Controlled Trial. *Ann Surg* 2019; **270**: 762-767 [PMID: 31592811 DOI: 10.1097/SLA.0000000000003519]

43 **Garofalo E**, Selvaggi F, Spinelli A, Pellino G, Flashman K, Frasson M, Carvello M, de'Angelis N, Garcia-Granero A, Harper M, Warusavitarne J, Coleman M, Espin E, Celentano V. Surgical management of complex ileocolonic Crohn's disease: a survey of IBD colorectal surgeons to assess variability in operative strategy. *Int J Colorectal Dis* 2021; **36**: 1811-1815 [PMID: 33629119 DOI: 10.1007/s00384-021-03892-z]

44 **Puleo S**, Sofia M, Trovato MA, Pesce A, Portale TR, Russello D, La Greca G. Ileocolonic anastomosis: preferred techniques in 999 patients. A multicentric study. *Surg Today* 2013; **43**: 1145-1149 [PMID: 23111464 DOI: 10.1007/s00595-012-0381-8]

45 **Lee KH**, Lee SM, Oh HK, Lee SY, Ihn MH, Kim DW, Kang SB. Comparison of anastomotic configuration after laparoscopic right hemicolectomy under enhanced recovery program: side-to-side versus end-to-side anastomosis. *Surg Endosc* 2016; **30**: 1952-1957 [PMID: 26198156 DOI: 10.1007/s00464-015-4420-6]

46 **Liu Z**, Wang G, Yang M, Chen Y, Miao D, Muhammad S, Wang X. Ileocolonic anastomosis after right hemicolectomy for colon cancer: functional end-to-end or end-to-side? *World J Surg Oncol* 2014; **12**: 306 [PMID: 25287418 DOI: 10.1186/1477-7819-12-306]

47 **Kim MH**, Kang SI, Cho JR, Lee J, Yang IJ, Suh JW, Oh HK, Kim DW, Kang SB. Objective recovery time with end-to-side versus side-to-side anastomosis after laparoscopic right hemicolectomy for colon cancer: a randomized controlled trial. *Surg Endosc* 2022; **36**: 2499-2506 [PMID: 34008107 DOI: 10.1007/s00464-021-08536-5]

48 **Baqar AR**, Wilkins S, Wang WC, Oliva K, Centauri S, Yap R, McMurrick P. A comparison of extracorporeal side to side or end to side anastomosis following a laparoscopic right hemicolectomy for colon cancer. *ANZ J Surg* 2022; **92**: 1472-1479 [PMID: 35403808 DOI: 10.1111/ans.17701]

49 **Tewari M**, Shukla HS. Right colectomy with isoperistaltic side-to-side stapled ileocolic anastomosis. *J Surg Oncol* 2005; **89**: 99-101 [PMID: 15660366 DOI: 10.1002/jso.20191]

50 **Matsumoto S**, Wakatsuki K, Migita K, Ito M, Nakade H, Kunishige T, Kitano M, Nakatani M, Sho M. Predictive Factors for Delayed Gastric Emptying after Distal Gastrectomy with Roux-en-Y Reconstruction. *Am Surg* 2018; **84**: 1086-1090 [PMID: 29981653 DOI: 10.1177/000313481808400670]

51 **Ibáñez N**, Abrisqueta J, Luján J, Hernández Q, Rufete MD, Parrilla P. Isoperistaltic versus antiperistaltic ileocolic anastomosis. Does it really matter? *Surg Endosc* 2019; **33**: 2850-2857 [PMID: 30426254 DOI: 10.1007/s00464-018-6580-7]

52 **Chander Roland B**, Mullin GE, Passi M, Zheng X, Salem A, Yolken R, Pasricha PJ. A Prospective Evaluation of Ileocecal Valve Dysfunction and Intestinal Motility Derangements in Small Intestinal Bacterial Overgrowth. *Dig Dis Sci* 2017; **62**: 3525-3535 [PMID: 28871499 DOI: 10.1007/s10620-017-4726-4]

53 **Tarta C**, Bishawi M, Bergamaschi R. Intracorporeal ileocolic anastomosis: a review. *Tech Coloproctol* 2013; **17**: 479-485 [PMID: 23519986 DOI: 10.1007/s10151-013-0998-7]

54 **Matsuda A**, Miyashita M, Matsumoto S, Sakurazawa N, Takahashi G, Yamada M, Uchida E. Isoperistaltic versus antiperistaltic stapled side-to-side anastomosis for colon cancer surgery: a randomized controlled trial. *J Surg Res* 2015; **196**: 107-112 [PMID: 25818976 DOI: 10.1016/j.jss.2015.02.059]

55 **Zhang M**, Lu Z, Hu X, Zhou H, Zheng Z, Liu Z, Wang X. Comparison of the short-term outcomes between intracorporeal isoperistaltic and antiperistaltic totally stapled side-to-side anastomosis for right colectomy: A retrospective study on 214 consecutive patients. *Surg Open Sci* 2022; **9**: 7-12 [PMID: 35498389 DOI: 10.1016/j.sopen.2022.03.006]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1702-1711

DOI: 10.12998/wjcc.v11.i8.1702

ISSN 2307-8960 (online)

MINIREVIEWS

Evolving paradigm of thrombolysis in pulmonary embolism: Comprehensive review of clinical manifestations, indications, recent advances and guideline

Rohan Kumar Ochani, Rafi Aibani, Hafsa Nazir Jatoi, Masroor Anwar, Syed Anjum Khan, Iqbal Ratnani, Salim Surani

Specialty type: Critical care medicine

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Ding X, China; Maslennikov R, Russia

Received: November 26, 2022
Peer-review started: November 26, 2022
First decision: January 17, 2023
Revised: January 27, 2023
Accepted: February 21, 2023
Article in press: February 21, 2023
Published online: March 16, 2023

Rohan Kumar Ochani, Rafi Aibani, Hafsa Nazir Jatoi, Department of Internal Medicine, Dow University of Health Science, Karachi 74200, Sindh, Pakistan

Masroor Anwar, Department of Internal Medicine, Khyber Teaching Hospital, Peshawar 00000, Pakistan

Syed Anjum Khan, Department of Critical Care Medicine, Mayo Clinic Health System, Mankato, MN 56001, United States

Iqbal Ratnani, Department of Anesthesiology & Critical Care, Houston Methodist Hospital, Houston, TX 77030, United States

Salim Surani, Department of Medicine, Texas A&M University, College Station, TX 77843, United States

Salim Surani, Department of Medicine, Aga Khan University, Nairobi, Kenya

Corresponding author: Salim Surani, FCCP, MD, MS, Professor, Department of Medicine, Texas A&M University, Administration Building, 400 Bizzell St, College Station, TX 77843, United States. srsurani@hotmail.com

Abstract

Thrombolytic therapy has been the mainstay for patients with pulmonary embolism (PE). Despite being linked to a higher risk of significant bleeding, clinical trials demonstrate that thrombolytic therapy should be used in patients with moderate to high-risk PE, in addition to hemodynamic instability symptoms. This prevents the progression of right heart failure and impending hemodynamic collapse. Diagnosing PE can be challenging due to the variety of presentations; therefore, guidelines and scoring systems have been established to guide physicians to correctly identify and manage the condition. Traditionally, systemic thrombolysis has been utilized to lyse the emboli in PE. However, newer techniques for thrombolysis have been developed, such as endovascular ultrasound-assisted catheter-directed thrombolysis for massive and intermediate-high submassive risk groups. Additional newer techniques explored are the use of extracorporeal membrane oxygenation, direct aspiration, or fragmentation with aspiration. Because of the constantly changing therapeutic options and the

scarcity of randomized controlled trials, choosing the best course of treatment for a given patient may be difficult. To help, the Pulmonary Embolism Reaction Team is a multidisciplinary, rapid response team that has been developed and is used at many institutions. Hence to bridge the knowledge gap, our review highlights various indications of thrombolysis in addition to the recent advances and management guidelines

Key Words: Pulmonary embolism; Thrombolytics; Systemic; Catheter-directed; Pulmonary embolism reaction team; Guidelines

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: There are now many treatments to treat acute pulmonary embolism (PE). Patients are divided into low, moderate, and high-risk PE groups to identify those needing more advanced treatment. Unless contraindicated, systemic thrombolysis is advised for high-risk pulmonary embolism. Other than systemic thrombolysis, a number of treatment options for PE are being investigated, such as catheter-directed thrombolysis, extracorporeal membrane oxygenation, direct aspiration, or fragmentation with aspiration. Choosing the appropriate course of treatment for a certain patient may be challenging due to the plethora of therapeutic choices that are continually evolving and the paucity of randomized controlled trials. Therefore, the Pulmonary Embolism Reaction Team, is a multidisciplinary, rapid response team has been developed and is employed by various institutions to customize therapeutic options according to the need of the patient to address the ever-evolving therapeutic care.

Citation: Ochani RK, Aibani R, Jatoi HN, Anwar M, Khan SA, Ratnani I, Surani S. Evolving paradigm of thrombolysis in pulmonary embolism: Comprehensive review of clinical manifestations, indications, recent advances and guideline. *World J Clin Cases* 2023; 11(8): 1702-1711
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1702.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1702

INTRODUCTION

Pulmonary embolism (PE) is a common and potentially fatal form of venous thromboembolic disease with an estimated incidence of 1 case per 1000 persons per year in the United States. It is the third most common cause of cardiovascular death, with a diverse presentation from asymptomatic disease to death; diagnosis and sometimes challenging diagnosis[1]. Massive PEs necessitate immediate treatment to reestablish pulmonary circulation and blood flow.

Anticoagulation as a treatment for venous thromboembolism (VTE) dates back less than a century, and thrombolysis was only recently introduced, despite the fact that the thrombotic origin of PE has been extensively recognized for about two centuries. In patients with acute PE with hemodynamic compromise, thrombolytic therapy is used to lyse the emboli; however, new applications for thrombolysis emerge as the field of medicine advances[2].

In 1962, according to Browse and James, streptokinase was found to be able to lyse pulmonary emboli in both people and dogs. Four patients who received various dose regimens showed remarkable clinical improvement[3]. According to a randomized controlled trial conducted by Goldhaber and colleagues, recombinant tissue-type plasminogen activator (rtPA), introduced for the treatment of acute PE in the late 1980s, was found to act more quickly and be safer than urokinase[4].

rtPA (such as alteplase), streptokinase, and urokinase are three different thrombolytic agents that are effective in breaking up clots[5,6]. However, these agents came with considerable risks, including the potential for frequent severe bleeding and intracranial hemorrhage[7,8]. Although most of the research concurs that thrombolytic drugs accelerate the lysis of pulmonary thromboemboli better than heparin alone, their benefits for decreased PE death rates, influence on survival, and dangers of related hemorrhagic sequelae are still unclear. Therefore, this review article discusses the clinical manifestations, recent advances, and management guidelines to address the knowledge gap of the evolving treatment regimens for PE.

CLINICAL MANIFESTATIONS OF PE

Understanding and acknowledging the variable clinical manifestations amongst patients with PE is key to their identification and prompt medical intervention. The inability to accurately diagnose the patients

is considered an error that can potentially result in mortality; among patients with PE, 30% die due to a delay in their management[9]. Hence, devising an algorithm sensitive to the clinical picture of PE becomes essential to reach a diagnosis.

The clinical presentation of patients with PE can vary from an asymptomatic state to sudden death, and hence reaching a diagnosis can be challenging, limiting the physicians to mostly rely on history and physical examination[9]. Most of the signs and symptoms are broad-spectrum and typically non-specific; some of the non-specific signs may include tachycardia, dyspnea, chest pain, shock, and hypoxemia which are also found in patients presenting with other complaints such as myocardial infarction (MI), congestive heart failure and pneumonia[9]. Based on the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) trial, patients with PE frequently presented with some of these nonspecific signs; 54% of patients presented with tachypnea, 24% with tachycardia, 73% presented with dyspnea (at rest or on exertion), 44% with pleuritic pain, and 34% complained of cough[9]. However, since this trial did not include patients with serious risk factors such as recent MI and chronic kidney disease, the pertinence of these values is limited; hence, an evaluation of the patient's risk factors at the time of diagnosis becomes crucial[9]. It is researched that 80 to 90% of the patients have comorbidities that serve as risk factors for PE and that the absence of certain signs and symptoms, including dyspnea and tachypnea, indicates that the likelihood of the patient having PE is low[10].

Hamad *et al*[11] state that the clinical probability of PE relies on two elements. These include the risk factors and evidence of an alternative diagnosis. A low clinical probability is established in case of the absence of risk factors along with an alternative diagnosis, while a high clinical probability is established if there are no risk factors and there is no alternative diagnosis to explain the clinical presentation of the patient[11].

PIOPED study by Lee *et al*[10] describes that a correct diagnosis for PE was reached in 91% of cases where a low risk of PE was expected; however, in case of intermediate and high risk, a correct diagnosis was reached only 64%-68% of times, suggesting that it is less challenging to predict the diagnosis in the absence of PE and increasingly more difficult to predict the diagnosis when the underlying cause is PE. Miniati *et al*[12] report that according to their survey of 800 patients, who were divided into 2 groups based on their location, the frequently reported clinical symptoms included sudden-onset dyspnea (81% and 78%), chest pain (56% and 39%), syncope (26% and 22%), and hemoptysis (7% and 5%) while the reported asymptomatic patients were merely 1% of the study participants.

These results highlight the fact that transiently worsening dyspnea, especially sudden onset, is the most common symptom amongst patients with PE. It could be caused by bronchospasm, reduced effort of the diaphragm, or due to obstruction of the embolus, which results in reduced blood flow and hence a ventilatory/perfusion (V/Q) mismatch in the lungs[10,13,14]. This then results in reduced oxygenation of the blood and causes breathlessness or dyspnea[10,12]. Results also suggest that the second most common presentation was chest pain with an angina-like character, further complicating clinical diagnosis[14]. This could be associated with effects on pleura and the local impairment of blood circulation in the lungs or the coronary arteries[13]. Based on the same study results, fever, tachycardia, abnormal pulmonary signs, and peripheral vessel collapse are among the most common physical exam findings[13]. Hemodynamic instability is another uncommon but noteworthy clinical sign since it highlights the presence of central or extensive PE associated with a diminished hemodynamic reserve [15]. Moreover, atrial arrhythmias, particularly atrial fibrillation, may present with acute PE[15].

With the challenging and varying set of features in each patient with PE, it is recommended that in the setting of patients presenting with at least one of these four symptoms (sudden-onset dyspnea, chest pain, syncope, and hemoptysis), the physicians should remain vigilant and must keep PE as one of the differentials followed by appropriate investigations to confirm the diagnosis[13].

INDICATIONS OF THROMBOLYSIS

PE is categorized as high, intermediate, or low risk. According to European guidelines, massive PE, also known as high-risk PE, is acute PE with hypotension, which is defined as a systolic blood pressure (SBP) < 90 mmHg or a decrease of > 40 mmHg that cannot be attributed to another cause. Unless it is contraindicated, thrombolytic treatment should be given because this category of patients has a 30-d mortality risk that is more than 15%[15,16].

According to some recommendations, PE that results in profound bradycardia or pulselessness (heart rate < 40 bpm) should be regarded as massive[17]. Although according to the statement by the American Heart Association, thrombolytic therapy should be administered to patients with sub-massive or intermediate-risk PE, the utilization in such scenarios is debatable. These are defined by right ventricular dysfunction (RVD), including right ventricle (RV) hypokinesis, dilation, or elevated brain natriuretic peptide, or cardiac injury defined by elevated troponin and without hypotension. The use of thrombolytic, although, has a high efficacy, with a 30% reduction in mortality, however, the effect size on mortality of submassive PE patients is < 1%. Furthermore, in patients with intermediate risk, none of the patients treated adjunctively with alteplase showed an increase in right ventricular systolic pressure on the 6-mo followup. Such patients' 30-d mortality rates are lower than those of massive PE, ranging

from 3% to 15%[17,18]. The risk of bleeding could lessen this group's overall benefit[17].

In low-risk PE without hypotension, RVD, or cardiac damage, systemic thrombolytic treatment is not advised because the 30-d mortality is often less than 2% when treated with conventional anticoagulation [17,19,20]. We have also illustrated the indications in Figure 1.

CONTRAINDICATIONS TO THROMBOLYSIS

Absolute contraindications to thrombolytic therapy include an intracranial neoplasm, recent (within two months) intracranial or spinal surgery or trauma, a history of a hemorrhagic stroke, active bleeding or bleeding diathesis, or a non-hemorrhagic stroke within the previous three months. Pregnancy, non-hemorrhagic stroke older than three months, surgery within the last ten days, and severe uncontrolled hypertension (SBP > 200 mmHg or diastolic blood pressure > 110 mmHg) are all relative contraindications[21,22]. Contraindications to thrombolysis according to societal guidelines, have been demonstrated in Figure 2.

In an attempt to improve outcomes in patients with PE, the European Society of Cardiology, along with the European Respiratory Society, introduced certain changes to the 2014 guidelines for the diagnosis and management of patients with PE in August 2019[14]. These are key alterations that have ensured the appropriate management of this medical emergency. It has been noted in recent years that deaths due to PE have significantly declined[16].

According to the updated guidelines, patients presenting with PE are initially divided into different categories based on their clinical outcomes, symptoms, and risk factors for venous thromboembolism [14]. As stated earlier, clinical presentations of our demographic are often variable, and hence much of the diagnosis depends upon the knowledge of risk factors and the stability of the patient. Certain systems have been devised that aid in the determination of the likelihood of the patient having PE[9]. These diagnostic scoring systems include the Wells criteria and the Geneva score, which help clinicians determine the possibility of thrombosis[9].

The Wells criteria has a score assigned to specific clinical presentations. A score of greater than 4 indicates a higher likelihood of PE, while a score of less than or equal to 4 indicates a low likelihood of PE. Similarly, the Geneva score also assigns scores to patients based on the absence or presence of certain clinical indications. A score of greater than 5 would suggest a higher possibility of PE (Table 1).

Additionally, PE Rule-Out Criteria (PERC) is used by clinicians to rule out PE amongst low-risk patients[9]. These criteria include eight clinical variables; if all of the PERC criteria are satisfied and the patient has a low likelihood of PE based on the Wells criteria, the physician can satisfactorily rule out PE, and no further tests are required[23]. These variables include age < 50 years, pulse < 100 bpm, SaO_2 > 94%, absence of unilateral leg swelling, absence of hemoptysis, no history of recent trauma or surgery, absence of any VTE history, and no use of oral hormones[14]. However, the use of these systems amongst critically ill patients is limited as they merely serve as tools to assess the need for additional investigations in a stable patient[9,14].

A D-dimer test is warranted among patients with low or intermediate risk of PE[24]. The elevated levels of D-dimer indicate the existence of acute thrombosis due to concurrent coagulation and fibrinolysis; however, in post-operative cases and critically ill patients such as those with cancer, D-dimer levels are normally high due to an increase in coagulation and fibrinolysis, rendering the test unproductive[14]. A normal level of D-dimer suggests there is no need for further testing as the possibility of PE or deep vein thrombosis (DVT) is significantly low[9,14,24]. According to the updated ESC guidelines, an age-adjusted cut-off value of D-dimers has replaced the fixed cut-off value of 500 ng/mL for excluding the diagnosis of PE in low or intermediate-risk patients[25]. An age-adjusted cut-off value can be calculated using the patient's age and multiplying it by 10 for those > 50 years of age. In patients < 50 years of age, the use of the fixed value of 500ng/mL is maintained[25].

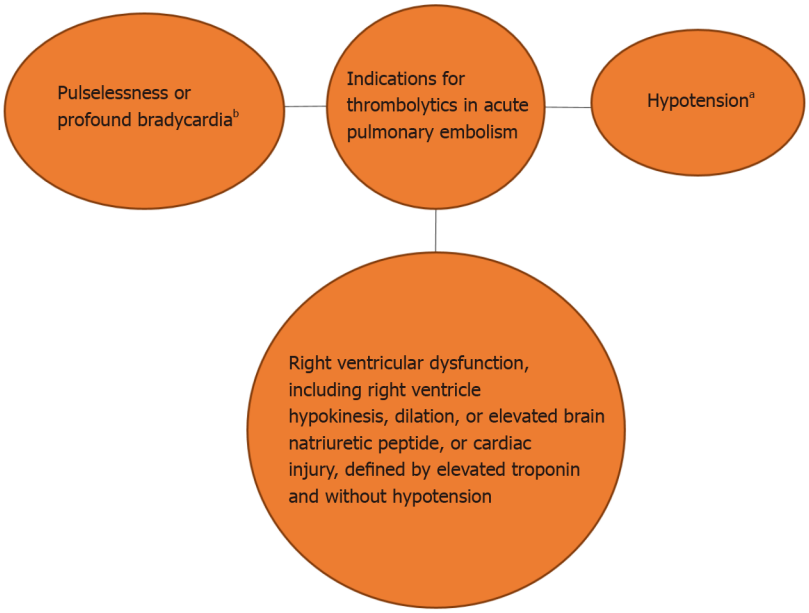
If D-dimer levels are below 1000 ng/mL and clinical signs of Wells criteria (signs of DVT, Hemoptysis, or PE) are absent or if the D-dimer level is less than 500 ng/mL, in patients with a low or intermediate possibility of PE, the diagnosis of PE can be successfully excluded without chest imaging since research suggests that in this group of patients, the post-test likelihood of PE is less than 1.85%[24, 25]. Patients with a high possibility of PE, however, must undergo chest imaging[24]. A multicenter study suggests that in patients presenting during pregnancy or the post-partum period, a diagnosis can be excluded after a thorough clinical assessment based on the likelihood of PE, D-dimer levels, compression ultrasonography (CUS), and computed pulmonary tomography angiography (CTPA). Clinical assessment for PE according to Well's Criteria has been shown in Figure 3[26].

The 2019 guidelines by the European Society of Cardiology suggest that the management of a patient must be planned based on positive lower limb CUS findings along with PE risk assessment[25]. In order to identify DVT, CUS reduces the need for invasive procedures; however, it has some limitations in its use in case of obesity and edema as well as identification of pelvic thrombosis, and it must only be used in case of nondiagnostic V/Q scan or CTPA[9,11]. The updated guidelines also highlight the importance of V/Q SPECT for establishing a PE diagnosis[25]. In patients who are unable to undergo CUS due to the aforementioned limitations or due to intravenous contrast dye contraindications, a V/Q scan can be

Table 1 Modified wells criteria

Features	Score
Suspected DVT	3.0
No alternative diagnosis	3.0
Heart rate > 100 bpm	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Malignancy	1.0

DVT: Deep vein thrombosis; PE: Pulmonary embolism.



DOI: 10.12998/wjcc.v11.i8.1702 **Copyright** ©The Author(s) 2023.

Figure 1 Indications for thrombolysis. [a]Systolic blood pressure < 90 mm Hg or drop of > 40 mm Hg not explained by another cause. [b]Heart rate < 40 bpm

employed[9]. A normal scan excludes the diagnosis of PE effectively[9,11]. However, pulmonary angiography remains the gold standard in investigation regardless of its invasive nature. Additionally, in patients with low or intermediate clinical probability, anticoagulative therapy can be safely withheld if they have a negative CTPA and CUS; however, vigilance is required before stopping therapy, especially in cases of intermediate clinical probability[11]. A study by Hogg *et al*[27] concluded that computed tomography (CT) pulmonary angiography, when used in conjunction with investigations for DVT, provides substantial evidence to rule in or out the diagnosis of PE. Additionally, echocardiography or electrocardiogram can also be used to establish a diagnosis in cases of suspected PE. An increase in right-sided stress on the heart and McConnell's sign suggests a high possibility of PE[9].

Once the diagnosis is established, hemodynamically stable patients are urgently administered anticoagulants parenterally in order to minimize the risk of deterioration, as the progression is rapid in severe cases[9]. In case of SBP of greater than 90 mmHg, direct anticoagulants, apixaban, rivaroxaban, or dabigatran are administered orally rather than heparin combined with a vitamin K antagonist as it has a 0.6% lower risk of bleeding[24]. In contrast, patients with SBP of less than 90 mmHg must be given systemic thrombolysis, as it has shown a mortality reduction of 1.6%[24].

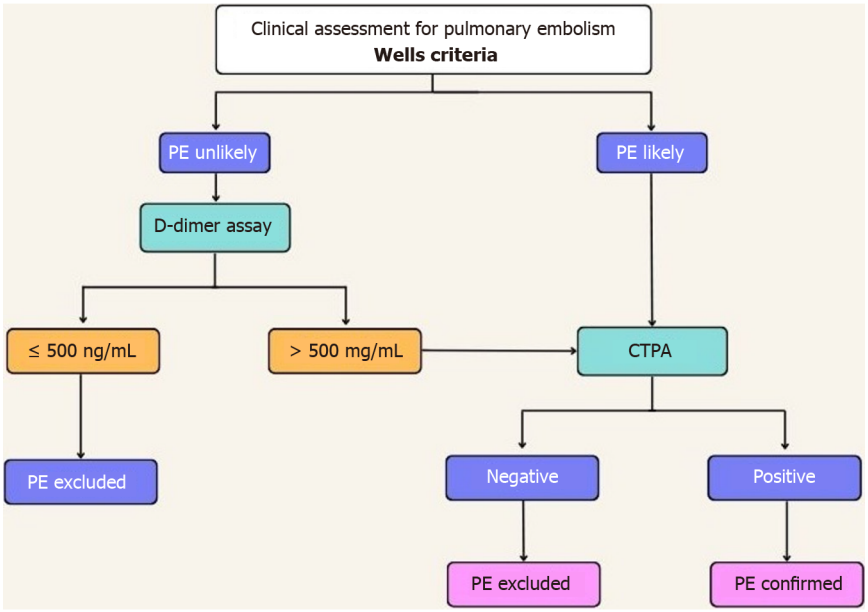
ADVERSE EVENTS

Comprehending the clinical risks of thrombolytic therapy is vital for patient selection. The adverse events (AEs) due to use of thrombolysis can be divided into five broad categories: Intracranial

American college of chest physicians	*American heart association*	*European society of cardiology*
Relative contraindications Black race Female Diabetic retinopathy Recent surgery Ischemic stroke > 3 mo ago Weight < 60 kg Systolic BP > 180 or Diastolic BP > 110 Pericarditis or pericardial fluid Recent non-intracranial bleeding Traumatic CPR Recent invasive procedure Pregnancy Anticoagulant therapy Age > 75 yr	**Relative contraindications** Major surgery within 3 wk Ischemic stroke > 3 mo ago Systolic BP > 180 or diastolic BP > 110 Dementia Recent internal bleeding (within 2 to 4 wk) Traumatic or prolonged CPR (> 10 min) Noncompressible vascular punctures Pregnancy Anticoagulant therapy Age > 75 year	**Relative contraindications** Advanced liver disease Refractory hypertension (systolic BP > 180) Infective endocarditis Active peptic ulcer disease Traumatic resuscitation Noncompressible puncture site Pregnancy Anticoagulant therapy Transient ischemic attack in preceding 6 mo
Major contraindications Recent head trauma with fracture or brain injury Recent brain or spinal surgery Bleeding diathesis Active bleeding Ischemic stroke within 3 mo Structural intracranial disease Previous intracranial hemorrhage	**Absolute contraindications** Recent closed-head or facial trauma with radiographic evidence of bony fracture or brain injury Recent surgery encroaching on the spinal canal or brain Active bleeding or bleeding diathesis Suspected aortic dissection Ischemic stroke within 3 mo Structural intracranial disease Previous intracranial hemorrhage	**Absolute contraindications** Known bleeding risk Recent major trauma, surgery in the preceding 3 wk Gastrointestinal bleeding within 1 month Ischemic stroke within 6 mo Central nervous system damage or neoplasms Previous hemorrhagic stroke or stroke of unknown origin

DOI: 10.12998/wjcc.v11.i8.1702 **Copyright** ©The Author(s) 2023.

Figure 2 Thrombolysis contraindications according to societal guidelines. BP: Blood pressure; CPR: Cardiopulmonary resuscitation.



DOI: 10.12998/wjcc.v11.i8.1702 **Copyright** ©The Author(s) 2023.

Figure 3 Diagnostic strategy in suspected cases of pulmonary embolism. PE: Pulmonary embolism; CTPA: Computed pulmonary tomography angiography.

hemorrhage, systemic hemorrhage, immunologic complications, hypotension, and myocardial rupture [28]. These AEs are more commonly observed with streptokinase or agents with a streptokinase moiety, including anistreplase (anisoylated plasminogen--streptokinase activator complex, APSAC), amongst all fibrinolytic agents due to its antigenic properties. The most common AE reported is intracranial hemorrhage. Furthermore, immunologic complications (anaphylaxis, immune complex diseases) are also observed, in addition to systemic hemorrhage, which is usually reported in patients who have had a major vascular puncture. Patients who have used streptokinase and anistreplase have also experienced manageable hypotension. Lastly, cardiac rupture is a potential delayed complication in patients taking thrombolysis.

Table 2 Ultrasound-assisted catheter-directed thrombolysis use in patients with intermediate or high-risk proximal pulmonary embolism

Study	Ultima[32]	Seattle II[33]	Optalyse[34]
Aim of the study	The aim of the study was to investigate whether ultrasound-assisted catheter-directed thrombolysis (USAT) is superior to anticoagulation alone in the reversal of RV dilatation in intermediate-risk patients	To evaluate the safety and efficacy of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis	To determine the lowest optimal tissue plasminogen activator (tPA) dose and delivery duration using ultrasound-facilitated catheter-directed thrombolysis (USCDT) for the treatment of acute intermediate-risk (sub-massive) PE
Study design	Two arms	Single arm	Single arm
Single-center/multi-center	Multi-center	Multi-center	Multi-center
Completed/ongoing	Completed	Completed	Completed
Year of publication	2014	2015	2018
Primary endpoint	The difference in the RV/LV ratio at 24 h	The difference in RV/LV ratio at 48 h and bleeding at 72 h	reduction in RV/LV ratio on CT imaging at 48 h
Total number of patients	59	150	101
Mean age of patients	63 +/- 14	59	60
% of males	47%	48.7	53
Drug used	UFH and USAT VS UFH alone	t-PA	t-PA and heparin
Results	The mean difference in RV/LV ratio from baseline to 24 h was 0.30 ± 0.20 *vs* 0.03 ± 0.16 ($P < 0.001$), respectively	The mean RV/LV diameter ratio decreased from baseline to 48 h post-procedure (1.55 *vs* 1.13; mean difference, -0.42; $P < 0.0001$)	Improvements in RV/LV ratio were as follows: Arm 1 (4 mg/lung/2 h), 0.40 (24%; $P = 0.0001$); arm 2 (4 mg/lung/4 h), 0.35 (22.6%; $P = 0.0001$); arm 3 (6 mg/lung/6 h), 0.42 (26.3%; $P = 0.0001$); and arm 4 (12 mg/lung/6 h), 0.48 (25.5%; $P = 0.0001$)
Adverse effects	4 minor bleedings. No major bleeding	17 major bleeding events within 30 d of the procedure observed in 15 patients (10%). One of these major bleeding events was a GUSTO severe/life-threatening hemorrhage (a right groin vascular access site hematoma with transient hypotension requiring vasopressor support). The remainder (94%) were GUSTO moderate bleeds, 3 of which were related to vascular access	4 patients had a total of 5 major bleeding events

CT: Computed tomography; DVT: Deep vein thrombosis; PE: Pulmonary embolism; RV: Right ventricle; LV: Left ventricular; t-PA: Tissue-plasminogen activator.

WHAT'S NEW ON THE HORIZON?

Catheter-directed thrombolysis (CDT) is one of the evolving treatment options for PE. The American College of Chest Physicians currently recommends CDT as a class 2C treatment for acute PE patients with hypotension who have contraindications to thrombolysis, failed thrombolysis, or shock that is likely to result in death before systemic thrombolysis can take effect (*e.g.*, within hours), provided that the necessary expertise and resources are available. This recommendation is for the massive and intermediate-high sub-massive risk groups[29]. CDT comprises a variety of endovascular procedures to eliminate or dissolve acute thrombus. It serves as an alternative to surgical embolectomy, transcatheter embolectomy, and systemic thrombolysis for revascularization. Because of the synergistic effects of higher local fibrinolytic medication concentrations and mechanical disruption with more exposed thrombus surface area and decreased hemorrhagic complications, this therapy has the advantage of improved thrombus-dissolving efficacy[30]. Theoretically, applying low-frequency sonic waves to the thrombus causes the fibrin monomers to break down, allowing thrombolytic penetration.

The use of ultrasound-assisted CDT in patients with intermediate or high-risk proximal PE has been studied in three recent trials (Table 2).

The popularity of catheter-directed thrombolysis is increasing in the United States as more and more healthcare professionals are becoming trained in CDT. Overall, long-term data on right ventricular function, exercise tolerance, quality of life, and the likelihood of developing chronic thromboembolic pulmonary hypertension after CDT is still lacking. The optimal technique for catheter-based thrombus removal will ultimately be determined by trials concentrating on novel devices in the future[31].

When first-line therapy fails, and a patient has hemodynamic instability, mechanical hemodynamic support is an option to investigate. Extracorporeal membrane oxygenation (ECMO), venovenous and veno-arterial, and RV support devices are among the modalities.

Another alternative for patients with an unacceptably high risk of bleeding is mechanical disruption or removal of the thrombus without thrombolysis. Direct aspiration or fragmentations with aspiration are two methods of clot clearance. The FlowTriever (Inari Medical, Irivine, California, United States) and the Penumbra Indigo (Penumbra Inc, Alameda, California, United States) system are two examples of devices for this use that have received Food and Drug Administration (FDA) approval[32-34].

Selecting the best course of treatment for a given patient might be difficult because of the constantly changing therapeutic alternatives and the paucity of randomized controlled studies. To assist, the Pulmonary Embolism Reaction Team (PERT) type of multidisciplinary, fast response team has been created and is used at many institutions[32,33].

When caring for patients with PE, PERT aims to deliver a quick, suitable, multidisciplinary, team-based approach with the shared objective of customizing the best therapeutic decision-making while always placing the needs of the patient first. As soon as a clinician encounters a patient with complex acute PE, PERTs can be activated from anywhere in the hospital. A team member gathers pertinent clinical data about patients after the referring doctor activates the PERT and offers it to the other team members for quick consultation and decision-making. Along with managing and offering outpatient follow-up, PERT can also act as a research platform for patient registries or clinical studies.

CONCLUSION

Acute PE can now be treated in a variety of ways. Individuals who may need more advanced therapy are identified by risk stratifying patients into low, middle, and high-risk PE categories. In cases with a contraindication, systemic thrombolysis are recommended for high-risk and part intermediate risk pulmonary embolisms.

Endovascular treatment, including CDT, Medical Pulmonary Thromboendarterectomy, or catheter aspiration with or without fragmentation is a promising method for high-risk PE, especially under the support of ECMO. Further research is necessary to elucidate the significance of VA-ECMO in patients with major pulmonary emboli. PERT is a multidisciplinary, fast-response team which can assist in selecting the best treatment option for these patients and facilitate communication between various specialists for individualized care.

FOOTNOTES

Author contributions: Ochani RK, Aibani R, Jatoi HN and Anwar M were involved in the literature search and writing of the manuscript; Ochani RK was lead in writing and revising; Ratnani I and Khan SA were involved in proofreading the manuscript and revision; Surani S was involved in idea creation, writing and revision of the manuscript.

Conflict-of-interest statement: None of the authors have any conflict of interest to disclose.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: United States

ORCID number: Rohan Kumar Ochani 0000-0002-0075-2267; Rafi Aibani 0000-0002-3222-9454; Hafsa Nazir Jatoi 0000-0002-6380-1687; Masroor Anwar 0000-0003-0453-0458; Syed Anjum Khan 0000-0002-2452-2079; Iqbal Ratnani 0000-0002-1168-3-41; Salim Surani 0000-0001-7105-4266.

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

REFERENCES

1 **Horlander KT**, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. *Arch Intern Med* 2003; **163**: 1711-1717 [PMID: 12885687 DOI:

10.1001/archinte.163.14.1711]
2 **Essien EO**, Rali P, Mathai SC. Pulmonary Embolism. *Med Clin North Am* 2019; **103**: 549-564 [PMID: 30955521 DOI: 10.1016/j.mcna.2018.12.013]
3 **Browse NL**, James DC. Streptokinase and Pulmonary Embolism. *Lancet* 1964; **2**: 1039-1043 [PMID: 14206016 DOI: 10.1016/s0140-6736(64)90991-2]
4 **Goldhaber SZ**, Kessler CM, Heit J, Markis J, Sharma GV, Dawley D, Nagel JS, Meyerovitz M, Kim D, Vaughan DE. Randomised controlled trial of recombinant tissue plasminogen activator versus urokinase in the treatment of acute pulmonary embolism. *Lancet* 1988; **2**: 293-298 [PMID: 2899718 DOI: 10.1016/s0140-6736(88)92354-9]
5 **Stambaugh RL**, Alexander MR. Therapeutic use of thrombolytic agents. *Am J Hosp Pharm* 1981; **38**: 817-824 [PMID: 7018230]
6 **Stewart LK**, Kline JA. Fibrinolytics for the treatment of pulmonary embolism. *Transl Res* 2020; **225**: 82-94 [PMID: 32434005 DOI: 10.1016/j.trsl.2020.05.003]
7 **Chatterjee S**, Chakraborty A, Weinberg I, Kadakia M, Wilensky RL, Sardar P, Kumbhani DJ, Mukherjee D, Jaff MR, Giri J. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA* 2014; **311**: 2414-2421 [PMID: 24938564 DOI: 10.1001/jama.2014.5990]
8 **Gao GY**, Yang P, Liu M, Ding M, Liu GH, Tong YL, Yang CY, Meng FB. Thrombolysis for acute intermediate-risk pulmonary embolism: A meta-analysis. *Thromb Res* 2015; **136**: 932-937 [PMID: 26384442 DOI: 10.1016/j.thromres.2015.09.012]
9 **Tarbox AK**, Swaroop M. Pulmonary embolism. *Int J Crit Illn Inj Sci* 2013; **3**: 69-72 [PMID: 23724389 DOI: 10.4103/2229-5151.109427]
10 **Lee LC**, Shah K. Clinical manifestation of pulmonary embolism. *Emerg Med Clin North Am* 2001; **19**: 925-942 [PMID: 11762280 DOI: 10.1016/s0733-8627(05)70227-3]
11 **Hamad MM**, Bhatia P, Ellidir E, Abdelaziz MM, Connolly V. Diagnostic approach to pulmonary embolism and lessons from a busy acute assessment unit in the UK. *Breathe* 2011; **7**: 315-323 [DOI: 10.1183/20734735.020210]
12 **Miniati M**, Cenci C, Monti S, Poli D. Clinical presentation of acute pulmonary embolism: survey of 800 cases. *PLoS One* 2012; **7**: e30891 [PMID: 22383978 DOI: 10.1371/journal.pone.0030891]
13 **Morrone D**, Morrone V. Acute Pulmonary Embolism: Focus on the Clinical Picture. *Korean Circ J* 2018; **48**: 365-381 [PMID: 29737640 DOI: 10.4070/kcj.2017.0314]
14 **Konstantinides SV**, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ní Áinle F, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020; **41**: 543-603 [PMID: 31504429 DOI: 10.1093/eurheartj/ehz405]
15 **Konstantinides SV**, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, Svitil P, Vonk Noordegraaf A, Zamorano JL, Zompatori M; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014; **35**: 3033-3069, 3069a [PMID: 25173341 DOI: 10.1093/eurheartj/ehu283]
16 **Jiménez D**, de Miguel-Díez J, Guijarro R, Trujillo-Santos J, Otero R, Barba R, Muriel A, Meyer G, Yusen RD, Monreal M; RIETE Investigators. Trends in the Management and Outcomes of Acute Pulmonary Embolism: Analysis From the RIETE Registry. *J Am Coll Cardiol* 2016; **67**: 162-170 [PMID: 26791063 DOI: 10.1016/j.jacc.2015.10.060]
17 **Jaff MR**, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite P, Vedantham S, White RJ, Zierler BK; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011; **123**: 1788-1830 [PMID: 21422387 DOI: 10.1161/CIR.0b013e318214914f]
18 **Jiménez D**, Kopecna D, Tapson V, Briese B, Schreiber D, Lobo JL, Monreal M, Aujesky D, Sanchez O, Meyer G, Konstantinides S, Yusen RD, On Behalf Of The Protect Investigators. Derivation and validation of multimarker prognostication for normotensive patients with acute symptomatic pulmonary embolism. *Am J Respir Crit Care Med* 2014; **189**: 718-726 [PMID: 24471575 DOI: 10.1164/rccm.201311-2040OC]
19 **Kearon C**, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**: e419S-e496S [PMID: 22315268 DOI: 10.1378/chest.11-2301]
20 **Kearon C**, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JRE, Wells P, Woller SC, Moores L. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest* 2016; **149**: 315-352 [PMID: 26867832 DOI: 10.1016/j.chest.2015.11.026]
21 **Zuo Z**, Yue J, Dong BR, Wu T, Liu GJ, Hao Q. Thrombolytic therapy for pulmonary embolism. *Cochrane Database Syst Rev* 2021; **4**: CD004437 [PMID: 33857326 DOI: 10.1002/14651858.CD004437.pub6]
22 **Dieck JA**, Ferguson JJ 3rd. Indications for thrombolytic therapy in acute pulmonary embolism. *Tex Heart Inst J* 1989; **16**: 19-26 [PMID: 15227232]
23 **Kline JA**, Courtney DM, Kabrhel C, Moore CL, Smithline HA, Plewa MC, Richman PB, O'Neil BJ, Nordenholz K. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost* 2008; **6**: 772-780 [PMID: 18318689 DOI: 10.1111/j.1538-7836.2008.02944.x]
24 **Freund Y**, Cohen-Aubart F, Bloom B. Acute Pulmonary Embolism: A Review. *JAMA* 2022; **328**: 1336-1345 [PMID: 36194215 DOI: 10.1001/jama.2022.16815]

25 **Erythropoulou-Kaltsidou A**, Alkagiet S, Tziomalos K. New guidelines for the diagnosis and management of pulmonary embolism: Key changes. *World J Cardiol* 2020; **12**: 161-166 [PMID: 32547711 DOI: 10.4330/wjc.v12.i5.161]

26 **Righini M**, Robert-Ebadi H, Elias A, Sanchez O, Le Moigne E, Schmidt J, Le Gall C, Cornuz J, Aujesky D, Roy PM, Chauleur C, Rutschmann OT, Poletti PA, Le Gal G; CT-PE-Pregnancy Group. Diagnosis of Pulmonary Embolism During Pregnancy: A Multicenter Prospective Management Outcome Study. *Ann Intern Med* 2018; **169**: 766-773 [PMID: 30357273 DOI: 10.7326/M18-1670]

27 **Hogg K**, Brown G, Dunning J, Wright J, Carley S, Foex B, Mackway-Jones K. Diagnosis of pulmonary embolism with CT pulmonary angiography: a systematic review. *Emerg Med J* 2006; **23**: 172-178 [PMID: 16498151 DOI: 10.1136/emj.2005.029397]

28 **Califf RM**, Fortin DF, Tenaglia AN, Sane DC. Clinical risks of thrombolytic therapy. *Am J Cardiol* 1992; **69**: 12A-20A [PMID: 1729875 DOI: 10.1016/0002-9149(92)91168-4]

29 **Brown KN**, Devarapally SR, Lee LS, Gupta N. Catheter Directed Thrombolysis Of Pulmonary Embolism. 2022 May 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [PMID: 30725603]

30 **Piazza G**. Advanced Management of Intermediate- and High-Risk Pulmonary Embolism: JACC Focus Seminar. *J Am Coll Cardiol* 2020; **76**: 2117-2127 [PMID: 33121720 DOI: 10.1016/j.jacc.2020.05.028]

31 **Xue X**, Sista AK. Catheter-Directed Thrombolysis for Pulmonary Embolism: The State of Practice. *Tech Vasc Interv Radiol* 2018; **21**: 78-84 [PMID: 29784125 DOI: 10.1053/j.tvir.2018.03.003]

32 **Kucher N**, Boekstegers P, Müller OJ, Kupatt C, Beyer-Westendorf J, Heitzer T, Tebbe U, Horstkotte J, Müller R, Blessing E, Greif M, Lange P, Hoffmann RT, Werth S, Barmeyer A, Härtel D, Grünwald H, Empen K, Baumgartner I. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation* 2014; **129**: 479-486 [PMID: 24226805 DOI: 10.1161/CIRCULATIONAHA.113.005544]

33 **Piazza G**, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, Jones NJ, Gurley JC, Bhatheja R, Kennedy RJ, Goswami N, Natarajan K, Rundback J, Sadiq IR, Liu SK, Bhalla N, Raja ML, Weinstock BS, Cynamon J, Elmasri FF, Garcia MJ, Kumar M, Ayerdi J, Soukas P, Kuo W, Liu PY, Goldhaber SZ; SEATTLE II Investigators. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: The SEATTLE II Study. *JACC Cardiovasc Interv* 2015; **8**: 1382-1392 [PMID: 26315743 DOI: 10.1016/j.jcin.2015.04.020]

34 **Sista AK**. The OPTALYSE PE Trial: Another Step Toward Understanding the Truth About Catheter-Directed Thrombolysis for Submassive Pulmonary Embolism. *JACC Cardiovasc Interv* 2018; **11**: 1411-1413 [PMID: 30025735 DOI: 10.1016/j.jcin.2018.05.014]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1712-1718

DOI: 10.12998/wjcc.v11.i8.1712

ISSN 2307-8960 (online)

MINIREVIEWS

Corneal endothelial cells and acoustic cavitation in phacoemulsification

Kai Chen, Wen-Ya Xu, Si-Si Sun, Hong-Wei Zhou

Specialty type: Ophthalmology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Cheraqpour K, Iran; Dragonieri S, Italy

Received: December 14, 2022
Peer-review started: December 14, 2022
First decision: January 3, 2023
Revised: January 14, 2023
Accepted: February 22, 2023
Article in press: February 22, 2023
Published online: March 16, 2023

Kai Chen, Wen-Ya Xu, Si-Si Sun, Department of Ophthalmology, Lianshui County People's Hospital, Huai'an 223400, Jiangsu Province, China

Hong-Wei Zhou, Department of Ophthalmology, Huai'an 82 Hospital, Huai'an 223001, Jiangsu Province, China

Hong-Wei Zhou, Department of Industrial Engineering, Tsinghua University, Beijing 100084, China

Corresponding author: Hong-Wei Zhou, MD, PhD, Chief Physician, Director, Doctor, Department of Ophthalmology, Huai'an 82 Hospital, No. 100 Jiankang Road, Qingjiang District, Huai'an 223001, Jiangsu Province, China. leave0307@163.com

Abstract

Postoperative complications of phacoemulsification, such as corneal edema caused by human corneal endothelial cell (CEC) injury, are still a matter of concern. Although several factors are known to cause CEC damage, the influence of ultrasound on the formation of free radicals during surgery should be considered. Ultrasound in aqueous humor induces cavitation and promotes the formation of hydroxyl radicals or reactive oxygen species (ROS). ROS-induced apoptosis and autophagy in phacoemulsification have been suggested to significantly promote CEC injury. CEC cannot regenerate after injury, and measures must be taken to prevent the loss of CEC after phacoemulsification or other CEC injuries. Antioxidants can reduce the oxidative stress injury of CEC during phacoemulsification. Evidence from rabbit eye studies shows that ascorbic acid infusion during operation or local application of ascorbic acid during phacoemulsification has a protective effect by scavenging free radicals or reducing oxidative stress. Both in experiments and clinical practice, hydrogen dissolved in the irrigating solution can also prevent CEC damage during phacoemulsification surgery. Astaxanthin (AST) can inhibit oxidative damage, thereby protecting different cells from most pathological conditions, such as myocardial cells, luteinized granulosa cells of the ovary, umbilical vascular endothelial cells, and human retina pigment epithelium cell line (ARPE-19). However, existing research has not focused on the application of AST to prevent oxidative stress during phacoemulsification, and the related mechanisms need to be studied. The Rho related helical coil kinase inhibitor Y-27632 can inhibit CEC apoptosis after phacoemulsification. Rigorous experiments are required to confirm whether its effect is realized through improving the ROS clearance ability of CEC.

Key Words: Cataract; Phacoemulsification; Corneal endothelial cells; Ultrasound; Acoustic cavitation; Oxidative stress; Antioxidant

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Ultrasound in aqueous solution induces cavitation and promotes the formation of hydroxyl radicals or reactive oxygen species (ROS). ROS-induced apoptosis and autophagy in phacoemulsification have been suggested to significantly promote corneal endothelial cell (CEC) injury. Antioxidants can reduce the oxidative stress-induced injury to CECs during phacoemulsification.

Citation: Chen K, Xu WY, Sun SS, Zhou HW. Corneal endothelial cells and acoustic cavitation in phacoemulsification. *World J Clin Cases* 2023; 11(8): 1712-1718
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1712.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1712

INTRODUCTION

Phacoemulsification has recently become an increasingly popular surgical procedure for cataracts, with improvements in devices and surgical techniques. However, postoperative complications are still a problem worthy of concern, such as infective endophthalmitis, retinal detachment, and corneal edema due to damage to human corneal endothelial cells (CECs). Although several factors are known to cause CEC damage, the effects of free radical formation by ultrasound waves during the procedure should be considered. Ultrasound in aqueous humor induces acoustic cavitation[1] and promotes the formation of reactive oxygen species (ROS)[2]. ROS-induced corneal endothelial damage has been demonstrated to significantly promote apoptosis and autophagy during phacoemulsification[3]. CECs cannot regenerate after injuries[4], and strategies must be taken to prevent CEC loss after phacoemulsification or other endothelial injuries. This paper discusses corneal endothelial injury caused by oxidative stress secondary to acoustic cavitation during phacoemulsification and also related protective measures and implications for related fields.

THE IMPORTANCE OF PREVENTING CECS LOSS AND INJURY

Phacoemulsification surgery is the most commonly used surgery to treat cataracts. The complications of phacoemulsification, which affect the prognosis of visual acuity, are still a matter of concern. These complications include macular cystoid edema, infectious endophthalmitis, retinal detachment, and corneal edema due to loss of CEC. Corneal edema caused by decompensation of CEC is one of the most serious complications of phacoemulsification and can lead to severe visual loss and pain. CECs play a crucial role in regulating the constant dehydration of the corneal stroma and transparency[5]. CECs play a role mainly through active fluid pump and barrier function[6]. Both clinical and experimental studies have shown that the proliferation ability of human CECs is limited[7]. CEC density (ECD) usually starts from 4000 cells/mm^2 at birth and gradually decreases with age. The average value for adults is approximately 2500 cells/mm^2, while the average value for elderly individuals is less than 2000 cells/mm^2. Corneas with an ECD less than 1000 cells/mm^2 may not be able to tolerate intraocular surgery. When ECD is less than 500 cells/mm^2, corneal edema and compensatory imbalance usually occur[8]. In previous studies, uneventful cataract surgery has been proven to induce CEC loss ranging from 12% to 20%[9,10]. At present, the only effective option to treat corneal endothelial dysfunction is corneal transplantation (*e.g.*, full thickness penetrating keratoplasty or lamellar endothelial keratoplasty)[11]. In phacoemulsification, CEC damage is caused by ultrasonic mechanical damage, such as turbulence of the anterior chamber fluid and mechanical collision of bubbles and crystal fragments[12]. The application of viscoelastic materials in ophthalmology can limit the CEC damage caused by this aspect. Studies have confirmed that endogenous damage caused by oxidative stress plays a major role in CEC damage caused by phacoemulsification[3,13]. Therefore, how to maximize the prevention of CEC loss and injury during and after phacoemulsification and how to find the best effective safety strategy to protect CECs is a research priority.

ACOUSTIC CAVITATION AND ITS EFFECTS ON CECS

Ultrasonic energy is used in various surgical operations and is generated by the conversion of electrical energy by piezoelectric crystals located in the casing head. The probe is a hollow or solid metal conduit that directs ultrasonic vibration energy from the transducer to the target tissue (Figure 1). The low-frequency and high-energy ultrasonic radiation from the transducer can lead to the periodic compression and expansion of bubbles suspended in the liquid medium. Acoustic cavitation (that is, bubble expansion and rapid adiabatic collapse in solution) can generate enough energy to generate free radicals, sonoluminescence, high pressure and temperature rise in the bubble gas phase, bubble core and liquid interface[14]. In a water medium, water molecules decompose to form H^+ and OH^- radicals as the main primary radicals. The generation of acoustic cavitation in a water medium is a random, nonlinear, complex and multifactor-related phenomenon.

Bond[14] proposed a mechanical model to describe the interaction between phacoemulsification or other ultrasonic operations and various tissues. In the process of phacoemulsification, the direct mechanical vibration effect between the probe and the tissue will produce a large amount of heat accumulation, so continuous synchronous irrigation can be used to reduce the heat effect. The application of irrigating fluid in ophthalmic surgery can reduce friction and thermal effects; however, the gas nuclei in these aqueous solutions may produce acoustic cavitation. Acoustic cavitation may interact with tissues through chemical, electromagnetic radiation, thermal and mechanical effects and reportedly cause cell and intracellular damage. The combined effects of acoustic cavitation on the survival of damaged cells (that is, the generation of radiation, ultraviolet radiation, high temperature and high pressure leading to acoustic perforation) may lead to ultrasonic energy damage and may explain immediate cell damage, apoptosis and death[15,16].

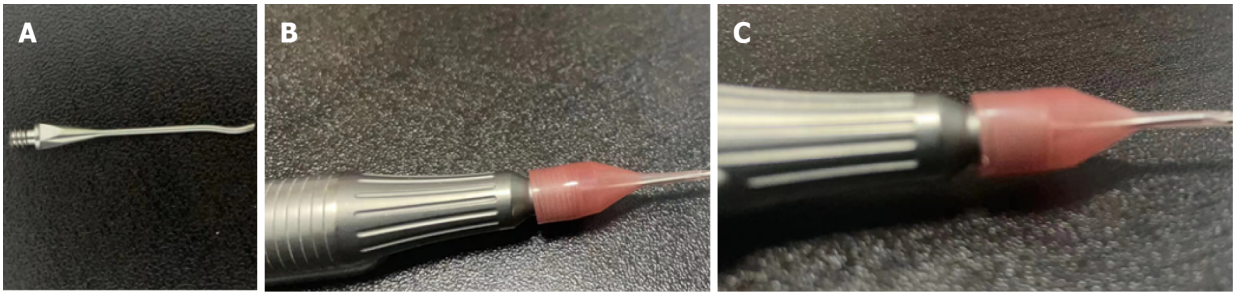
In phacoemulsification, because monolayer endothelial cells cannot regenerate, the damage and destruction of CECs should be minimized or eliminated. Aqueous humor contains natural antioxidants. In phacoemulsification, the irrigating solution circulates through the anterior chamber of the eye at a rate of approximately 20-30 mL/min to prevent heat accumulation. This effectively irrigates all aqueous humor within a few seconds, thus removing all natural antioxidants that usually protect the anterior chamber from oxidative damage. Therefore, ultrasonic emulsification in the irrigating solution environment can produce acoustic cavitation, but it depletes the natural antioxidants of aqueous humor.

The main expected effect of phacoemulsification is to chop, emulsify and empty the cataractous lens through the small clear corneal incision. To reduce heat accumulation and help lens fragmentation and emulsification, as well as the removal of debris, synchronous irrigation must be carried out continuously. However, for the generation of free radicals and sonoluminescence, cavitation may be considered an undesirable byproduct of phacoemulsification. Free radicals have been shown to cause toxic ocular oxidative damage, such as in the retina, lens and cornea[17]. The cytotoxicity of ROS to photosensitizer-treated and light-treated bovine CEC has been proven to be mediated by a parallel pathway leading to apoptosis and necrosis[18].

INHIBITING OXIDATIVE STRESS INDUCED BY ACOUSTIC CAVITATION PROTECTS CECS

Studies have confirmed that endogenous damage caused by oxidative stress plays an important role in CEC damage caused by phacoemulsification[3,16]. Therefore, some antioxidants can reduce the damage to CECs in phacoemulsification.

Holst *et al*[18] determined the formation of free radicals by adding luminol to the buffer solution and measuring the chemiluminescence *in vitro* and in rabbit eyes during phacoemulsification. They found that free radicals were formed during the process of phacoemulsification, and the number of free radicals was related to the power of ultrasound. In addition, the free radical scavenger superoxide dismutase (SOD) can inhibit the formation of free radicals, indicating that adding SOD to the irrigating solution during phacoemulsification can reduce the damage to CECs. Rubowitz *et al*[19] performed long-term phacoemulsification in the anterior chamber on 17 rabbit eyes. In 9 eyes, balanced salt eye solution was used in the phacoemulsification, and in 8 eyes, 0.001 M ascorbic acid was added to the solution. All other parameters were the same between the two groups. They found that there was no significant difference between the two groups in the number of CECs before the operation, but the ECD of the ascorbic acid treated group was higher compared to the other group after the operation (P = 0.011). They believed that adding ascorbic acid in the irrigating solution could significantly reduce the loss of CEC during phacoemulsification by approximately 70% and that it was due to the free radical scavenging properties of ascorbic acid. M Padua *et al*[12] showed that during phacoemulsification surgery in dogs, the application of ascorbic acid at a final concentration of 0.001 M in the irrigating solution significantly reduced the loss of CEC, the loss of hexagonal cells, and the coefficient of variation of CEC. Lee *et al*[20] reported the clinical application of ascorbic acid to prevent CEC damage related to phacoemulsification surgery in 2 patients during the perioperative period. In addition to cataracts, 2 patients suffered from Fuchs corneal endothelial dystrophy and corneal endotheliitis. Nakamura *et al*



DOI: 10.12998/wjcc.v11.i8.1712 **Copyright** ©The Author(s) 2023.

Figure 1 Photograph of the probe and sleeve. A: Probe; B: Front of probe with sleeve; C: Side of probe with sleeve.

[21] emphasized the protective effect of the antioxidant glutathione on CEC caused by ROS and found that oxidized glutathione has a better effect. Both oxidized glutathione and reduced glutathione can protect CECs.

The most relevant studies on acoustic cavitation and its effects on CECs are summarized in Table 1. A figure describing acoustic cavitation and its effects on CECs is included (Figure 2).

IMPLICATIONS FOR RELEVANT FIELDS

Endogenous injury of CECs induced by oxidative stress is the main cause of CEC injury induced by phacoemulsification. Reducing the damage to CECs during cataract surgery has been a hot topic in the field of ophthalmology.

Astaxanthin (AST) is an orange red carotenoid pigment that is the strongest antioxidant in nature. It has a variety of biological activities, including anticancer, anti-inflammatory, antiaging, antidiabetic, immune regulation and neuroprotective activities. However, it is unclear whether AST can protect CECs from endogenous damage caused by oxidative stress during phacoemulsification.

AST does not exist in human eyes and aqueous humor. At present, there are some studies on AST in ophthalmology. Otsuka *et al*[22] found that AST can prevent retinal ischemic damage through its antioxidant effect in a retinal ischemia□reperfusion model. Dong *et al*[23] found that in the diabetes db/db mouse model, AST can reduce the apoptosis of retinal ganglion cells, reduce the oxidative stress pressure of retinal tissue in db/db mice, reduce superoxide anion, reduce malondialdehyde, reduce 8-hydroxy-2-deoxyguanosine (8-OHdG) and increase manganese superoxide dismutase (Mn SOD) activity. Hashimoto *et al*[24] conducted a clinical experiment to evaluate the antioxidant effect of AST through changes in superoxide scavenging activity, hydrogen peroxide level and total organic peroxide in human aqueous humor. The subjects were 35 patients who underwent bilateral cataract surgery before and after taking AST (6 mg/day for 2 wk), and aqueous humor was taken during the surgery. After AST intake, the superoxide scavenging activity increased significantly, and the total organic peroxide level decreased significantly. The superoxide scavenging activity was significantly, negatively correlated with the total organic peroxide level (R = -0.485, P < 0.01), indicating that AST intake obviously enhanced the superoxide scavenging activity of human aqueous humor and inhibited the production of total organic peroxide in aqueous humor.

Many scholars have conducted in-depth research on the mechanism of AST in various cells. In a recent study, an ultraviolet (UV) B-induced oxidative stress model was used to evaluate the antioxidant effect of AST on a human retina pigment epithelium cell line (ARPE-19). The results showed that 20 μM and 40 μM AST can increase cell viability and have synergistic effects with ascorbic acid[25,26]. Increasing evidence shows that ROS production stimulates Phosphatidylinositol-3-kinase-serine/threonine kinase Akt (PI3K-Akt) mediated autophagy, while AST improves cell survival under oxidative inflammation conditions by activating the Akt signaling pathway[27]. Li Z and colleagues have proven that AST plays a protective role in H_2O_2-induced oxidative damage by activating the PI3K-Akt pathway, and then PI3K-Akt further activates several downstream signal transduction media, such as mammalian target of rapamycin (mTOR) and the Nuclear factor erythroid 2-related factor 2-antioxidant response elements (Nrf2-ARE) pathway[28].

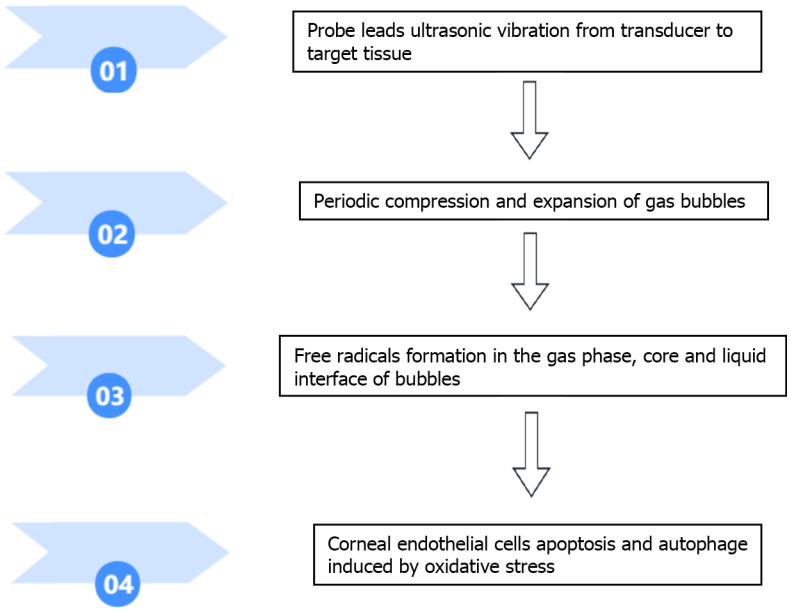
However, no previous studies have focused on the role of AST in the oxidative stress injury of CEC during phacoemulsification and its related mechanisms. In fact, in addition to phacoemulsification, there are many risk factors for the increase in CEC, such as solar ultraviolet radiation, aging and malnutrition. Therefore, local application of AST may contribute to the protection of patients with fragile CEC.

Previous papers have suggested that Rho related helical coil kinase (ROCK) plays important roles in cell cycle control because ROCK inhibits the premature separation of two centrioles in G1 period and is indispensable for the contraction of the cleavage groove (a necessary step for the completion of

Table 1 The most relevant studies about acoustic cavitation effects and its effects on corneal endothelial cells

Ref.	Journal	Key points
Hsueh *et al*[3]	*Cells*	ROS-induced CECs damage has been demonstrated to significantly promote apoptosis and autophagy during phacoemulsification
M Padua *et al*[12]	*Vet Ophthalmol*	Oxidative stress plays a major role in CECs damage and ascorbic acid significantly protected CECs during phacoemulsification
Ashush *et al*[13]	*Cancer Res*	Acoustic cavitation can generate free radicals, sonoluminescence, high pressure and temperature rise
Holst *et al*[18]	*Curr Eye Res*	SOD can inhibit the formation of free radicals during phacoemulsification
Rubowitz *et al*[19]	*Invest Ophthalmol Vis Sci*	The number of postoperative CECs in the study group treated with ascorbic acid was significantly more
Lee *et al*[20]	*World J Clin Cases*	Clinical application of ascorbic acid can prevent CECs damage related to phacoemulsification

CECs: Corneal endothelial cells; SOD: Superoxide dismutase; ROS: Reactive oxygen species.



DOI: 10.12998/wjcc.v11.i8.1712 **Copyright** ©The Author(s) 2023.

Figure 2 Acoustic cavitation and its effects on corneal endothelial cells.

cytokinesis)[29]. The ROCK inhibitor Y-27632 has been proven to increase proliferation and even immortalize primary keratinocytes in the presence of feeder cells[30]. Achiron *et al*[30] divided the corneal ring of a human donor into fragments, stored them in commercial storage medium with or without 10 mmol/L ROCK inhibitor, and then exposed them to phacoemulsification. The sample was separated into single cells by trypsin digestion. CEC was labeled with anti-CD166 antibodies to evaluate the early and late apoptosis rate of survival of CEC by flow cytometry analysis of annexin V and propidium iodide (PI) double staining. Six corneal and scleral rings from 4 donors were studied. After phacoemulsification, compared with the control group, the CEC exposed to Y-27632 showed that the early apoptosis rate decreased by 37.06%, and the late apoptosis rate decreased by 45.27%. The authors believe that ROCK inhibitors can be used before cataract surgery, especially in high-risk patients. This may be a promising new method to prevent pseudophakic bullous keratopathy. However, the author has not clarified the mechanism behind the effect. Zhou *et al*[31] found that the primary limbal epithelial cells of rabbits treated with Y-27632 also showed improved colony formation efficiency by enhancing the expansion of stem/progenitor cells. They proved that Y-27632 improved the cloning efficiency of rabbit limbal stem/progenitor cells by improving their adhesion and ROS clearance ability. Therefore, rigorous experiments are required to confirm whether the effect of Y-27632 on inhibiting the apoptosis of CECs after phacoemulsification is realized through the mechanism of improving the ROS clearance ability of CECs.

CONCLUSION

Ultrasound in aqueous humor can induce cavitation and promote the formation of ROS. ROS-induced apoptosis and autophagy have been suggested to significantly promote CEC injury during phacoemulsification. AST can inhibit oxidative damage, thus protecting different cells from most pathological conditions. However, existing research has not focused on the application of AST to prevent oxidative stress during phacoemulsification. Y-27632 inhibited CEC apoptosis after phacoemulsification. Further experiments are required to confirm whether the effect is realized by improving the ROS clearance ability of CECs.

FOOTNOTES

Author contributions: Chen K and Xu WY searched the references, designed and discussed the manuscript; Zhou HW and Sun SS searched the references, designed, composed, revised and submitted the manuscript.

Conflict-of-interest statement: Chen K has received research funding from Scientific Research Project of Lianshui County Health Committee in 2022; Xu WY, Sun SS, and Zhou HW have nothing to disclose.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Kai Chen 0000-0003-4707-8246; Wen-Ya Xu 0000-0003-1955-6642; Si-Si Sun 0000-0001-9640-1455; Hong-Wei Zhou 0000-0002-5320-3886.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

REFERENCES

1 **Topaz M**, Motiei M, Assia E, Meyerstein D, Meyerstein N, Gedanken A. Acoustic cavitation in phacoemulsification: chemical effects, modes of action and cavitation index. *Ultrasound Med Biol* 2002; **28**: 775-784 [PMID: 12113790 DOI: 10.1016/s0301-5629(02)00514-8]
2 **Augustin AJ**, Dick HB. Oxidative tissue damage after phacoemulsification: influence of ophthalmic viscosurgical devices. *J Cataract Refract Surg* 2004; **30**: 424-427 [PMID: 15030835 DOI: 10.1016/S0886-3350(03)00577-7]
3 **Hsueh YJ**, Meir YJ, Yeh LK, Wang TK, Huang CC, Lu TT, Cheng CM, Wu WC, Chen HC. Topical Ascorbic Acid Ameliorates Oxidative Stress-Induced Corneal Endothelial Damage *via* Suppression of Apoptosis and Autophagic Flux Blockage. *Cells* 2020; **9** [PMID: 32290365 DOI: 10.3390/cells9040943]
4 **Català P**, Thuret G, Skottman H, Mehta JS, Parekh M, Ní Dhubhghaill S, Collin RWJ, Nuijts RMMA, Ferrari S, LaPointe VLS, Dickman MM. Approaches for corneal endothelium regenerative medicine. *Prog Retin Eye Res* 2022; **87**: 100987 [PMID: 34237411 DOI: 10.1016/j.preteyeres.2021.100987]
5 **Sahu PK**, Das GK, Agrawal S, Kumar S. Comparative Evaluation of Corneal Endothelium in Patients with Diabetes Undergoing Phacoemulsification. *Middle East Afr J Ophthalmol* 2017; **24**: 74-80 [PMID: 28936050 DOI: 10.4103/meajo.MEAJO_242_15]
6 **Hsueh YJ**, Chen HC, Wu SE, Wang TK, Chen JK, Ma DH. Lysophosphatidic acid induces YAP-promoted proliferation of human corneal endothelial cells *via* PI3K and ROCK pathways. *Mol Ther Methods Clin Dev* 2015; **2**: 15014 [PMID: 26029725 DOI: 10.1038/mtm.2015.14]
7 **Rouhbakhshzaeri M**, Rabiee B, Azar N, Ghahari E, Putra I, Eslani M, Djalilian AR. New ex vivo model of corneal endothelial phacoemulsification injury and rescue therapy with mesenchymal stromal cell secretome. *J Cataract Refract Surg* 2019; **45**: 361-366 [PMID: 30527441 DOI: 10.1016/j.jcrs.2018.09.030]
8 **Choi JY**, Han YK. Long-term (≥10 years) results of corneal endothelial cell loss after cataract surgery. *Can J Ophthalmol* 2019; **54**: 438-444 [PMID: 31358141 DOI: 10.1016/j.jcjo.2018.08.005]
9 **Al-Mohtaseb Z**, He X, Yesilirmak N, Waren D, Donaldson KE. Comparison of Corneal Endothelial Cell Loss Between Two Femtosecond Laser Platforms and Standard Phacoemulsification. *J Refract Surg* 2017; **33**: 708-712 [PMID: 28991340 DOI: 10.3928/1081597X-20170731-01]
10 **Shen L**, Sun P, Zhang C, Yang L, Du L, Wu X. Therapy of corneal endothelial dysfunction with corneal endothelial cell-like cells derived from skin-derived precursors. *Sci Rep* 2017; **7**: 13400 [PMID: 29042661 DOI: 10.1038/s41598-017-13787-1]
11 **Wilkinson SW**, Park SSE, Ungricht EL, Trapnell M, Nydegger J, Cardenas IA, Brintz BJ, Mamalis N, Olson RJ, Werner

L. Effect of simulated lenticular debris on corneal endothelial cells: experimental study in rabbit eyes. *J Cataract Refract Surg* 2022; **48**: 1325-1330 [PMID: 36026701 DOI: 10.1097/j.jcrs.0000000000001032]

12 **M Padua IR**, P Valdetaro G, B Lima T, K Kobashigawa K, E S Silva P, Aldrovani M, M Padua PP, Laus JL. Effects of intracameral ascorbic acid on the corneal endothelium of dogs undergoing phacoemulsification. *Vet Ophthalmol* 2018; **21**: 151-159 [PMID: 28714237 DOI: 10.1111/vop.12490]

13 **Ashush H**, Rozenszajn LA, Blass M, Barda-Saad M, Azimov D, Radnay J, Zipori D, Rosenschein U. Apoptosis induction of human myeloid leukemic cells by ultrasound exposure. *Cancer Res* 2000; **60**: 1014-1020 [PMID: 10706118]

14 **Bond LJ**, Cimino WW. Physics of ultrasonic surgery using tissue fragmentation. *Ultrasonics* 1996; **34**: 579-585 [PMID: 8701547 DOI: 10.1016/0041-624x(96)00039-x]

15 **Murano N**, Ishizaki M, Sato S, Fukuda Y, Takahashi H. Corneal endothelial cell damage by free radicals associated with ultrasound oscillation. *Arch Ophthalmol* 2008; **126**: 816-821 [PMID: 18541846 DOI: 10.1001/archopht.126.6.816]

16 **Giblin FJ**, McCready JP. The effect of inhibition of glutathione reductase on the detoxification of H2O2 by rabbit lens. *Invest Ophthalmol Vis Sci* 1983; **24**: 113-118 [PMID: 6826306]

17 **Cho KS**, Lee EH, Choi JS, Joo CK. Reactive oxygen species-induced apoptosis and necrosis in bovine corneal endothelial cells. *Invest Ophthalmol Vis Sci* 1999; **40**: 911-919 [PMID: 10102288]

18 **Holst A**, Rolfsen W, Svensson B, Ollinger K, Lundgren B. Formation of free radicals during phacoemulsification. *Curr Eye Res* 1993; **12**: 359-365 [PMID: 8391415 DOI: 10.3109/02713689308999460]

19 **Rubowitz A**, Assia EI, Rosner M, Topaz M. Antioxidant protection against corneal damage by free radicals during phacoemulsification. *Invest Ophthalmol Vis Sci* 2003; **44**: 1866-1870 [PMID: 12714617 DOI: 10.1167/iovs.02-0892]

20 **Lee CY**, Chen HT, Hsueh YJ, Chen HC, Huang CC, Meir YJ, Cheng CM, Wu WC. Perioperative topical ascorbic acid for the prevention of phacoemulsification-related corneal endothelial damage: Two case reports and review of literature. *World J Clin Cases* 2019; **7**: 642-649 [PMID: 30863764 DOI: 10.12998/wjcc.v7.i5.642]

21 **Nakamura M**, Nakano T, Hikida M. Effects of oxidized glutathione and reduced glutathione on the barrier function of the corneal endothelium. *Cornea* 1994; **13**: 493-495 [PMID: 7842706]

22 **Otsuka T**, Shimazawa M, Inoue Y, Nakano Y, Ojino K, Izawa H, Tsuruma K, Ishibashi T, Hara H. Astaxanthin Protects Against Retinal Damage: Evidence from In Vivo and In Vitro Retinal Ischemia and Reperfusion Models. *Curr Eye Res* 2016; **41**: 1465-1472 [PMID: 27158842 DOI: 10.3109/02713683.2015.1127392]

23 **Dong LY**, Jin J, Lu G, Kang XL. Astaxanthin attenuates the apoptosis of retinal ganglion cells in db/db mice by inhibition of oxidative stress. *Mar Drugs* 2013; **11**: 960-974 [PMID: 23519150 DOI: 10.3390/md11030960]

24 **Hashimoto H**, Arai K, Hayashi S, Okamoto H, Takahashi J, Chikuda M, Obara Y. Effects of astaxanthin on antioxidation in human aqueous humor. *J Clin Biochem Nutr* 2013; **53**: 1-7 [PMID: 23874063 DOI: 10.3164/jcbn.13-6]

25 **Oh S**, Kim YJ, Lee EK, Park SW, Yu HG. Antioxidative Effects of Ascorbic Acid and Astaxanthin on ARPE-19 Cells in an Oxidative Stress Model. *Antioxidants (Basel)* 2020; **9** [PMID: 32899990 DOI: 10.3390/antiox9090833]

26 **Zhang J**, Ding C, Zhang S, Xu Y. Neuroprotective effects of astaxanthin against oxygen and glucose deprivation damage *via* the PI3K/Akt/GSK3β/Nrf2 signalling pathway in vitro. *J Cell Mol Med* 2020; **24**: 8977-8985 [PMID: 32567157 DOI: 10.1111/jcmm.15531]

27 **Li Z**, Dong X, Liu H, Chen X, Shi H, Fan Y, Hou D, Zhang X. Astaxanthin protects ARPE-19 cells from oxidative stress *via* upregulation of Nrf2-regulated phase II enzymes through activation of PI3K/Akt. *Mol Vis* 2013; **19**: 1656-1666 [PMID: 23901249]

28 **Riento K**, Ridley AJ. Rocks: multifunctional kinases in cell behaviour. *Nat Rev Mol Cell Biol* 2003; **4**: 446-456 [PMID: 12778124 DOI: 10.1038/nrm1128]

29 **Liu X**, Ory V, Chapman S, Yuan H, Albanese C, Kallakury B, Timofeeva OA, Nealon C, Dakic A, Simic V, Haddad BR, Rhim JS, Dritschilo A, Riegel A, McBride A, Schlegel R. ROCK inhibitor and feeder cells induce the conditional reprogramming of epithelial cells. *Am J Pathol* 2012; **180**: 599-607 [PMID: 22189618 DOI: 10.1016/j.ajpath.2011.10.036]

30 **Achiron A**, Feldman A, Karmona L, Avizemer H, Barequet IS, Rosner M, Knyazer B, Bartov E, Burgansky Z, Vishnevskia-Dai V. Prophylactic exposure of human corneal endothelial cells to Rho-associated kinase inhibitor reduced apoptosis rate after phacoemulsification: Ex vivo study. *J Cataract Refract Surg* 2018; **44**: 1261-1266 [PMID: 30172567 DOI: 10.1016/j.jcrs.2018.04.044]

31 **Zhou Q**, Duan H, Wang Y, Qu M, Yang L, Xie L. ROCK inhibitor Y-27632 increases the cloning efficiency of limbal stem/progenitor cells by improving their adherence and ROS-scavenging capacity. *Tissue Eng Part C Methods* 2013; **19**: 531-537 [PMID: 23151007 DOI: 10.1089/ten.TEC.2012.0429]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1719-1729

DOI: 10.12998/wjcc.v11.i8.1719

ISSN 2307-8960 (online)

MINIREVIEWS

Modern blepharoplasty: From bench to bedside

Giovanni Miotti, Marco Zeppieri, Giacomo Pederzani, Carlo Salati, Pier Camillo Parodi

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): D
Grade E (Poor): 0

P-Reviewer: Convery C, United Kingdom; Grawish ME, Egypt

Received: December 16, 2022
Peer-review started: December 16, 2022
First decision: January 3, 2023
Revised: January 7, 2023
Accepted: February 22, 2023
Article in press: February 22, 2023
Published online: March 16, 2023

Giovanni Miotti, Giacomo Pederzani, Department of Medical, Surgical and Health Sciences, Plastic and Reconstructive Surgery Unit, University of Trieste, Trieste 34123, Italy

Giovanni Miotti, Pier Camillo Parodi, Department of Plastic Surgery, University Hospital of Udine, Udine 33100, Italy

Marco Zeppieri, Carlo Salati, Department of Ophthalmology, University Hospital of Udine, Udine 33100, Italy

Corresponding author: Marco Zeppieri, BSc, MD, PhD, Doctor, Department of Ophthalmology, University Hospital of Udine, p.le S. Maria della Misericordia 15, Udine 33100, Italy.
markzeppieri@hotmail.com

Abstract

The demand for procedures aiming to rejuvenate the upper third part of the face and the periocular region has increased in the past several years. Blepharoplasty is one of the most frequently performed procedures worldwide to date. Surgery is currently the first choice in order to achieve permanent and effective results; however, it is burdened by potential surgical complications feared by patients. There is an increasing trend in individuals to request less invasive, non-surgical, effective, and safe procedures for eyelid treatment. The aim of this minireview is to present a brief overview of non-surgical blepharoplasty techniques that have been reported in the literature in the past 10 years. Numerous modern techniques that provide a rejuvenation of the entire area have been described. Numerous less invasive methods have been proposed in the current literature and in modern-day routine clinical settings. Dermal fillers are a commonly chosen option for providing enhanced aesthetic results, especially considering that volume loss can be one of the main underlying causes of facial and periorbital aging. Deoxycholic acid use may be considered when the problem is represented by periorbital excess fat deposits. The simultaneous excess and loss of elasticity of the skin can be assessed with techniques such as lasers and plasma exeresis. Furthermore, techniques such as platelet-rich plasma injections and the insertion of twisted polydioxanone threads are emerging as viable methods to rejuvenate the periorbital region.

Key Words: Non-surgical blepharoplasty; Laser treatment; Dermatochalasis; Aesthetic; Non-invasive procedures; Hyaluronic acid; Plasma exeresis; Eyelids

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Non-surgical procedures represent a valid alternative to surgery in the rejuvenation of the periorbital area. When the problem can be corrected by 'filling' more and 'removing' less, fillers may be of use. Laser treatment and microsurgical techniques can provide a viable solution when the main concern is based on excess and/or inelasticity of the skin.

Citation: Miotti G, Zeppieri M, Pederzani G, Salati C, Parodi PC. Modern blepharoplasty: From bench to bedside. *World J Clin Cases* 2023; 11(8): 1719-1729
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1719.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1719

INTRODUCTION

The periocular region represents one of the most fascinating and interesting elements of the face that others usually first notice in us. The first signs of aging of the face are typically seen in this area[1]. The search for a younger and "fresher" appearance of the face is one of the main reasons that individuals search for clinical assistance, be it surgical or non-surgical. The demand for upper facial rejuvenation in both females and males has dramatically increased in the past decade. Blepharoplasty, which is performed for cosmetic and/or functional reasons, is one of the most performed procedures worldwide [2]. In the last 10 years, blepharoplasty has been one of the top five most commonly performed surgical procedures, along with facelift (rhytidectomy) and rhinoplasty[3].

Blepharoplasty can be defined as the surgical repair or reconstruction of the upper and/or lower eyelids. These procedures are performed to correct the signs of aging that occur in the periorbital region and enhance unaesthetic lids. The procedure typically involves the management of excess eyelid skin, lid laxity, ptosis, orbital septum, and orbital fat. Upper and lower lid blepharoplasty can be performed for cosmetic reasons and/or reconstructive reasons. Cosmetic and reconstructive procedures can be undertaken at different times or can sometimes be performed during the same operation[4,5].

The upper and lower eyelids consist of the anterior, middle, and posterior lamellae. The anterior lamella is composed of the skin and orbicularis oculi muscle of the eyelid, whereas the posterior lamella refers to the retractors, superior or inferior tarsal muscle, tarsus, and conjunctiva. The orbital septum is sometimes referenced as the middle lamella[6]. Despite being one of the most frequently performed operations, surgical blepharoplasty tends to be an invasive and non-definitive procedure that can produce scars and may require further surgical retouches in the future. Like all surgical procedures, blepharoplasty involves risks that include infection, bleeding, and other postoperative complications. In light of the fears and risks involved with traditional invasive surgery, there has been an increasing demand for innovative cosmetic procedures that are less invasive and provide good outcomes with fewer side effects compared to surgical procedures[2]. The aim of our minireview is to present a brief overview of non-surgical blepharoplasty techniques, which have been reported in the literature and used in clinical settings in the past 10 years.

MATERIALS AND METHODS

We conducted a search of the literature published from January 1, 2012 to December 1, 2022 using MEDLINE (PubMed). The database was first searched using the key words "non-surgical blepharoplasty, blepharoplasty NOT surgery, non-surgical blepharoplasty techniques, non-invasive blepharoplasty, blepharoplasty AND fillers, blepharoplasty AND hyaluronic acid, blepharoplasty AND laser, blepharoplasty AND peeling, blepharoplasty AND chemical peels, blepharoplasty AND plasma". We considered only studies in English and those referring to humans and with an abstract, thus reducing the count to 538 papers. The reference lists of all retrieved articles were assessed to identify additional relevant studies. The research of articles was performed using PubMed (https://pubmed.ncbi.nlm.nih.gov) and *Reference Citation Analysis* (https://www.referencecitationanalysis.com).

Only articles with an abstract were considered. After excluding all works in which only surgical techniques were described and those that assessed non-surgical techniques as only complementary to surgery, 40 studies were analyzed. A quality score was calculated for each article using a check list from the American Society of Plastic Surgeons guidelines for therapeutic studies[7]. Each study was independently assessed by at least two reviewers (Miotti G and Zeppieri M), and rating decisions were based on the consensus of the reviewing authors. The results of the most relevant studies are shown in Table 1.

Table 1 Studies in current literature regarding blepharoplasty

Ref.	Technique	Type of the study	Where (upper/lower eyelid)	Number of cases	Conclusions
Balzani *et al*[21], 2013	Laser	Prospective	Upper	20	Lift of 1.63 ± 0.68 mm of the upper eyelid at 6 mo
Bae-Harboe *et al*[16], 2014		Review	Both	/	Fractional ablative CO_2 laser is a valid solution to improve the appearance of periocular area
Toyos[20], 2017		Retrospective	Upper	16	Increase in the measurements for dermatochalasis and skin laxity at 6 mo follow-up and few side effects
Guida *et al*[23], 2018		Retrospective	Both	20	Increase in the Global Assessment Improvement Scale; reduction of medium protrusions and depressions; improved texture at 2 mo also at 3D image reconstructions
Garcia *et al*[22], 2019		Cohort, uncontrolled	Lower	263	Improvement in the eyelid area characterized by fewer rhytids and a younger appearance at 6 mo
Rossi *et al*[30], 2018	Plasma exeresis	Prospective, controlled, evaluator-blinded	Both	10	Change in the conformation of the collagen fibers from huddled and coalesce presentation to long and straight fibers
Giroux *et al*[33], 2019		Prospective, single center	Upper	25	About 2.5 mm of mean reduction at 12 mo follow-up
Theppornpitak *et al*[35], 2019		Prospective, controlled, evaluator-blinded	Both	18	Effective and safe for treatment of mild-to-moderate periorbital wrinkles and darkening
Verner *et al*[32], 2020		Prospective, single center	Upper	17	All patients had an improvement of dermathocalasis scale
Baroni[2], 2020		Prospective, single center	Upper	10	General satisfaction for the patients (8 or more on VAS scale) and the absence of permanent side effects
Ziade and Desiree[29], 2020		Case report	Both	2	Safe and efficient non-surgical option. Few complications; hyperpigmentation is the most common, preventable whit small precautions
Ferreira *et al*[31], 2021		Observational	Upper	16	General post-treatment satisfaction (modified Q-bleph) and limited adverse events
Martín-Oviedo *et al*[38], 2013	HA	Retrospective	Upper	26	Effective in reducing paralytic lagophthalmos and controlling keratopathy in patients with temporary facial palsy
Romero *et al*[42], 2013		Retrospective	Lower	12	Retraction was completely corrected in 96.3% of patients; improvement of the standardized MRD2 of 0.84 mm immediately after injection and 1.19 mm 9 mo later
Kohn *et al*[39], 2014		Prospective, non-randomized	Upper	8	HA injection may be an effective and minimally invasive method to improve upper eyelid position for patients with mild eyelid retraction in both the active and inactive stages of TED
Romeo[12], 2016		Cohort, prospective	Upper	154	Upper eyelid area filling with HA was compared to surgical blepharoplasty as means of reaching eye rejuvenation. The study showed high patient satisfaction in regards of the aesthetic endpoint and long lasting results in a 12 mo period
Jiang *et al*[47], 2016		Retrospective, single center clinical study	Lower (tear-trough deformity)	78	Compared the use of HA to autologous fat injections. Fillers may be used alone in the treatment of TTD in patients with mild to moderate periorbital volume loss without severe orbital fat bulging
Romeo[46], 2019		Retrospective	Upper	500	Upper eyelid area filling with HA was compared to surgical blepharoplasty as means of reaching eye rejuvenation. The study showed high patient satisfaction in regards of the aesthetic endpoint and long lasting results in a 12 mo period
Xi *et al*[42], 2019		Retrospective	Lower	27	Retraction was completely corrected in 96.3% of patients; improvement of the standardized MRD2 of 0.84 mm immediately after injection and 1.19 mm nine months later
Bladen and Malhotra[43], 2019		Retrospective, single center case review	Upper	8	6 patients showed improvement; HA injection is considered a feasible option for treatment of epibleharon

Mani *et al*[49], 2013	PMMA	Retrospective, single center	Lower	289	Subdermal PMMA microspheres injection is a safe technique in the correction of infraorbital rhytids
Amore *et al*[50], 2019	Deoxycholate	Multi-center, observational prospective	Lower fat pads	120	Moderate to high patient satisfaction and therapeutic success in 85.83% of the patients enrolled
Lee *et al*[51], 2020	Twisted polydioxanone threads	Retrospective, single center	Lower	40	More than 77.5% of patients were satisfied with the outcome
Aust *et al*[52], 2018	Platelet rich plasma	Prospective	Lower	20	Statistically significant increase in skin firmness and skin elasticity, high level of patient satisfaction, and progressive improvement of the aesthetic outcome

PMMA: Polymethylmethacrylate; HA: Hyaluronic acid; MRD2: Marginal reflex distance 2; TTD: Tear trough deformity; TED: Thyroid eye disease; VAS: Visual analogue scale.

BACKGROUND

Like any surgical procedure, blepharoplasty, especially performed on the lower one, is burdened by potential complications such as dry eye syndrome, corneal abrasion, lid asymmetry, lagophthalmos (the inability to close the eyelids completely), lacrimal gland injury, canthal webbing, postoperative hemorrhage, diplopia or infection, blepharoptosis, wound dehiscence, scleral show, and ectropion[8-11]. In the past several years, there has been an increasing demand in enhanced aesthetic outcomes with procedures that can offer quicker operative and postoperative wound-healing times, and preferably with fewer complications and discomforts with anesthesia. Non-invasive and less invasive procedures have become relatively popular in providing effective and safe alternatives for eyelid treatment. There has been great interest in those techniques that can guarantee good outcomes, while minimizing the side effects usually associated with surgical procedures[2].

When we talk about non-surgical procedures for treating the periocular region, we must consider all the emerging techniques that determine a rejuvenation of the entire area (*i.e.*, techniques for volumizing or reducing unwanted localized fat deposits), not only those based on surgical approaches to redundant skin or fat pads. Techniques such as hyaluronic acid (HA) fillers, lasers, deoxycholic acid, and plasma exeresis are considerably emerging, providing interesting and viable options in aesthetic treatments of the eyelids[12].

The dynamics of eyelid aging are not completely known to date. They are characterized by various physiological processes that lead to inelastic and excessive skin and/or subcutaneous soft tissue or bone volume loss[1,13,14]. Due to the emerging evidence from studies based on the dynamics of periocular aging and the concept of beauty (empty eyelid *vs* full eyelids), surgical approaches have evolved and changed over time to meet the new demands of individuals. Plastic surgery in this specific field has gone from a subtractive surgery approach to modern-day augmentation blepharoplasty techniques, in which adipose tissue is repositioned or even increased (*i.e.*, lipofilling, HAs, *ect.*) [1,15]. The following sections of the manuscript will briefly deal with the different conservative options for eyelid rejuvenation.

LASERS

One of the most characteristic aspects of eyelid aging is represented by the simultaneous excess and loss of elasticity of the skin. Laser treatment has shown to provide interesting options to address these morphological and functional changes of the lid. The objective of laser treatment is to ensure a contraction of the skin, which can give rise to a smoother and toned appearance[16]. Before promoting any treatment, it is fundamental to understand the mechanisms of aging and needs of each individual patient seeking aesthetic procedures to enhance facial appearance. In addition to changes to the skin, fat pads, muscle, or bone tissue can be affected by aging processes[1]. The laser approaches that are typically considered in these patients include resurfacing and ablative or non-ablative techniques. Laser treatments can also be used to complete and enhance traditional blepharoplastic surgical procedures [16].

There are several different laser technologies that can be used for the treatment of the eyelid region, which include: Ablative CO_2 laser; erbium-doped yttrium-aluminum-garnet (Er:YAG) laser; fractional ablative CO_2 laser; fractionated erbium:YAG laser; and non-ablative fractional laser[16,17]. Fractionated ablative laser treatments target water and cause selective photothermolysis[17]. The main differences between ablative and non-ablative lasers are the layers of the skin affected, laser dosage, and efficacy, which tends to be greater for ablative ones. Ablative lasers usually present a longer recovery time and involve greater risks. The selection of the appropriate laser device is fundamental, which should be based on the morphological and functional characteristics of the areas to be treated, the clinical needs of

the patient, and the postprocedural recovery time. Fractionated lasers typically have a faster skin-healing time and reduced risk of scarring, dyschromia, and postprocedural infections.

When dealing with patients that seek blepharoplasty for enhanced lid aesthetics, the clinician should provide various pertinent options for each individual, by specifying all details regarding pros, cons, risks, and expected outcomes and healing times. Complete clearly understood information is necessary in obtaining written informed consent before surgery. Nguyen *et al*[18] nicely reported how patients mistakenly believed that laser blepharoplasty was better than the traditional one (because it is considered simpler, less painful, and with a shorter recovery). The study shows how the advice given by physicians can have a huge impact on decisions made by patients. It is thus of utmost importance that clinicians be careful and complete in explaining all options, and should avoid setting false expectations when dealing with patients[18].

Historically, ablative CO_2 resurfacing has been the gold standard for skin resurfacing. This laser has been described to provide an effective approach to treat the dermatochalasis of the eyelid skin because it was believed to be better at giving tissue contraction and rhytid improvement than Erb:YAG ablation [17]. Fitzpatrick *et al*[19] demonstrated that both CO_2 laser and Er:YAG laser have similar degrees of tightening; however, Er:YAG laser showed 33% of scarring in patients and a lower ability of coagulation when compared with CO_2 laser. The study by Bae-Harboe *et al*[16] provides a careful analysis of advantages, disadvantages, and potential side effects of ablative, ablative-fractioned, and non-ablative techniques. The study also shows that fractioned ablative CO_2 laser represents a valid solution to improve the appearance of periocular area.

With regard to patients with eyelid skin excess, several studies have reported the positive use of laser for mild or moderate cases of dermatochalasis. Toyos[20] published a study based on 16 patients affected by mild dermatochalasis and treated with fractional continuous wave CO_2 laser. The study showed an increase in the common lid measurements for dermatochalasis and skin laxity at the follow-up at 6 mo and fewer side effects, which tended to be only minor. Balzani *et al*[21] provided satisfying outcomes with CO_2 laser. The study was based on 20 patients treated at upper eyelid and eyebrow regions with fractional ultrapulse CO_2 laser. The mean lid lift after treatment was 1.63 ± 0.68 mm and 2.300 ± 0.67 mm at 6 mo, respectively. Fractional ultrapulse CO_2 laser reduces collateral thermal damage through selective skin vaporization and causes tissue tightening and collagen shrinkage. This laser technique tends to show low costs and low risks with short operative and recovery times. Garcia and Badin[22] retrospectively analyzed 263 patients with mild inferior dermatochalasis treated solely with ablative fractioned CO_2 laser. They showed an improvement in the eyelid area characterized by fewer rhytids and a younger appearance 6 mo postoperatively. The treatment of the lower eyelid has also been shown by Guida *et al*[23]. They retrospectively considered 20 patients treated with freehand CO_2 ablative resurfacing, using the technique of resurfacing with ablation of periorbital skin. Results demonstrated an increase in the Global Assessment Improvement Scale (subjective and objective) score and a reduction of medium protrusions and depressions, with an improved texture at 2 mo that was confirmed by 3D image reconstructions. The histological explanation of what happens to the skin after a laser treatment has been reported in a recent article by de Filippi Sartori *et al*[24] published in 2022. The study showed an increase of skin collagen I and III concentrations 30 d after resurfacing treatment performed with fractioned CO_2 laser, with an evident improvement in periorbital rhytidosis.

Another element that patients typically seek consultation is for periorbital hyperpigmentation. Various treatments can be performed for this unsightly condition, including laser. The etiology can be linked to pigmentary, structural, vascular, and/or mixed causes[25]. Vrcek *et al*[26] and Samaan and Cartee[27] have carried out a thorough analysis of the all-possible solutions for this problem, providing three possible solutions using lasers. The first option exploits the Q-switched laser, which is ideal for selectively treating melanosomes while causing minimal trauma to the surrounding structures. The evolution of technology has led to the experimentation of the laser Nd:Yag, which can penetrate deep into the skin and have minimal effects on melanosomes, allowing increased safety when treating more pigmented individuals, such as Fitzpatrick types V and VI skin. The second treatment option is based on pulsed dye lasers, which are useful for individuals that have dark circles with a vascular etiology. The last option, which tends to be considered as the most effective, is based on ablative or fractioned laser resurfacing. When comparing CO_2 and Erb:YAG technologies, the latter option tends to offer more precision with a more limited depth of penetration and minimal thermal damage. Fractioned laser technology reduces the confluent thermal damage when compared with ablative lasers. This determines the presence of behind untreated skin, which allows for less downtime and a lower complication rate. As already reported by other reviewers, such as Vrcek *et al*[26], the results of fractionated CO_2 laser resurfacing have been shown to be comparable with traditional ablative resurfacing, but with a lower rate of complications and less downtime. Given its bias of being an uncontrolled cohort study, similar results have also been reported in a paper published by Garcia and Badin[22].

With regard to possible complications related to laser treatments, the incidence generally tends to be low and minor. Patients should be informed of the possible onset of edema, swelling, hypo or hyper-pigmentation, infections (bacterial or viral), and visible scarring (that can give rise to ectropion if severe). One of the largest series in the literature that focuses on complications after laser treatment includes the study by Kim *et al*[28] using fractional ablative CO_2 laser resurfacing. The results show a low risk of infection, which was limited to less than 1%, with a prevalence of viral etiology (4 viral cases

vs 2 bacterial cases). Hyperpigmentation caused by post-treatment inflammation was the most common complication, which was found in about 10% of patients, but easily with topical medical therapy. Visible scars were reported in 0.9% of cases that needed steroid injections. The study showed a grade of "very satisfied" (or more) in global post-treatment satisfaction in about 97% of the patients treated.

PLASMA EXERESIS

When a patient refuses a surgical approach to correct the signs of eyelid aging, the plasma exeresis technique can be proposed as a viable option. The plasma technique is becoming an increasingly interesting non-surgical alternative for the treatment of dermatochalasis. It consists of a handpiece producing ionized energy from an air gap that causes superficial tissue heating without any direct contact. A controlled and limited thermal damage transforms solid tissue into a gaseous state that creates mild coagulation, resulting in increased collagenosis and contraction of the skin.

Plasma technology is considered as a safe and efficient non-surgical option. There have been only a few minor complications reported in the literature, which include delayed healing, skin bacterial infection, herpes simplex virus infection, tissue scarring, and post inflammatory hyperpigmentation (most common). Easy precautionary measures can be applied, such as those reported by Ziade and Desiree[29] to reduce risks. Studies by Rossi *et al*[30] have given possible histological explanations as to what happens to the skin after treatment with plasma technology. Treatment appeared to induce a change in the conformation of the collagen fibers observed with confocal microscopy, going from huddled and coalesce presentation to form long and straight fibers. There were no major side effects observed.

Ferreira *et al*[31] showed promising results in a cohort of 16 patients that underwent upper blepharoplasty using plasma technology. What emerged in this prospective study is both a general post-treatment satisfaction (calculated by modified Q-bleph) and a limited number of adverse events (hyperpigmentation was one of the possible side effects in patients with Fitzpatrick III-IV phototype, but was easily resolved). Rossi *et al*[30] and Verner *et al*[32] showed effective and comparable results in patients treated with plasma exeresis for upper eyelid dermatochalasis. Hassan *et al*[10] found a statistically significant decrease in eye lid laxity after treatment in a study based on 40 patients treated by this method. Studies by Baroni[2] showing effective treatment and good aesthetic results were based on a long-wave P-RF ablation plasma device to treat 10 patients affected by dermatochalasis. His protocol consisted of two treatments distanced 1 mo apart. The general satisfaction of patients was quite good [8 > visual analogu scale (VAS)], with no reported permanent side effects. High levels of satisfaction (about 80% of both patients and investigators) were reported in a prospective study by Giroux *et al*[33]. They treated 25 patients affected by moderate dermatochalasis, and obtained a mean lid reduction of about 2.5 mm at the 12-mo follow-up.

Studies in the current literature also report the possible use of plasma technique for treating periocular hyperpigmentation, as well as dermatochalasis and wrinkles[34]. A pilot study carried out by Theppornpitak *et al*[35] reported effective and positive clinical outcomes in mild and moderate cases of periocular hyperpigmentation.

DERMAL FILLERS

In the field of facial rejuvenation, dermal fillers have been widely used for numerous years. They have recently become an alternative to surgical procedures for both aesthetic and functional indications, such as upper and lower blepharoplasty, tear-trough deformity for the lower lid, lagophthalmos, orbital volume deficiency, upper and lower eyelid retraction, and eyelid malposition. Dermal fillers represent a valid alternative to surgery in aesthetic indications. Injectable fillers provide numerous advantages that make them a suitable alternative to surgery, considering that they are minimally invasive, titratable, repeatable and, in some cases, reversible. Soft tissue fillers/injectables can be classified based on their source, which include autologous (fat), biological (collagen and HA), and synthetic [poly-L-lactic acid, calcium hydroxyapatite and polymethylmethacrylate (PMMA)]. Fillers can also be classified according to the duration of cosmetic benefit in short (< 3 mo, bovine collagen), medium (3-12 mo, HA), long lasting (12-24 mo, calcium hydroxyapatite, poly-L-lacticacid), and very long lasting (PMMA, fat). There is also a distinction that can be made based on their reversibility, which include fillers that are reversible (bovine collagen, HA) and irreversible (PMMA, calcium hydroxyapatite, poly-L-lacticacid, and fat)[36].

HA

HA derivatives are the most commonly used dermal fillers especially considering that they derive from a ubiquitous molecule in the human body and thus do not require allergy testing prior to use. HA derivatives display a medium to long duration (6-12 mo) thanks to their cross-linking to other chemicals that prevents biodegradation from enzymes. A wide variety of HA derivatives displaying different

characteristics have been produced over the years, leading to the abundant use in a variety of fields of surgery, such as in the management of periocular and orbital pathology[36].

Lagophthalmos is defined as the inability to fully close the eyelids due to paralysis of the orbicularis oculi (paralytic), retraction of the upper or lower lids (restrictive), and proptosis. This important lid disorder can result in exposure of the cornea and lead to severe dry eye syndrome and keratopathy. Paralytic lagophthalmos can be treated using HA gel (such as Restylane or Juvéderm Ultra) injected in the pretarsal and/or prelevator aponeurosis regions along the length of the upper eyelid and deep to orbicularis oculi muscle in a feathered layered fashion, as demonstrated by two retrospective studies conducted separately by Mancini *et al*[37] and Martín-Oviedo *et al*[38]. The use of HA gel in the treatment of lagophthalmos is ideal for patients not suitable for surgery and those unable to tolerate an external weight applied to the lid. HA provides a flexible and temporary approach that can be ideal to treat reversible and non-permanent causes of lagophthalmos.

HA gel injections are an effective non-surgical treatment for upper eyelid retraction. Studies by Kohn *et al*[39] showed how multiple subconjunctival injections of Restylane-L in the elevator aponeurosis plane in patients with active thyroid eye disease, led to a reduction in marginal reflex distance-1 that persisted for a mean of 15 mo post-injection. Leyngold *et al*[40] reported good clinical outcomes in patients with sunken superior sulcus, in which injections of Juvéderm Ultra XC in the superior sulcus deep to the orbital septum led to a 70% decrease of lagophthalmos at the longest follow-up with a mean 9.5 mo[40].

Lower eyelid retraction secondary to different aetiologias can also be treated with HA gel injections, as demonstrated by Xi *et al*[41]. The study was based on injecting HA under the orbicularis muscle in 27 cases and evaluating the results by the standardized marginal reflex distance 2 (MRD2). The retraction was completely corrected in 96.3% of patients with no recurrence at 9 mo post-injection, showing an improvement of the standardized MRD2 of 0.84 mm immediately after injection and 1.19 mm 9 mo later [41].

Romero *et al*[42] analyzed the effects of HA injections in the primary management of cicatricial ectropion, which can be defined as the eversion of the eyelid away from the globe due to the shortening of the anterior lamella secondary to many conditions including surgery and trauma. The authors injected 1 mL of Restylane in each eyelid along the infraorbital rim, in preseptal area, and in the infraciliary region, obtaining improvement in the eyelid position in all patients with at least partial ectropion correction. Since this technique provided a poor cosmetic outcome in some of the cases treated, the authors suggested to consider this treatment in patients who are poor surgical candidates.

A recent retrospective case review conducted by Bladen and Malhotra[43] considered the use of HA in the treatment of epiblepharon in pediatric patients as an alternative to traditional surgery, since this condition usually shows an improvement as the child grows older. Of eight eyelids treated with Restylane, six showed improvements with an 87% success rate, making HA injection a feasible option for the treatment of epiblepharon, with the advantage of avoiding or delaying surgery in selected cases.

The safety profile and variety of HA derivatives have rendered these dermal fillers suitable for various aesthetic use, including periorbital area rejuvenation. There has been a paradigm shift over the last two decades in this field of aesthetic medicine considering that volume loss has been recognized as one of the main causes of facial and periorbital aging, determining symmetric or asymmetric hollowing, excess upper lid showing, and dermatochalasis[12,44]. As a result, volume restoration has become a preferred approach in order to achieve natural rejuvenate results. HA derivatives seem to ideal candidates for this methodology, considering that they do not require surgery, are quick to perform, reversible within minutes, and display medium to long lasting effects. HA injections in the upper eyelid and superior orbital region are performed in order to improve the aesthetic appearance in patients presenting with superior sulcus hollowness, which may be secondary to the aging process or iatrogenic after excessive fat removal during surgical blepharoplasty[45]. Filling the upper eyelid can provide improvements in eyelid closure and function in select cases. In two studies conducted by Romeo[46], upper eyelid area filling with HA was compared to surgical blepharoplasty as means of reaching eye rejuvenation in a cohort of 154 and 500 patients, respectively. Both studies showed high patient satisfaction in regards of the aesthetic endpoint and long-lasting results in a 12-mo follow-up, defining HA filling as an effective means of rejuvenation for the upper eyelid that can be used independently[12].

Another application of HA injection in the periorbital area is represented by the treatment of tear trough deformity (TTD) of the lower eyelid. In these cases, the filler is placed at the preperiosteal plane below the orbicularis muscle. The tear trough is composed of thin skin adherent to the orbicularis muscle that is attached to the orbital rim. In young patients, the tear trough is located in the medial third of the orbital rim, whereas in ageing individuals, it gradually extends laterally up to the lateral canthus [44]. Jiang *et al*[47] compared the use of HA gel to autologous fat injections and fat repositioning surgery *via* arcus marginalis release for the treatment of TTD in 78 patients. Results showed that HA fillers may be used alone in the treatment of TTD in patients with mild to moderate periorbital volume loss without severe orbital fat bulging. An observational study by Diaspro *et al*[48] involving 600 patients showed that HA injection alone can be considered for the treatment of TTD in patients between 30 and 40 years of age, based on the statistical analysis that showed an inverse correlation between age and aesthetic outcome.

Other injectables

PMMA is a synthetic, extremely long lasting, and potentially irreversible filler. In a retrospective case series enrolling 289 patients, Mani *et al*[49] analyzed the use of PMMA microspheres in the infraorbital eyelid area for the treatment of rhytids. Results showed subdermal PMMA microspheres injection to be a safe technique in the correction of infraorbital rhytids, with results that seem to be predictable and natural. Only four patients developed late minor complications in the form of small granulomas, which resolved with the intralesional injection of triamcinolone. A correlation between granulomas formation and previous lower blepharoplasty was found[49].

Sodium deoxycholate (DC) is another injectable substance that may be taken into account in periorbital area rejuvenation procedures. DC has been widely used to reduce unwanted localized fat deposits for many years. The treatment of lower eyelid fat pads with monthly injections of sodium DC 1.25% (DB125) was evaluated by Amore *et al*[50] in a multi-center observational prospective study on 120 patients with the aim of assessing the safety and effectiveness of DB125. Results showed a moderate to high patient satisfaction and therapeutic success in 85.83% of the patients enrolled with no significant differences between sex, a high degree of effectiveness, and minimal adverse events. This procedure, however, should be considered for the treatment of lower eyelid fat pads in patients preferably under the age of 40, since higher success rates in studies tend to be reported in the younger age groups[50].

Polydioxanone threads

Infraorbital groove correction may be achieved with different techniques, such as filler injections, lower blepharoplasty, and microfat grafting. A new technique to achieve facial rejuvenation is represented by the insertion of transcutaneous synthetic threads for infraorbital groove correction, such as multiple twisted polydioxanone (PDO) threads. Lee *et al*[51] examined the efficacy and the risks of this technique on a group of 40 patients aged 25-56 years old by assessing Barton's grade and Global Aesthetic Improvement Scale scores and patients' satisfaction. Results showed a significant and persistent improvement in the mean Barton grade, hence indicating the effectiveness and the benefits of this technique, with no significant concerns about safety. More than 77.5% of patients were satisfied with the outcomes[51].

Platelet rich plasma

Another option available for the treatment of the lower eyelid area has been investigated by Aust *et al*[52]. The authors evaluated the use of platelet rich plasma (PRP) in order to rejuvenate the skin of the lower eyelid region and treat actinic elastosis. The study enrolled 20 patients who received three 2 mL PRP injections per side in the lower eyelid area at monthly intervals. The endpoints were evaluated using a cutometer to measure skin elasticity and questionnaires to objectify patients' satisfaction. Results showed a statistically significant increase in skin firmness and skin elasticity, as well as a high level of patient satisfaction and progressive improvement of the aesthetic outcomes. Side effects were minimal and only represented by swelling after the PRP injection, while the procedure was reported to be pain-free.

CONCLUSION

The eyelid region has always been and will continue to represent a fundamental part of the face that provides treatment options geared at improving aesthetic outcomes and younger age-related effects. There are numerous methods, techniques, and tools currently available, which can provide improvements in mild and moderate cases. Surgery tends to be the first choice to provide radical and long-term effects, especially in severe cases. Less invasive and non-surgical options have been of increasing use in the past decade, especially considering the possibility of obtaining a comparable result by limiting risks, complications, and healing times. New less invasive methods, lasers, innovative technologies, and alternative tissue fillers are destined to pave the way to the future in modern aesthetic medicine.

FOOTNOTES

Author contributions: Miotti G wrote the outline, did the research, wrote the paper, and approved the final version of the article; Zeppieri M assisted in the conception and design of the study, writing and outlining of the manuscript, approved the final version of the article to be published, and completed the English and scientific editing (a native English speaking MD, PhD, BSc); Pederzani G assisted in the research and writing of the manuscript; Salati C and Parodi PC assisted in the editing and critical revisions of the manuscript.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by

external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Italy

ORCID number: Giovanni Miotti 0000-0003-3185-7595; Marco Zeppieri 0000-0003-0999-5545; Giacomo Pederzani 0000-0003-3797-4231; Carlo Salati 0000-0003-4736-5296; Pier Camillo Parodi 0000-0002-4677-8198.

S-Editor: Wang JJ
L-Editor: Wang TQ
P-Editor: Wang JJ

REFERENCES

1 **De Biasio F**, Miotti G, Zingaretti N, Castriotta L, Parodi PC. Study on the Aging Dynamics of the Periorbital Region: From Observation to Knowledge of Physiopathology. *Ophthalmic Plast Reconstr Surg* 2019; **35**: 333-341 [PMID: 30320720 DOI: 10.1097/IOP.0000000000001247]
2 **Baroni A**. Non-surgical blepharoplasty with the novel plasma radiofrequency ablation technology. *Skin Res Technol* 2020; **26**: 121-124 [PMID: 31535742 DOI: 10.1111/srt.12774]
3 **Joshi K**, Hohman MH, Seiger E. SMAS Plication Facelift. 2022 Nov 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan- [PMID: 30285353]
4 **Rebowe RE**, Runyan C. Blepharoplasty. 2022 Jul 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan- [PMID: 29494003]
5 **Patel BC**, Malhotra R. Upper Eyelid Blepharoplasty. 2022 Jul 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan- [PMID: 30725763]
6 **Sand JP**, Zhu BZ, Desai SC. Surgical Anatomy of the Eyelids. *Facial Plast Surg Clin North Am* 2016; **24**: 89-95 [PMID: 27105794 DOI: 10.1016/j.fsc.2015.12.001]
7 **DePalma JA**. Evidence-based clinical practice guidelines. *Semin Perioper Nurs* 2000; **9**: 115-120 [PMID: 12029704]
8 **Yang P**, Ko AC, Kikkawa DO, Korn BS. Upper Eyelid Blepharoplasty: Evaluation, Treatment, and Complication Minimization. *Semin Plast Surg* 2017; **31**: 51-57 [PMID: 28255290 DOI: 10.1055/s-0037-1598628]
9 **Klapper SR**, Patrinely JR. Management of cosmetic eyelid surgery complications. *Semin Plast Surg* 2007; **21**: 80-93 [PMID: 20567662 DOI: 10.1055/s-2007-967753]
10 **Hassan AM**, Rady AAE, Shalaby OE, Shafik HM, Shaker ESE. Evaluation of plasma exeresis as a new technique for non surgical treatment of dermatochalasis. *J Dermatolog Treat* 2022; **33**: 1017-1022 [PMID: 32698635 DOI: 10.1080/09546634.2020.1800569]
11 **Zoumalan CI**, Roostaeian J. Simplifying Blepharoplasty. *Plast Reconstr Surg* 2016; **137**: 196e-213e [PMID: 26710052 DOI: 10.1097/PRS.0000000000001906]
12 **Romeo F**. Upper Eyelid Filling With or Without Surgical Treatment. *Aesthetic Plast Surg* 2016; **40**: 223-235 [PMID: 26893281 DOI: 10.1007/s00266-016-0619-8]
13 **Mendelson B**, Wong CH. Changes in the facial skeleton with aging: implications and clinical applications in facial rejuvenation. *Aesthetic Plast Surg* 2012; **36**: 753-760 [PMID: 22580543 DOI: 10.1007/s00266-012-9904-3]
14 **Lambros V**. Observations on periorbital and midface aging. *Plast Reconstr Surg* 2007; **120**: 1367-1376 [PMID: 17898614 DOI: 10.1097/01.prs.0000279348.09156.c3]
15 **Tonnard PL**, Verpaele AM, Zeltzer AA. Augmentation blepharoplasty: a review of 500 consecutive patients. *Aesthet Surg J* 2013; **33**: 341-352 [PMID: 23515379 DOI: 10.1177/1090820X13478966]
16 **Bae-Harboe YS**, Geronemus RG. Eyelid tightening by CO2 fractional laser, alternative to blepharoplasty. *Dermatol Surg* 2014; **40** Suppl 12: S137-S141 [PMID: 25417564 DOI: 10.1097/DSS.0000000000000165]
17 **Fathi R**, Pfeiffer ML, Tsoukas M. Minimally invasive eyelid care in dermatology: medical, laser, and cosmetic therapies. *Clin Dermatol* 2015; **33**: 207-216 [PMID: 25704940 DOI: 10.1016/j.clindermatol.2014.10.012]
18 **Nguyen AX**, Leung VC, Antaki F, Antonios R, Hardy I, Boulos PR. Public perception of laser-assisted blepharoplasty versus blade-assisted blepharoplasty. *Can J Ophthalmol* 2022 [PMID: 35397233 DOI: 10.1016/j.jcjo.2022.03.006]
19 **Fitzpatrick RE**, Rostan EF, Marchell N. Collagen tightening induced by carbon dioxide laser versus erbium: YAG laser. *Lasers Surg Med* 2000; **27**: 395-403 [PMID: 11126433 DOI: 10.1002/1096-9101(2000)27:5<395::AID-LSM1000>3.0.CO;2-4]
20 **Toyos MM**. Continuous Wave Fractional CO(2) Laser for the Treatment of Upper Eyelid Dermatochalasis and Periorbital Rejuvenation. *Photomed Laser Surg* 2017; **35**: 278-281 [PMID: 28085575 DOI: 10.1089/pho.2016.4225]
21 **Balzani A**, Chilgar RM, Nicoli M, Sapountzis S, Lazzeri D, Cervelli V, Nicoli F. Novel approach with fractional ultrapulse CO2 laser for the treatment of upper eyelid dermatochalasis and periorbital rejuvenation. *Lasers Med Sci* 2013; **28**: 1483-1487 [PMID: 23307441 DOI: 10.1007/s10103-012-1255-4]
22 **Garcia CP**, Badin AZD. Treating Excess Lower Eyelid Skin Without Incisions. *Aesthetic Plast Surg* 2019; **43**: 1320-1325 [PMID: 31218381 DOI: 10.1007/s00266-019-01427-0]
23 **Guida S**, Nisticò SP, Farnetani F, Del Duca E, De Carvalho N, Persechino F, Verdina T, Giannetti L, D'Alessandro M, Urtis GG, Pellacani G, D'Alessandro G. Resurfacing with Ablation of Periorbital Skin Technique: Indications, Efficacy,

Safety, and 3D Assessment from a Pilot Study. *Photomed Laser Surg* 2018; **36**: 541-547 [PMID: 30234414 DOI: 10.1089/pho.2018.4479]

24 **de Filippi Sartori J**, Osaki TH, Osaki MH, de Souza RB, Allemann N. "Split-Face" Evaluation of Collagen Changes Induced by Periorbital Fractional CO2 Laser Resurfacing. *Aesthet Surg J* 2022; **42**: 239-248 [PMID: 34618888 DOI: 10.1093/asj/sjab357]

25 **Michelle L**, Pouldar Foulad D, Ekelem C, Saedi N, Mesinkovska NA. Treatments of Periorbital Hyperpigmentation: A Systematic Review. *Dermatol Surg* 2021; **47**: 70-74 [PMID: 32740208 DOI: 10.1097/DSS.0000000000002484]

26 **Vrcek I**, Ozgur O, Nakra T. Infraorbital Dark Circles: A Review of the Pathogenesis, Evaluation and Treatment. *J Cutan Aesthet Surg* 2016; **9**: 65-72 [PMID: 27398005 DOI: 10.4103/0974-2077.184046]

27 **Samaan CB**, Cartee TV. Treatment of Periorbital Vascularity, Erythema, and Hyperpigmentation. *Facial Plast Surg Clin North Am* 2022; **30**: 309-319 [PMID: 35934433 DOI: 10.1016/j.fsc.2022.03.005]

28 **Kim JS**, Ginter A, Ranjit-Reeves R, Woodward JA. Patient Satisfaction and Management of Postoperative Complications Following Ablative Carbon Dioxide Laser Resurfacing of the Lower Eyelids. *Ophthalmic Plast Reconstr Surg* 2021; **37**: 450-456 [PMID: 33481534 DOI: 10.1097/IOP.0000000000001902]

29 **Ziade G**, Desiree K. Hyperpigmentation after nonsurgical blepharoplasty using plasma technology. *Dermatol Ther* 2020; **33**: e13493 [PMID: 32362046 DOI: 10.1111/dth.13493]

30 **Rossi E**, Farnetani F, Trakatelli M, Ciardo S, Pellacani G. Clinical and Confocal Microscopy Study of Plasma Exeresis for Nonsurgical Blepharoplasty of the Upper Eyelid: A Pilot Study. *Dermatol Surg* 2018; **44**: 283-290 [PMID: 28930794 DOI: 10.1097/DSS.0000000000001267]

31 **Ferreira FC**, Sathler CSCO, Hida IY, Leite SC, Kusabara AA, de Castro ACV, Ribeiro MZML, Nahas TR. Upper eyelid blepharoplasty using plasma exeresis: Evaluation of outcomes, satisfaction, and symptoms after procedure. *J Cosmet Dermatol* 2021; **20**: 2758-2764 [PMID: 33252188 DOI: 10.1111/jocd.13868]

32 **Verner I**, Naveh HP, Cotofana S. A novel ablative radiofrequency microplasma nonsurgical blepharoplasty for dermatochalasis. *Dermatol Ther* 2020; **33**: e14002 [PMID: 32652885 DOI: 10.1111/dth.14002]

33 **Giroux PA**, Hersant B, SidAhmed-Mezi M, Pizza C, La Padula S, Meningaud JP. The Outcomes Assessment of the Plasma Blade Technology in Upper Blepharoplasties: A Prospective Study on a Series of 25 Patients. *Aesthetic Plast Surg* 2019; **43**: 948-955 [PMID: 30927022 DOI: 10.1007/s00266-019-01360-2]

34 **Sawant O**, Khan T. Management of periorbital hyperpigmentation: An overview of nature-based agents and alternative approaches. *Dermatol Ther* 2020; **33**: e13717 [PMID: 32472659 DOI: 10.1111/dth.13717]

35 **Theppornpitak N**, Udompataikul M, Chalermchai T, Ophaswongse S, Limtanyakul P. Nitrogen plasma skin regeneration for the treatment of mild-to-moderate periorbital wrinkles: A prospective, randomized, controlled evaluator-blinded trial. *J Cosmet Dermatol* 2019; **18**: 163-168 [PMID: 30146783 DOI: 10.1111/jocd.12767]

36 **Tan P**, Kwong TQ, Malhotra R. Non-aesthetic indications for periocular hyaluronic acid filler treatment: a review. *Br J Ophthalmol* 2018; **102**: 725-735 [PMID: 29146758 DOI: 10.1136/bjophthalmol-2017-310525]

37 **Mancini R**, Taban M, Lowinger A, Nakra T, Tsirbas A, Douglas RS, Shorr N, Goldberg RA. Use of hyaluronic Acid gel in the management of paralytic lagophthalmos: the hyaluronic Acid gel "gold weight". *Ophthalmic Plast Reconstr Surg* 2009; **25**: 23-26 [PMID: 19273918 DOI: 10.1097/IOP.0b013e318192568d]

38 **Martín-Oviedo C**, García I, Lowy A, Scola E, Aristegui M, Scola B. Hyaluronic acid gel weight: a nonsurgical option for the management of paralytic lagophthalmos. *Laryngoscope* 2013; **123**: E91-E96 [PMID: 24122715 DOI: 10.1002/lary.23936]

39 **Kohn JC**, Rootman DB, Liu W, Goh AS, Hwang CJ, Goldberg RA. Hyaluronic acid gel injection for upper eyelid retraction in thyroid eye disease: functional and dynamic high-resolution ultrasound evaluation. *Ophthalmic Plast Reconstr Surg* 2014; **30**: 400-404 [PMID: 24833450 DOI: 10.1097/IOP.0000000000000130]

40 **Leyngold IM**, Berbos ZJ, McCann JD, Pariseau B, Leyngold AR, Anderson RL. Use of hyaluronic acid gel in the treatment of lagophthalmos in sunken superior sulcus syndrome. *Ophthalmic Plast Reconstr Surg* 2014; **30**: 175-179 [PMID: 24614548 DOI: 10.1097/IOP.0000000000000040]

41 **Xi W**, Han S, Feng S, Li K, Brunetti B, Lazzeri D, Tong Y, Zhang Y. The Injection for the Lower Eyelid Retraction: A Mechanical Analysis of the Lifting Effect of the Hyaluronic Acid. *Aesthetic Plast Surg* 2019; **43**: 1310-1317 [PMID: 31399822 DOI: 10.1007/s00266-019-01440-3]

42 **Romero R**, Sanchez-Orgaz M, Granados M, Arbizu A, Castano A, Romero A, Molia P. Use of hyaluronic acid gel in the management of cicatricial ectropion: results and complications. *Orbit* 2013; **32**: 362-365 [PMID: 24063354 DOI: 10.3109/01676830.2013.833250]

43 **Bladen JC**, Malhotra R. Reporting outcomes of hyaluronic gel filler as a treatment for epiblepharon. *Graefes Arch Clin Exp Ophthalmol* 2019; **257**: 2769-2773 [PMID: 31641882 DOI: 10.1007/s00417-019-04479-9]

44 **Montes JR**. Volumetric considerations for lower eyelid and midface rejuvenation. *Curr Opin Ophthalmol* 2012; **23**: 443-449 [PMID: 22871878 DOI: 10.1097/ICU.0b013e3283560ab5]

45 **Hoenig J**, Hoenig D. Minimally invasive periorbital rejuvenation. *Facial Plast Surg* 2013; **29**: 295-309 [PMID: 23884851 DOI: 10.1055/s-0033-1349363]

46 **Romeo F**. Upper Eyelid Filling Approach [U.E.F.A.] Technique: State of the Art After 500 Consecutive Patients. *Aesthetic Plast Surg* 2019; **43**: 663-672 [PMID: 30607571 DOI: 10.1007/s00266-018-1296-6]

47 **Jiang J**, Wang X, Chen R, Xia X, Sun S, Hu K. Tear trough deformity: different types of anatomy and treatment options. *Postepy Dermatol Alergol* 2016; **33**: 303-308 [PMID: 27605904 DOI: 10.5114/ada.2016.61607]

48 **Diaspro A**, Calvisi L, Sito G. Hyaluronic Acid Gel Injection for the Treatment of Tear Trough Deformity: A Multicenter, Observational, Single-Blind Study. *Aesthetic Plast Surg* 2022; **46**: 1860-1867 [PMID: 35478038 DOI: 10.1007/s00266-022-02887-7]

49 **Mani N**, McLeod J, Sauder MB, Sauder DN, Bothwell MR. Novel use of polymethyl methacrylate (PMMA) microspheres in the treatment of infraorbital rhytids. *J Cosmet Dermatol* 2013; **12**: 275-280 [PMID: 24305426 DOI: 10.1111/jocd.12065]

50 **Amore R**, Sbarbati A, Amuso D, Leonardi V, Alsanafi S, Greco Lucchina A, Scarano A. Non-surgical treatment of lower eyelid fat pads with an injectable solution acid deoxycholic based. *J Biol Regul Homeost Agents* 2019; **33**: 109-114 [PMID:

32425031]
51 **Lee W**, Oh W, Kim HM, Chan BL, Yang EJ. Novel technique for infraorbital groove correction using multiple twisted polydioxanone thread. *J Cosmet Dermatol* 2020; **19**: 1928-1935 [PMID: 31900989 DOI: 10.1111/jocd.13269]
52 **Aust M**, Pototschnig H, Jamchi S, Busch KH. Platelet-rich Plasma for Skin Rejuvenation and Treatment of Actinic Elastosis in the Lower Eyelid Area. *Cureus* 2018; **10**: e2999 [PMID: 30515364 DOI: 10.7759/cureus.2999]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1730-1740

DOI: 10.12998/wjcc.v11.i8.1730

ISSN 2307-8960 (online)

MINIREVIEWS

Pregnancy and medications for inflammatory bowel disease: An updated narrative review

Shintaro Akiyama, Joshua M Steinberg, Mariko Kobayashi, Hideo Suzuki, Kiichiro Tsuchiya

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Wen XL, China; Wu SC, China

Received: January 4, 2023
Peer-review started: January 4, 2023
First decision: January 14, 2023
Revised: January 14, 2023
Accepted: February 21, 2023
Article in press: February 21, 2023
Published online: March 16, 2023

Shintaro Akiyama, Mariko Kobayashi, Hideo Suzuki, Kiichiro Tsuchiya, Department of Gastroenterology, Faculty of Medicine, University of Tsukuba, Tsukuba 305-8575, Ibaraki, Japan

Joshua M Steinberg, Department of Inflammatory Bowel Disease, Gastroenterology of the Rockies, Denver, CO 80027, United States

Corresponding author: Shintaro Akiyama, MD, MSc, PhD, Lecturer, Department of Gastroenterology, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba 305-8575, Ibaraki, Japan. akiyama@md.tsukuba.ac.jp

Abstract

Inflammatory bowel disease (IBD) is often diagnosed during the peak reproductive years of young women. Women with active IBD around conception are at a significantly increased risk of disease relapse during pregnancy, which is associated with poor pregnancy and neonatal outcomes. Given these substantial risks, it is prudent that disease remission should ideally be achieved before conception. Unfortunately, some patients may experience a disease flare-up even if they are in a state of remission before pregnancy. Patients must continue their IBD medications to reduce the risk of disease flare and subsequent poor outcomes during the gestational and postpartum periods. When treating IBD flare-ups during pregnancy, the management is quite similar to the therapeutic approach for non-pregnant patients with IBD, including 5-aminosalicylate, steroids, calcineurin inhibitors (CNIs), and biologic therapies. While the data regarding the safety of CNIs in pregnant women with IBD is limited, the findings in our recent meta-analysis suggest that CNIs may be safer to use in those with IBD than in solid organ transplant recipients. There are several types of biologics and small-molecule therapies currently approved for IBD, and physicians should thoroughly understand their clinical benefits and safety profiles when utilizing these treatments in the context of pregnancy. This review highlights recent studies, including our systematic review and meta-analysis, and discusses the clinical advantages and safety considerations of biologics and small molecules for pregnant women with IBD.

Key Words: Inflammatory bowel disease; Pregnancy; Safety; Biologics; Small molecules

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Anti-tumor necrosis factor monotherapy is safe during pregnancy in women with Inflammatory bowel disease (IBD). However, their use in combination with thiopurines may be associated increased risk of neonatal prematurity and infection, although these data are conflicting. According to meta-analyses, vedolizumab and ustekinumab may be associated with early pregnancy loss; however, these data might be biased by IBD activity or small sample sizes. Recent prospective studies have demonstrated these biologics are generally safe during pregnancy. Janus kinase inhibitors are contraindicated during pregnancy as animal studies have demonstrated harmful effects. Calcineurin inhibitors may be considered for pregnant women with IBD who develop clinical relapse.

Citation: Akiyama S, Steinberg JM, Kobayashi M, Suzuki H, Tsuchiya K. Pregnancy and medications for inflammatory bowel disease: An updated narrative review. *World J Clin Cases* 2023; 11(8): 1730-1740
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1730.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1730

INTRODUCTION

Pregnancy is a critical period requiring coordinated, specialized health care for many women during their reproductive years. As most women with inflammatory bowel disease (IBD) experience the onset of the disease in their 20s and 30s, physicians should understand the clinical benefits and safety profiles of biologics and small molecules as they apply to pregnant women with IBD.

In general, patients with IBD have a higher incidence of adverse pregnancy outcomes, including miscarriage, preterm delivery (a live birth before 37 wk of pregnancy), low birth weight (LBW: A birth weight of < 2500 g), poor maternal weight gain, and complications of labor and delivery (*e.g.*, preeclampsia, placental abruption, increased probability of delivery by cesarean section)[1-3]. Many studies have previously confirmed that active or flaring IBD around conception increases the risk of disease relapse and is associated with several poor outcomes, including increased risk of LBW, preterm birth, small for gestational age, spontaneous abortion, and stillbirth[4]. These data imply that proactive family planning with the goal of sustained disease remission before conception should be practiced routinely. However, up to one-third of the patients with IBD in remission before pregnancy experience flare-ups during pregnancy[5]. Given these findings and subsequent risks, patients should continue their IBD medications throughout pregnancy, as there may be a clinical benefit in reducing the risk of disease flare-ups during both the gestational and postpartum periods[6-9]. A prospective study evaluating women with quiescent IBD at the time of conception reported that 38% of the patients experienced clinical relapse during pregnancy and that disease flare-up was significantly associated with higher rates of preterm delivery, hospitalization during pregnancy, and a lower gestational age at delivery. This study further analyzed the contributing factors to disease relapse during pregnancy, and reported that the use of biological therapies at the time of conception was negatively associated with the risk of disease flare-up, suggesting that biologics may be protective against clinical relapse during pregnancy[5].

There are several types of biologics and small molecules currently approved for treating IBD. While tumor necrosis factor (TNF) inhibitors, including infliximab, adalimumab, golimumab, and certolizumab, have been used for patients with immune-mediated inflammatory diseases (IMIDs) for several decades[10], vedolizumab, an $\alpha_4\beta_7$ integrin inhibitor, and ustekinumab, an interleukin- (IL-) 12/IL-23 inhibitor, are newer treatments for IBD[11,12]. In addition, Janus kinase (JAK) inhibitors, including tofacitinib, filgotinib, and upadacitinib[13-15], calcineurin inhibitors (CNIs), including tacrolimus and cyclosporine[16], as well as a sphingosine-1 phosphate receptor modulator, ozanimod[17], are small-molecule therapies that can be used for treating moderate-to-severe ulcerative colitis (UC). It should be noted that all biologics other than certolizumab pegol are actively transported across the placenta[18] and theoretically could affect pregnancy and neonatal outcomes.

While there are concerns regarding the potential negative effects of IBD medications on pregnancy and fetal development, previous retrospective studies with large sample sizes demonstrated that pregnant women with IBD who continued their biologic therapy during pregnancy did not have increased adverse fetal outcomes. A multicenter retrospective European TEDDY study including 841 children, 46% of whom had been exposed to anti-TNF agents, found that the incidence rate of severe infection was similar between anti-TNF exposed and non-exposed children (2.8% *vs* 1.6% per person-year)[19]. Also, another retrospective cohort study that evaluated 8726 pregnant women with IBD using data from the French national health system database demonstrated no increased risk of infection in children born to mothers exposed to anti-TNF agents during pregnancy. While this study concluded that anti-TNF agents during pregnancy increased the risk of overall maternal complications, particularly infections, compared to non-exposed patients, discontinuing anti-TNF agents before week 24 increased the risk of a disease flare[8]. Several prospective studies published in the United States, France, Israel,

and the Czech Republic have recently demonstrated the safety of IBD medications during pregnancy [20-24]. The Pregnancy and Inflammatory Bowel Disease and Neonatal Outcome (PIANO) registry[20], a national United States registry that prospectively enrolled pregnant women with IBD, demonstrated that biologics and thiopurines do not increase the risk of maternal and neonatal outcomes in patients with IBD.

The American Gastroenterological Association (AGA) IBD Parenthood Project Working Group highlighted that most IBD medications, including aminosalicylates, biologics, and thiopurines, can be safely continued during pregnancy and through delivery[18]. The European Crohn's and Colitis Organization (ECCO) guideline published in 2022 recommended the continuation of TNF inhibitors before the third trimester for women in remission because discontinuation can increase the risk of relapse and lead to unfavorable outcomes[25]. Regarding newer therapies such as ustekinumab and vedolizumab, the decision to discontinue treatment should be individualized for women in remission on these therapies. Importantly, the continuation of biologics for patients in an active IBD disease flare just before or during pregnancy is recommended throughout the pregnancy in these guidelines[18,25]. The ECCO guidelines also highlight that if a pregnant woman with IBD develops a flare, a multidisciplinary care team, including a gastroenterologist, an obstetrician, a pediatrician, and an experienced surgeon, should be sought out to optimize outcomes[25].

In this review, we introduce recent investigations using large-scale national registry databases, prospective studies, and updated systematic reviews and meta-analyses, including our research findings, and discuss the clinical advantages and safety profiles of IBD medications during pregnancy.

SAFETY OF BIOLOGICS AND THIOPURINES FOR PREGNANCY IN IBD

The PIANO registry is the most extensive prospective observational multicenter study in the United States, having enrolled 1712 pregnant women with IBD. In this registry, 1490 patients completed pregnancies with 1431 Live births, and 869 patients were exposed to biologics (predominantly TNF inhibitors) or combination therapies with thiopurines. Although the risk of cesarean section was higher in patients exposed to biologics or combination therapies than that in the unexposed population, there were no observed differences between the two groups in the rates of the following pregnancy-related complications: spontaneous abortion, preterm delivery, LBW, intrauterine growth restriction, small for gestational age, neonatal intensive care unit stay, and congenital malformations[20]. While combination therapy of biologics and immunomodulators may be discouraged by some providers due to concerns of an increased risk of infection, the PIANO registry data showed that the use of biologics, thiopurines, or combination therapy was not associated with an increased risk of any infection in the first year of life [20]. A recent systematic review and meta-analysis, including 48 studies with 6963 patients with IBD exposed to biologics, showed their pooled prevalence of adverse outcomes, including early pregnancy loss, preterm birth, stillbirth, LBW, and congenital malformations, was comparable with those found in the general population[26]. This meta-regression analysis showed no significant association between concomitant thiopurine use and adverse outcomes[26]. These data suggest that biologics and immunomodulators can be safely continued throughout pregnancy in women with IBD.

TNF inhibitors and immunomodulators

A recent nationwide emulation trial utilizing a French population-based database demonstrated the clinical benefits of continuing TNF inhibitors during pregnancy in patients with IBD[7]. This study included 5293 pregnancies with subsequent births exposed to TNF inhibitors between conception and week 24 of pregnancy. Among this group, TNF inhibitors were discontinued before 24 wk in 2890 pregnancies and continued beyond 24 wk in 2403 pregnancies[7]. This analysis revealed that patients who continued TNF inhibitors after week 24 of pregnancy had decreased risks of maternal IBD relapse [adjusted risk ratio (aRR) 0.93, 95% confidence interval (CI): 0.86-0.99] and neonatal prematurity (aRR 0.82, 95%CI: 0.68-0.99). Continuation of TNF inhibitors showed no differences in rates of stillbirths, small for gestational age, or serious infection, supporting the recommendation of maintaining TNF inhibitor therapy throughout pregnancy in patients with IBD[7].

Regarding the potential risks of TNF inhibitors in pregnancy and neonatal outcomes, a recent systematic review and meta-analysis assessing the outcomes in women with IMIDs showed an increased risk of preterm births and neonatal infections in those treated with TNF inhibitors compared with diseased controls[27]. No significant differences in cesarean section, miscarriage, LBW, small for gestational age, or congenital malformation were identified between the two groups. However, subgroup analysis did show an increased risk of preterm births, LBW, and cesarian section in patients with IBD treated with TNF inhibitors[27]. In this meta-analysis, diseased controls were usually exposed to other medications, including azathioprine. Overall, the data regarding the effects of combination therapy of TNF inhibitors with thiopurines on pregnancy outcomes are limited, and more studies are needed to elucidate such risks further.

A recent French nationwide study compared pregnancy and neonatal outcomes among patients with IBD treated with thiopurine monotherapy (n = 3554), anti-TNF monotherapy (n = 3525), combination

therapy (n = 839), and unexposed controls (n = 19811). No significant differences in the risk of adverse pregnancy outcomes were observed between pregnant women exposed to anti-TNF monotherapy and unexposed controls. In contrast, those exposed to combination therapy were more likely to have preterm birth[21]. Furthermore, a French nationwide study using the same data source included 26561 children born to women with IBD (3392 exposed to thiopurine monotherapy, 3399 exposed to anti-TNF monotherapy, 816 exposed to combination, and 18954 unexposed controls) and showed no significant difference in the risk of serious infection during the first five years of life between children exposed to thiopurine or anti-TNF monotherapies and the unexposed population. However, children exposed to combination therapies had a higher risk of serious infection during the first year of life (adjusted hazard ratio, 1.36, 95%CI: 1.04-1.79)[22]. Considering these findings, the ECCO guidelines suggest that when thiopurines are combined with biologics, discontinuation should be considered on an individualized basis if the patient is in sustained, long-term remission. Testing for and ensuring adequate serum anti-TNF levels may be helpful in this setting[25].

The PIANO registry predominantly included patients treated with TNF inhibitors. This study found no increased risks of adverse maternal or fetal outcomes at birth or in the first year of life in pregnant women treated with biologics and/or thiopurines[20]. Given that the French nationwide studies suggest that combination therapy of TNF inhibitors and thiopurines is associated with the risk of neonatal prematurity and infection[21,22], further investigations are needed to more clearly understand whether combination therapy is beneficial or harmful in the context of maternal and fetal outcomes in patients with IBD (Tables 1 and 2).

Vedolizumab

A prospective multicenter study in Denmark and Canada examined vedolizumab levels in neonates' umbilical cord blood, the rates of clearance after birth, and the risk of infection and delayed developmental milestones. This study identified 50 vedolizumab-exposed pregnancies and found that the rates of live births, miscarriages, and congenital malformations were 86%, 14%, and 0%, respectively. The mean period of vedolizumab clearance was 3.8 mo, and the newborns' developmental milestones were found to be normal or above average. No association was observed between the infants' vedolizumab level and the risk of infection during the first year of life, suggesting that vedolizumab is generally safe during pregnancy[28]. Another prospective comparison study including 24 pregnant women with IBD treated with vedolizumab, 82 with TNF inhibitors, and 224 with conventional therapy showed that the rate of spontaneous abortion was higher (21%) in the vedolizumab group than in the other groups. However, conception in the setting of active disease flare-ups occurred in more than 30% of the vedolizumab group, which was higher than the rates in the other groups, suggesting that disease activity at conception may affect outcomes[29].

Systematic reviews and meta-analyses, including four studies, showed that women treated with vedolizumab had an increased risk of preterm births and early pregnancy loss compared with those not exposed to vedolizumab during pregnancy[26,30]. No differences were observed in the number of live births or congenital abnormalities. However, there is concern regarding the number of included studies having small sample sizes and that disease activity may have confounded these findings. Meanwhile, a recent prospective multicenter observational study in the Czech Republic, including 39 pregnant women with IBD exposed to vedolizumab during pregnancy, reported that 90% of pregnancies resulted in a live birth, 5% in spontaneous abortion, and 5% in therapeutic abortion. However, no significant differences in the risk of pregnancy outcomes were observed between the vedolizumab- and TNF inhibitor-exposed populations[24].

Further prospective studies and meta-analyses with updated data are needed to confirm the safety of vedolizumab in pregnant patients with IBD (Tables 1 and 2).

Ustekinumab

A previous systematic review and meta-analysis, including two case studies, showed that female patients with IBD treated with ustekinumab had an increased risk of early pregnancy loss compared with those treated with TNF inhibitors[26]. However, this meta-analysis's small number of studies may have overestimated the prevalence of adverse pregnancy-related events. Recently, several prospective studies focusing on ustekinumab safety during pregnancy have been published. A Czech prospective study including 54 pregnant women treated with ustekinumab showed that 80% and 20% of pregnancies resulted in live births and spontaneous abortions, respectively. No significant difference in the risk of pregnancy outcomes was observed between ustekinumab- and anti-TNF-exposed controls [24]. Furthermore, an Israeli prospective multicenter cohort study recruited 129 pregnant patients (27 pregnant women exposed to ustekinumab, 52 exposed to TNF inhibitors, and 50 unexposed controls) and showed no significant differences among these groups in the rates of maternal obstetrical complications, preterm delivery, LBW, or newborn hospitalization during the first year of life[23]. These findings are consistent with those of the Czech study and support the relative safety of ustekinumab in the setting of pregnancy.

An investigation using the drug manufacturer's global safety database prospectively identified 408 ustekinumab-exposed pregnant women with IMIDs, such as Crohn's disease, UC, psoriasis, and psoriatic arthritis. For the 408 prospective ustekinumab-exposed pregnancies, 420 pregnancy outcomes

Table 1 Summary of prospective and nationwide studies regarding the safety of biologics and small molecules for pregnant women with inflammatory bowel disease

Biologics/small molecules	ECCO's guideline[25]	Summary of recent prospective and nationwide studies
TNF inhibitors (monotherapy)	Low risk	The PIANO registry predominantly including patients treated with TNF inhibitors found no increased risks of adverse maternal or fetal outcomes at birth or in the first year of life in pregnant women with IBD treated with biologics[20]. Two French nationwide studies reported no significant differences in the risk of pregnancy outcomes between pregnancies exposed to anti-TNF monotherapy and unexposed controls[21]. The risk of serious infection during the first 5 yr of life was not significantly different between children exposed to anti-TNF monotherapy and the unexposed population[22]
TNF inhibitors with thiopurines	Thiopurine discontinuation may be considered	The PIANO registry predominantly including patients treated with TNF inhibitors found no increased risks of adverse maternal or fetal outcomes at birth or in the first year of life in pregnant women with IBD treated with biologics combined with thiopurines[20]. Two French nationwide studies reported that patients on combination therapy were more likely to have preterm birth than unexposed controls[21]. Children exposed to combination therapies had a higher risk of serious infection during the first year of life[22]
Vedolizumab	Low risk, limited data	In 50 vedolizumab-exposed pregnancies, the rates of live birth, miscarriage, and congenital malformations were 86%, 14%, and 0%, respectively. Infant vedolizumab level was not associated with the risk of infection during the first year of life[28]. The first prospective study comparing 24 pregnant women treated with vedolizumab, 82 with TNF inhibitors, and 224 with conventional therapy showed that the rate of spontaneous abortion (21%) was higher in the vedolizumab group than in the other groups[29]. In this study, disease activity at conception may affect the result. A Czech prospective study including 39 pregnant women with IBD exposed to vedolizumab during pregnancy showed that 90% of pregnancies ended in a live birth, 5% in spontaneous abortion, and 5% in therapeutic abortion. No significant differences in the risk of pregnancy outcomes were observed between vedolizumab- and TNF inhibitor-exposed populations[24]
Ustekinumab	Low risk, limited data	A Czech prospective study including 54 pregnant women treated with ustekinumab showed that 80% and 20% of patients resulted in live births and spontaneous abortions, respectively. The risk of pregnancy outcomes was not significantly different between ustekinumab- and anti-TNF-exposed controls[24]. An Israeli prospective study including 27 pregnancies exposed to ustekinumab, 52 exposed to TNF inhibitors, and 50 unexposed controls showed no significant differences in the rates of obstetrical maternal complications, preterm delivery, LBW, and first-year newborn hospitalization[23]. The manufacturer's global safety database including 408 ustekinumab-exposed pregnancies with IMIDs showed that the rates of adverse pregnancy outcomes were comparable to those of United States general population[31]
JAK inhibitors	Contraindicated (no mention of upadacitinib)	Data from interventional studies of tofacitinib identified 11 patients with UC exposed to tofacitinib before/at the time of conception or during pregnancy and showed that 36% of patients delivered healthy newborns, 18% had a medical termination, and no cases of neonatal death, fetal death, or congenital malformation were reported[33]
Ozanimod	Contraindicated	N/A
Calcineurin inhibitors	Low risk, limited data	N/A

ECCO: European Crohn's and Colitis Organization; IBD: Inflammatory bowel disease; IMIDs: Immune-mediated inflammatory diseases; JAK: Janus kinase; LBW: Low birth weight; TNF: Tumor necrosis factor; UC: Ulcerative colitis; N/A: Not applicable.

were reported. The rates of live births, spontaneous abortions, elective/induced abortions, stillbirths, and fetal congenital anomalies were 81%, 12%, 6%, 0.7%, and 0.2%, respectively. Among 340 Live births, the percentage of preterm deliveries was 9.7%. The overall rates of pregnancy outcomes were consistent across disease indications. These data suggest that the rates of adverse pregnancy outcomes in women with IMIDs exposed to ustekinumab were comparable to those of the United States general population [31].

Recent prospective studies have supported the safety of ustekinumab in relation to pregnancy and neonatal outcomes in patients with IBD. However, further investigations are needed to validate the safety profile of ustekinumab for pregnant women with IBD (Tables 1 and 2).

SAFETY OF SMALL MOLECULES FOR PREGNANCY IN IBD

JAK inhibitors

Tofacitinib is a JAK1/3 inhibitor approved for UC[13]. Studies on rats and rabbits showed that tofacitinib is feticidal and teratogenic[32]. The teratogenic effects included external and soft tissue malformations (*e.g.*, anasarca and membranous ventricular septal defects) and skeletal malformations [32]. Therefore, current recommendations suggest that tofacitinib be discontinued in female patients with IBD who plan to start a family. However, human data regarding the safety profile of tofacitinib for pregnant women with IBD is generally limited. Data from interventional studies of tofacitinib in patients with UC identified 11 cases of maternal exposure to tofacitinib (5 mg or 10 mg twice daily) before or at the time of conception or during pregnancy. Among these cases, 36% of patients delivered healthy newborns, and 18% had a medical termination. While 18% of the patients experienced

Table 2 Summary of systematic review and meta-analyses regarding the safety profiles of biologics and small molecules for pregnant women with inflammatory bowel disease

Biologics/small molecules	ECCO's guideline[25]	Summaries of recent systematic review and meta-analysis
TNF inhibitors (monotherapy)	Low risk	There was an increased risk of preterm births, LBW, and cesarian section in patients with IBD treated with TNF inhibitors[27]. This study was limited in its understanding of whether anti-TNF monotherapy or its combination with thiopurines is associated with these risks
TNF inhibitors with thiopurines	Thiopurine discontinuation may be considered on an individualized basis	Meta-analyses including recent prospective studies that assess the risk of combination therapy for pregnant women with IBD are lacking
Vedolizumab	Low risk, limited data	Women treated with vedolizumab had an increased risk of preterm births and early pregnancy loss compared with those unexposed to vedolizumab during pregnancy. No differences were observed in the number of live births or congenital abnormalities[26,30]. The systematic review and meta-analyses' results may be biased by disease activity
Ustekinumab	Low risk, limited data	A meta-analysis including two case studies showed that women treated with ustekinumab had an increased risk of early pregnancy loss compared with those treated with TNF inhibitors[26]. The prevalence of adverse pregnancy events was likely to be overestimated due to the small number of studies in this meta-analysis
JAK inhibitors	Contraindicated (no mention of upadacitinib)	N/A
Ozanimod	Contraindicated	N/A
Calcineurin inhibitors	Low risk, limited data	A meta-analysis including 4450 CNI-treated patients (4372 solid organ transplant recipients and 78 patients with IMIDs including IBD) showed that the rates of preterm delivery, LBW, and preeclampsia were 3–4 times greater than the rates in the general population. The risk of neonatal prematurity was higher in solid organ transplant recipients than in patients with IMIDs due to the higher risk of preeclampsia in solid organ transplant recipients. CNIs may be safer for pregnant women with immune-mediated diseases than for solid organ transplant recipients[38]

CNI: Calcineurin inhibitor; ECCO: European Crohn's and Colitis Organization; IBD: Inflammatory bowel disease; IMIDs: Immune-mediated inflammatory diseases; JAK: Janus kinase; LBW: Low birth weight; TNF: Tumor necrosis factor; UC: Ulcerative colitis; N/A: Not applicable.

spontaneous abortion, no cases of neonatal death, fetal death, or congenital malformations were reported[33]. Although these study sizes are small, these findings suggest that pregnancy and neonatal outcomes in UC studies of tofacitinib are similar to those in the general population and clinical studies of other indications (such as rheumatoid arthritis, psoriatic arthritis, and psoriasis). Regardless, current best practice recommendations, including the ECCO guideline and the product labeling, state that tofacitinib use is contraindicated in pregnancy due to the very limited data on pregnant women with IBD[25].

Filgotinib is a small molecule that preferentially inhibits JAK1 and is approved for moderately to severely active UC in Europe and Japan[14]. Animal studies have shown that filgotinib is associated with decreased male fertility and impaired spermatogenesis. However, filgotinib exposure was not associated with decreased female fertility[34]. The MANTA study is currently being conducted to confirm the impact of filgotinib on male fertility[34]. Since filgotinib is considered harmful to the fetus, according to animal studies findings, both the ECCO guideline and the product labeling state that this drug is contraindicated during pregnancy[25] (Tables 1 and 2).

Upadacitinib is a selective JAK1 inhibitor approved for moderately to severely active UC in Europe, the US, and Japan[35]. Although no human studies have assessed the safety of upadacitinib for pregnancy, this drug was also found to be teratogenic in animal studies. Therefore, the product labeling recommends against using upadacitinib during pregnancy[36].

Sphingosine-1 phosphate receptor modulators

Ozanimod is the first oral agonist of the sphingosine-1 phosphate receptor subtypes 1 and 5, which was approved for moderately to severely active UC in the United States and Europe[17]. There is only very limited data regarding the safety of ozanimod during pregnancy from the trials of multiple sclerosis[37] and UC[17]. Due to the lack of human data, ozanimod is contraindicated during pregnancy according to the ECCO guideline[25].

CNIs

Many studies have demonstrated the safety of CNIs for solid organ transplant (SOT) recipients during pregnancy[38]. However, safety data for pregnant women with IMIDs are scarce[38]. A case series assessed the clinical outcomes in 8 pregnant women with steroid-refractory UC who were started on CNIs. All patients received oral steroid therapy and were treated with cyclosporine for UC. Of the eight

patients treated with cyclosporine, 7 (88%) clinically improved, and the remaining patient who did not respond to cyclosporine was started on infliximab and subsequently improved. Half of the patients continued steroids at the time of delivery, and the other half stopped steroids. No patient underwent colectomy during pregnancy. As for pregnancy outcomes, 7 (88%) out of 8 pregnancies were carried to term, and one (13%) in-utero death occurred at 22 wk of gestation. Among the two premature newborns, one had LBW (1820 g), and the other newborn's weight was 3340 g[39]. This report suggests that cyclosporine is effective and safe for pregnant women with UC. No prospective studies assessing the safety of CNIs for IBD have been performed to date.

INTRODUCTION OF OUR CURRENT RESEARCH

How to manage IBD flare-ups during pregnancy

When pregnant women present with symptoms such as hematochezia, frequent bowel movements, or rectal urgency, laboratory tests (*e.g.*, fecal calprotectin), diagnostic imaging studies (*e.g.*, magnetic resonance imaging or ultrasound), and endoscopy may be considered for the assessment of IBD recurrence. A flexible sigmoidoscopy should be considered and readily performed without sedation or preparation, especially when the findings might change disease management[18]. The ECCO guideline highlights that IBD flare-ups during pregnancy should be managed according to current guidelines for non-pregnant patients with IBD using 5-aminosalicylate, steroids, cyclosporine, anti-TNF agents, ustekinumab, or vedolizumab[25].

In the setting of pregnancy, physicians should be aware that there are several exceptions when treating women with IBD flare-ups[18]. For instance, thiopurine initiation during pregnancy is not recommended, particularly in thiopurine-naïve patients, due to the potential risks of pancreatitis or leukopenia, which can be devastating[18]. Furthermore, JAK inhibitors, including tofacitinib, filgotinib, and upadacitinib, methotrexate, and ozanimod, cannot be used during pregnancy. As described above, animal data have demonstrated an increased risk of congenital malformation with tofacitinib[18]. Methotrexate should be stopped at least three months before conception due to its well-described teratogenic effects[40]. Ozanimod is also contraindicated due to the lack of human data on its safety during pregnancy[25].

Our research findings

When treating pregnant women who develop acute severe UC, we must consider early hospitalization and the initiation of rapid-acting therapies, including IV steroids, infliximab, or CNIs, to induce remission. While previous investigations demonstrated the efficacy and safety of IV steroids[39] and infliximab[41] in pregnant women with IBD flares, the number of studies focusing on the safety of CNIs in this population is still limited, as previously described. CNIs are often used in SOT recipients to prevent allograft rejection and to control disease activity in patients with IMIDs[38]. In general, CNIs are indicated for patients with acute severe UC who fail to adequately respond to IV steroids within 3-5 d [42]. CNIs can cause arteriolar vasoconstriction and endothelial injury, and CNI-associated hypertension is a well-described adverse effect of this therapy[43]. Previous studies have shown that cyclosporine has a more substantial vasoconstrictive effect than tacrolimus[44,45]. CNI-associated hypertension can be managed by dose reduction and the addition of anti-hypertensive medications[38]. We recently conducted a systematic review and meta-analysis to evaluate the effects of CNIs on pregnancy and neonatal outcomes in SOT recipients and those with IMIDs, including IBD.

Our systematic review identified a total of 5355 pregnancies in 4450 CNI-treated patients (4372 SOT recipients and 78 patients with IMIDs such as IBD, systemic lupus erythematosus, and rheumatoid arthritis). Our meta-analysis showed that the rates of preterm delivery (33.2%, 95%CI: 29.2%-37.5%), LBW (35.8%, 95%CI: 27.7%-44.8%), and preeclampsia (13.5%, 95%CI: 9.4%-19.2%) in CNI-treated patients were 3-4 times greater than the rates in the general population[38]. The subgroup analysis revealed that the rates of gestational hypertension and preeclampsia in SOT recipients were higher than in patients with IMIDs. Furthermore, the pooled rate of LBW in SOT recipients was higher than that in patients with IMIDs. Notably, the meta-regression analysis showed a significant association between preeclampsia and the risks of preterm delivery and LBW. These findings suggest that the risk of neonatal prematurity with CNIs is higher in SOT recipients than in patients with IMIDs, due to the higher risk of preeclampsia in SOT recipients[38].

Additionally, our meta-regression analysis showed that pre-pregnancy hypertension and cyclosporine use significantly increased the risk of preeclampsia. The development of pre-pregnancy hypertension in SOT recipients may be attributed to CNI use and other risk factors, including allograft dysfunction, steroid use, volume overload, and particularly kidney transplantation[46]. On the other hand, patients with IMIDs may have a lower risk of pre-pregnancy hypertension, as this population is less likely to have such risk factors. Therefore, we suggest that risk stratification based on clinical indications for CNIs may help enable and subsequently inform discussions around appropriate preconception counseling and proactive blood pressure management in CNI-treated pregnant women. Moreover, given the stronger vasoconstriction effect of cyclosporine as compared with tacrolimus, our

findings also support that the vasoconstrictive effects of CNIs could be associated with the risk of preeclampsia and suggest that tacrolimus may be the preferred CNI to use in pregnant patients, particularly for those with a high risk of gestational hypertensive disorders (such as SOT recipients)[38].

Overall, our data support that CNIs may be safer in patients with IBD than SOT recipients. Due to the limited number of patients with IBD in our study, further studies with larger IBD sample sizes are needed to validate our findings (Tables 1 and 2).

CONCLUSION

The PIANO registry demonstrated that biologics and thiopurines are generally safe and do not increase the risk of adverse maternal and neonatal outcomes in patients with IBD. Recent prospective data have also revealed that anti-TNF monotherapy is safe during pregnancy. However, their combination with thiopurines may increase the risk of neonatal prematurity and infection. Nonetheless, the impact of this risk is still unclear, given the conflicting data reported among these studies. Although meta-analyses of a small number of studies showed that vedolizumab and ustekinumab could be associated with early pregnancy loss, recent prospective studies have demonstrated that these biologics are relatively safe to use in pregnant women with IBD.

On the other hand, there is a paucity of prospective data assessing the clinical benefits of the continuation of biologics during pregnancy. For example, while a French nationwide emulation study demonstrated that the continuation of TNF inhibitors after 24 wk of pregnancy decreased the risks of maternal IBD relapse and neonatal prematurity[7], the clinical benefits of non-TNF biologics during pregnancy remain to be elucidated. Further investigations are also needed to understand whether biologics are to be used preemptively among patients in remission on conventional therapies before pregnancy to reduce the risk of clinical relapse during pregnancy. Such analyses may provide meaningful information to strengthen the current evidence that supports the continuation of biological therapies during pregnancy in patients with IBD.

Regarding small-molecule therapies, JAK inhibitors are contraindicated for pregnancy as animal studies have demonstrated harmful fetal effects. Due to the lack of human data, ozanimod should not be used during pregnancy. Our meta-analysis assessing pregnancy and neonatal outcomes in CNI-treated patients found a significant association between preeclampsia and neonatal prematurity in exposed patients. The rate of preeclampsia was higher in SOT recipients than in patients with IMIDs, suggesting that CNIs may be safer in patients with IBD. To better understand the efficacy and safety of CNIs in pregnant women with IBD, our future research will include prospective and/or multicenter studies that facilitate more significant numbers of patients to participate and enroll, strengthening the validity of our findings further.

FOOTNOTES

Author contributions: Akiyama S designed the research; Akiyama S and Kobayashi M performed the research and analyzed the data; Akiyama S, Steinberg JM, Kobayashi M, Suzuki H, and Tsuchiya K wrote the paper.

Conflict-of-interest statement: Akiyama S, Kobayashi M, and Suzuki H have no relevant disclosures; Steinberg JM has done consulting and/or Advisory Board for Pfizer, Janssen, BMS, GistMD and is on the Speakers Bureau for Takeda, Eli Lilly, BMS, Abbvie; Tsuchiya K has received grants from Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharmaceutical Corp., and Hitachi Ltd.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Japan

ORCID number: Shintaro Akiyama 0000-0003-0727-7638; Joshua M Steinberg 0000-0002-8809-3437; Hideo Suzuki 0000-0002-1469-7449; Kiichiro Tsuchiya 0000-0002-1977-8707.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

REFERENCES

1 **Stephansson O**, Larsson H, Pedersen L, Kieler H, Granath F, Ludvigsson JF, Falconer H, Ekbom A, Sørensen HT, Nørgaard M. Crohn's disease is a risk factor for preterm birth. *Clin Gastroenterol Hepatol* 2010; **8**: 509-515 [PMID: 20202483 DOI: 10.1016/j.cgh.2010.02.014]

2 **Cornish J**, Tan E, Teare J, Teoh TG, Rai R, Clark SK, Tekkis PP. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* 2007; **56**: 830-837 [PMID: 17185356 DOI: 10.1136/gut.2006.108324]

3 **Mahadevan U**, Sandborn WJ, Li DK, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. *Gastroenterology* 2007; **133**: 1106-1112 [PMID: 17764676 DOI: 10.1053/j.gastro.2007.07.019]

4 **Kim MA**, Kim YH, Chun J, Lee HS, Park SJ, Cheon JH, Kim TI, Kim WH, Park JJ. The Influence of Disease Activity on Pregnancy Outcomes in Women With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *J Crohns Colitis* 2021; **15**: 719-732 [PMID: 33175122 DOI: 10.1093/ecco-jcc/jjaa225]

5 **Rottenstreich A**, Shifman Z, Grisaru-Granovksy S, Mishael T, Koslowsky B, Bar-Gil Shitrit A. Factors Associated with Inflammatory Bowel Disease Flare During Pregnancy Among Women with Preconception Remission. *Dig Dis Sci* 2021; **66**: 1189-1194 [PMID: 32356256 DOI: 10.1007/s10620-020-06282-7]

6 **Allen KD**, Kiefer MK, Butnariu M, Afzali A. Pregnant women with immune mediated inflammatory diseases who discontinue biologics have higher rates of disease flare. *Arch Gynecol Obstet* 2022; **306**: 1929-1937 [PMID: 35249153 DOI: 10.1007/s00404-022-06463-x]

7 **Meyer A**, Neumann A, Drouin J, Weill A, Carbonnel F, Dray-Spira R. Benefits and Risks Associated With Continuation of Anti-Tumor Necrosis Factor After 24 Weeks of Pregnancy in Women With Inflammatory Bowel Disease : A Nationwide Emulation Trial. *Ann Intern Med* 2022; **175**: 1374-1382 [PMID: 36162111 DOI: 10.7326/M22-0819]

8 **Luu M**, Benzenine E, Doret M, Michiels C, Barkun A, Degand T, Quantin C, Bardou M. Continuous Anti-TNFα Use Throughout Pregnancy: Possible Complications For the Mother But Not for the Fetus. A Retrospective Cohort on the French National Health Insurance Database (EVASION). *Am J Gastroenterol* 2018; **113**: 1669-1677 [PMID: 29961771 DOI: 10.1038/s41395-018-0176-7]

9 **Malhi G**, Tandon P, Perlmutter JW, Nguyen G, Huang V. Risk Factors for Postpartum Disease Activity in Women With Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Inflamm Bowel Dis* 2022; **28**: 1090-1099 [PMID: 34427643 DOI: 10.1093/ibd/izab206]

10 **Jang DI**, Lee AH, Shin HY, Song HR, Park JH, Kang TB, Lee SR, Yang SH. The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics. *Int J Mol Sci* 2021; **22** [PMID: 33800290 DOI: 10.3390/ijms22052719]

11 **Feagan BG**, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, Van Assche G, Axler J, Kim HJ, Danese S, Fox I, Milch C, Sankoh S, Wyant T, Xu J, Parikh A; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013; **369**: 699-710 [PMID: 23964932 DOI: 10.1056/NEJMoa1215734]

12 **Feagan BG**, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, Blank MA, Johanns J, Gao LL, Miao Y, Adedokun OJ, Sands BE, Hanauer SB, Vermeire S, Targan S, Ghosh S, de Villiers WJ, Colombel JF, Tulassay Z, Seidler U, Salzberg BA, Desreumaux P, Lee SD, Loftus EV Jr, Dieleman LA, Katz S, Rutgeerts P; UNITI–IM-UNITI Study Group. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med* 2016; **375**: 1946-1960 [PMID: 27959607 DOI: 10.1056/NEJMoa1602773]

13 **Sandborn WJ**, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, Danese S, Feagan BG, Reinisch W, Niezychowski W, Friedman G, Lawendy N, Yu D, Woodworth D, Mukherjee A, Zhang H, Healey P, Panés J; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2017; **376**: 1723-1736 [PMID: 28467869 DOI: 10.1056/NEJMoa1606910]

14 **Feagan BG**, Danese S, Loftus EV Jr, Vermeire S, Schreiber S, Ritter T, Fogel R, Mehta R, Nijhawan S, Kempiński R, Filip R, Hospodarskyy I, Seidler U, Seibold F, Beales ILP, Kim HJ, McNally J, Yun C, Zhao S, Liu X, Hsueh CH, Tasset C, Besuyen R, Watanabe M, Sandborn WJ, Rogler G, Hibi T, Peyrin-Biroulet L. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. *Lancet* 2021; **397**: 2372-2384 [PMID: 34090625 DOI: 10.1016/S0140-6736(21)00666-8]

15 **Danese S**, Vermeire S, Zhou W, Pangan AL, Siffledeen J, Greenbloom S, Hébuterne X, D'Haens G, Nakase H, Panés J, Higgins PDR, Juillerat P, Lindsay JO, Loftus EV Jr, Sandborn WJ, Reinisch W, Chen MH, Sanchez Gonzalez Y, Huang B, Xie W, Liu J, Weinreich MA, Panaccione R. Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials. *Lancet* 2022; **399**: 2113-2128 [PMID: 35644166 DOI: 10.1016/S0140-6736(22)00581-5]

16 **Loftus CG**, Egan LJ, Sandborn WJ. Cyclosporine, tacrolimus, and mycophenolate mofetil in the treatment of inflammatory bowel disease. *Gastroenterol Clin North Am* 2004; **33**: 141-169, vii [PMID: 15177532 DOI: 10.1016/j.gtc.2004.02.001]

17 **Paik J**. Ozanimod: A Review in Ulcerative Colitis. *Drugs* 2022; **82**: 1303-1313 [PMID: 35994200 DOI: 10.1007/s40265-022-01762-8]

18 **Mahadevan U**, Robinson C, Bernasko N, Boland B, Chambers C, Dubinsky M, Friedman S, Kane S, Manthey J, Sauberan J, Stone J, Jain R. Inflammatory Bowel Disease in Pregnancy Clinical Care Pathway: A Report From the American Gastroenterological Association IBD Parenthood Project Working Group. *Am J Obstet Gynecol* 2019; **220**: 308-323 [PMID: 30948039 DOI: 10.1016/j.ajog.2019.02.027]

19 **Chaparro M**, Verreth A, Lobaton T, Gravito-Soares E, Julsgaard M, Savarino E, Magro F, Biron AI, Lopez-Serrano P, Casanova MJ, Gompertz M, Vitor S, Arroyo M, Pugliese D, Zabana Y, Vicente R, Aguas M, Shitrit BA, Gutierrez A, Doherty GA, Fernandez-Salazar L, Cadilla MJ, Huguet JM, O'Toole A, Stasi E, Marcos MN, Villoria A, Karmiris K, Rahier JF, Rodriguez C, Palomares DM, Fiorino G, Benitez JM, Principi M, Naftali T, Taxonera C, Mantzaris G, Sebkova L, Iade B, Lissner D, Bradley FI, Roman LA, Marin-Jimenez I, Merino O, Sierra M, Van Domselaar M, Caprioli F, Guerra I, Peixe P, Piqueras M, Rodriguez-Lago I, Ber Y, van Hoeve K, Torres P, Gravito-Soares M, Rudbeck-Resdal D, Bartolo O,

Peixoto A, Martin G, Armuzzi A, Garre A, Donday MG, de Carpi MFJ, Gisbert JP. Long-Term Safety of In Utero Exposure to Anti-TNFα Drugs for the Treatment of Inflammatory Bowel Disease: Results from the Multicenter European TEDDY Study. *Am J Gastroenterol* 2018; **113**: 396-403 [PMID: 29460920 DOI: 10.1038/ajg.2017.501]

20 **Mahadevan U**, Long MD, Kane SV, Roy A, Dubinsky MC, Sands BE, Cohen RD, Chambers CD, Sandborn WJ; Crohn's Colitis Foundation Clinical Research Alliance. Pregnancy and Neonatal Outcomes After Fetal Exposure to Biologics and Thiopurines Among Women With Inflammatory Bowel Disease. *Gastroenterology* 2021; **160**: 1131-1139 [PMID: 33227283 DOI: 10.1053/j.gastro.2020.11.038]

21 **Meyer A**, Drouin J, Weill A, Carbonnel F, Dray-Spira R. Comparative study of pregnancy outcomes in women with inflammatory bowel disease treated with thiopurines and/or anti-TNF: a French nationwide study 2010-2018. *Aliment Pharmacol Ther* 2021; **54**: 302-311 [PMID: 34162011 DOI: 10.1111/apt.16448]

22 **Meyer A**, Taine M, Drouin J, Weill A, Carbonnel F, Dray-Spira R. Serious Infections in Children Born to Mothers With Inflammatory Bowel Disease With In Utero Exposure to Thiopurines and Anti-Tumor Necrosis Factor. *Clin Gastroenterol Hepatol* 2022; **20**: 1269-1281.e9 [PMID: 34298191 DOI: 10.1016/j.cgh.2021.07.028]

23 **Avni-Biron I**, Mishael T, Zittan E, Livne-Margolin M, Zinger A, Tzadok R, Goldenberg R, Kopylov U, Ron Y, Hadar E, Helman S, Granovsky SG, Ollech JE, Arazi A, Farkash R, Pauker MH, Yanai H, Dotan I, Shitrit AB. Ustekinumab during pregnancy in patients with inflammatory bowel disease: a prospective multicentre cohort study. *Aliment Pharmacol Ther* 2022; **56**: 1361-1369 [PMID: 36168705 DOI: 10.1111/apt.17224]

24 **Mitrova K**, Pipek B, Bortlik M, Bouchner L, Brezina J, Douda T, Drasar T, Klvana P, Kohout P, Leksa V, Minarikova P, Novotny A, Svoboda P, Skorpik J, Ulbrych J, Veinfurt M, Zborilova B, Lukas M, Duricova D; Czech IBD Working Group. Safety of Ustekinumab and Vedolizumab During Pregnancy-Pregnancy, Neonatal, and Infant Outcome: A Prospective Multicentre Study. *J Crohns Colitis* 2022; **16**: 1808-1815 [PMID: 35708729 DOI: 10.1093/ecco-jcc/jjac086]

25 **Torres J**, Chaparro M, Julsgaard M, Katsanos K, Zelinkova Z, Agrawal M, Ardizzone S, Campmans-Kuijpers M, Dragoni G, Ferrante M, Fiorino G, Flanagan E, Frias Gomes C, Hart A, Hedin CR, Juillerat P, Mulders A, Myrelid P, O'Toole A, Rivière P, Scharl M, Selinger CP, Sonnenberg E, Toruner M, Wieringa J, Van der Woude CJ. European Crohn's and Colitis Guidelines on Sexuality, Fertility, Pregnancy, and Lactation. *J Crohns Colitis* 2023; **17**: 1-27 [PMID: 36005814 DOI: 10.1093/ecco-jcc/jjac115]

26 **Nielsen OH**, Gubatan JM, Juhl CB, Streett SE, Maxwell C. Biologics for Inflammatory Bowel Disease and Their Safety in Pregnancy: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2022; **20**: 74-87.e3 [PMID: 32931960 DOI: 10.1016/j.cgh.2020.09.021]

27 **Barenbrug L**, Groen MT, Hoentjen F, van Drongelen J, Reek JMPAVD, Joosten I, de Jong EMGJ, van der Molen RG. Pregnancy and neonatal outcomes in women with immune mediated inflammatory diseases exposed to anti-tumor necrosis factor-α during pregnancy: A systemic review and meta-analysis. *J Autoimmun* 2021; **122**: 102676 [PMID: 34126302 DOI: 10.1016/j.jaut.2021.102676]

28 **Julsgaard M**, Baumgart DC, Baunwall SMD, Hansen MM, Grosen A, Bibby BM, Uldbjerg N, Kjeldsen J, Sørensen HG, Larsen L, Wildt S, Weimers P, Haderslev KV, Vind I, Svenningsen L, Brynskov J, Lyhne S, Vestergaard T, Hvas CL, Kelsen J; NOVA Study Group. Vedolizumab clearance in neonates, susceptibility to infections and developmental milestones: a prospective multicentre population-based cohort study. *Aliment Pharmacol Ther* 2021; **54**: 1320-1329 [PMID: 34472644 DOI: 10.1111/apt.16593]

29 **Bar-Gil Shitrit A**, Ben Ya'acov A, Livovsky DM, Cuker T, Farkash R, Hoyda A, Granot T, Avni-Biron I, Lahat A, Goldin E, Grisaru-Granovsky S. Exposure to Vedolizumab in IBD Pregnant Women Appears of Low Risk for Mother and Neonate: A First Prospective Comparison Study. *Am J Gastroenterol* 2019; **114**: 1172-1175 [PMID: 30920987 DOI: 10.14309/ajg.0000000000000186]

30 **Bell C**, Tandon P, Lentz E, Marshall JK, Narula N. Systematic review and meta-analysis: Safety of vedolizumab during pregnancy in patients with inflammatory bowel disease. *J Gastroenterol Hepatol* 2021; **36**: 2640-2648 [PMID: 34110640 DOI: 10.1111/jgh.15574]

31 **Mahadevan U**, Naureckas S, Tikhonov I, Wang Y, Lin CB, Geldhof A, van der Woude CJ. Pregnancy outcomes following periconceptional or gestational exposure to ustekinumab: Review of cases reported to the manufacturer's global safety database. *Aliment Pharmacol Ther* 2022; **56**: 477-490 [PMID: 35560249 DOI: 10.1111/apt.16960]

32 **Gisbert JP**, Chaparro M. Safety of New Biologics (Vedolizumab and Ustekinumab) and Small Molecules (Tofacitinib) During Pregnancy: A Review. *Drugs* 2020; **80**: 1085-1100 [PMID: 32562207 DOI: 10.1007/s40265-020-01346-4]

33 **Mahadevan U**, Dubinsky MC, Su C, Lawendy N, Jones TV, Marren A, Zhang H, Graham D, Clowse MEB, Feldman SR, Baumgart DC. Outcomes of Pregnancies With Maternal/Paternal Exposure in the Tofacitinib Safety Databases for Ulcerative Colitis. *Inflamm Bowel Dis* 2018; **24**: 2494-2500 [PMID: 29982686 DOI: 10.1093/ibd/izy160]

34 **Hellstrom WJG**, Dolhain RJEM, Ritter TE, Watkins TR, Arterburn SJ, Dekkers G, Gillen A, Tonussi C, Gilles L, Oortwijn A, Van Beneden K, de Vries DE, Sikka SC, Vanderschueren D, Reinisch W. MANTA and MANTA-RAy: Rationale and Design of Trials Evaluating Effects of Filgotinib on Semen Parameters in Patients with Inflammatory Diseases. *Adv Ther* 2022; **39**: 3403-3422 [PMID: 35614292 DOI: 10.1007/s12325-022-02168-4]

35 **Napolitano M**, D'Amico F, Ragaini E, Peyrin-Biroulet L, Danese S. Evaluating Upadacitinib in the Treatment of Moderate-to-Severe Active Ulcerative Colitis: Design, Development, and Potential Position in Therapy. *Drug Des Devel Ther* 2022; **16**: 1897-1913 [PMID: 35747444 DOI: 10.2147/DDDT.S340459]

36 **Padda IS**, Bhatt R, Parmar M. Upadacitinib. 2022 Nov 30. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan [PMID: 34283454]

37 **Selmaj KW**, Cohen JA, Comi G, Bar-Or A, Arnold DL, Steinman L, Hartung HP, Montalban X, Havrdova EK, Cree BAC, Minton N, Sheffield JK, Ding N, Kappos L. Ozanimod in relapsing multiple sclerosis: Pooled safety results from the clinical development program. *Mult Scler Relat Disord* 2021; **51**: 102844 [PMID: 33892317 DOI: 10.1016/j.msard.2021.102844]

38 **Akiyama S**, Hamdeh S, Murakami N, Cotter TG, Suzuki H, Tsuchiya K. Pregnancy and neonatal outcomes in women receiving calcineurin inhibitors: A systematic review and meta-analysis. *Br J Clin Pharmacol* 2022; **88**: 3950-3961 [PMID: 35593302 DOI: 10.1111/bcp.15414]

39 **Branche J**, Cortot A, Bourreille A, Coffin B, de Vos M, de Saussure P, Seksik P, Marteau P, Lemann M, Colombel JF. Cyclosporine treatment of steroid-refractory ulcerative colitis during pregnancy. *Inflamm Bowel Dis* 2009; **15**: 1044-1048 [PMID: 19137604 DOI: 10.1002/ibd.20858]

40 **Mahadevan U**, McConnell RA, Chambers CD. Drug Safety and Risk of Adverse Outcomes for Pregnant Patients With Inflammatory Bowel Disease. *Gastroenterology* 2017; **152**: 451-462.e2 [PMID: 27769809 DOI: 10.1053/j.gastro.2016.10.013]

41 **Bortlik M**, Machkova N, Duricova D, Malickova K, Hrdlicka L, Lukas M, Kohout P, Shonova O. Pregnancy and newborn outcome of mothers with inflammatory bowel diseases exposed to anti-TNF-α therapy during pregnancy: three-center study. *Scand J Gastroenterol* 2013; **48**: 951-958 [PMID: 23834232 DOI: 10.3109/00365521.2013.812141]

42 **Hindryckx P**, Jairath V, D'Haens G. Acute severe ulcerative colitis: from pathophysiology to clinical management. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 654-664 [PMID: 27580687 DOI: 10.1038/nrgastro.2016.116]

43 **Hoorn EJ**, Walsh SB, McCormick JA, Zietse R, Unwin RJ, Ellison DH. Pathogenesis of calcineurin inhibitor-induced hypertension. *J Nephrol* 2012; **25**: 269-275 [PMID: 22573529 DOI: 10.5301/jn.5000174]

44 **Klein IH**, Abrahams A, van Ede T, Hené RJ, Koomans HA, Ligtenberg G. Different effects of tacrolimus and cyclosporine on renal hemodynamics and blood pressure in healthy subjects. *Transplantation* 2002; **73**: 732-736 [PMID: 11907418 DOI: 10.1097/00007890-200203150-00012]

45 **Nankivell BJ**, Chapman JR, Bonovas G, Gruenewald SM. Oral cyclosporine but not tacrolimus reduces renal transplant blood flow. *Transplantation* 2004; **77**: 1457-1459 [PMID: 15167607 DOI: 10.1097/01.tp.0000121196.71904.e0]

46 **Chatzikyrkou C**, Menne J, Gwinner W, Schmidt BM, Lehner F, Blume C, Schwarz A, Haller H, Schiffer M. Pathogenesis and management of hypertension after kidney transplantation. *J Hypertens* 2011; **29**: 2283-2294 [PMID: 21970935 DOI: 10.1097/HJH.0b013e32834bd1e7]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1741-1752

DOI: 10.12998/wjcc.v11.i8.1741

ISSN 2307-8960 (online)

MINIREVIEWS

Pathogenesis, clinical manifestations, diagnosis, and treatment progress of achalasia of cardia

Ming-Yue Li, Qing-Hua Wang, Run-Peng Chen, Xiao-Fang Su, Dong-Yang Wang

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Mestrovic A, Croatia; Primadhi RA, Indonesia

Received: January 11, 2023
Peer-review started: January 11, 2023
First decision: February 2, 2023
Revised: February 6, 2023
Accepted: February 21, 2023
Article in press: February 21, 2023
Published online: March 16, 2023

Ming-Yue Li, Qing-Hua Wang, Run-Peng Chen, Xiao-Fang Su, Dong-Yang Wang, School of Nursing, Binzhou Medical University, Yantai 264003, Shandong Province, China

Dong-Yang Wang, Faculty of Nursing, Mahidol University, Nakhon Pathom 73170, Thailand

Corresponding author: Dong-Yang Wang, PhD, RN, Lecturer, Nurse, Researcher, School of Nursing, Binzhou Medical University, No. 346 Guanhai Road, Yantai 264003, Shandong Province, China. wangdongyang1994@gmail.com

Abstract

Achalasia cardia, type of esophageal dynamic disorder, is a relatively rare primary motor esophageal disease characterized by the functional loss of plexus ganglion cells in the distal esophagus and lower esophageal sphincter. Loss of function of the distal and lower esophageal sphincter ganglion cells is the main cause of achalasia cardia, and is more likely to occur in the elderly. Histological changes in the esophageal mucosa are considered pathogenic; however, studies have found that inflammation and genetic changes at the molecular level may also cause achalasia cardia, resulting in dysphagia, reflux, aspiration, retrosternal pain, and weight loss. Currently, the treatment options for achalasia focus on reducing the resting pressure of the lower esophageal sphincter, helping to empty the esophagus and relieve symptoms. Treatment measures include botulinum toxin injection, inflatable dilation, stent insertion, and surgical myotomy (open or laparoscopic). Surgical procedures are often subject to controversy owing to concerns about safety and effectiveness, particularly in older patients. Herein, we review clinical epidemiological and experimental data to determine the prevalence, pathogenesis, clinical presentation, diagnostic criteria, and treatment options for achalasia to support its clinical management.

Key Words: Achalasia cardia; Pathogenesis; Clinical manifestations; Diagnosis; Treatment

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Achalasia is a relatively rare primary motility esophageal disorder characterized by loss of function of the plexus ganglion cells of the distal esophagus and the lower esophageal sphincter. Histological changes in the esophageal mucosa are considered pathogenic; however, studies have found that inflammation and genetic changes at the molecular level may also cause achalasia cardia, resulting in dysphagia, reflux, aspiration, retrosternal pain, and weight loss. This review article aims to conduct a comprehensive literature review and present current knowledge about achalasia.

Citation: Li MY, Wang QH, Chen RP, Su XF, Wang DY. Pathogenesis, clinical manifestations, diagnosis, and treatment progress of achalasia of cardia. *World J Clin Cases* 2023; 11(8): 1741-1752
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1741.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1741

INTRODUCTION

As a core part of the digestive system, the esophagus plays a vital role in the transportation of nutrients. The diseases of the esophagus can be classified as anatomical injuries to the organ cavity (*e.g.*, digestive or eosinophilic stenosis) or severe dysphagia in the progression of digestive tract injection (*e.g.*, severe dysphagia of neurological origin or achalasia cardia)[1]. Esophageal achalasia is a type of esophageal dynamic disorder (EMD). It refers to esophageal outflow tract obstruction due to impaired lower esophageal sphincter (LES) relaxation and loss of esophageal peristalsis or spasmodic contraction when the esophageal body or esophagogastric junction (EGJ) is not structurally obstructed. There are primary and secondary types of achalasia[2,3]. Achalasia cardia is characterized by the loss of functional muscle ganglion cells in the distal esophagus and LES[4]. Although histological changes in the esophageal mucosa have long been considered part of the pathogenesis of achalasia cardia, recent studies have found that inflammation and genetic changes may also contribute to achalasia at the molecular level. Currently, achalasia is a chronic, incurable condition. Different subtypes of achalasia respond differently to drugs and surgical treatments[5], after which some patients develop submucosal fibrosis; this may relapse and require additional treatment. In this study, we reviewed the clinical, epidemiological, and experimental data on the prevalence, pathogenesis, clinical presentation, diagnostic criteria, and treatment options for achalasia to support its clinical management.

PREVALENCE AND ETIOLOGY

Achalasia is a relatively rare disease of the esophagus, with an incidence of 2.92 per 100000 adults and 0.11 per 100000 children and a male-to-female ratio of approximately 1:1. However, recent studies have shown that the incidence of achalasia is increasing, particularly in South America, and varies among countries[6-8]. Achalasia has a bimodal age distribution, with most patients aged between either 20-40 or 60-70 years. Studies have also shown that the incidence of this disease increases with age[9,10]. However, there is a lack of clinical data on adult achalasia owing to the limited number of epidemiological studies on adult achalasia and the fact that most of the data are 10 years old. van Hoeij *et al*[11] surveyed 25% of Dutch residents from 2006 to 2014 and found that the average incidence of achalasia in the Netherlands was 2.2 per 100000 people. In 2016, Tebaibia *et al*[12] found that the average annual incidence of achalasia in Algeria increased from 0.04 [95% confidence interval (CI): 0.028-0.052] in the 1990s to 0.27/105 inhabitants per year in the 2000s (95%CI: 0.215-0.321), and the incidence was 2.5 times higher in the north and center than in the south of the country. Thus, additional research is required to gain a better understanding of achalasia in adults.

A recent large cohort study based on the IBM MarketScan Commercial Claims and Encounters database of the United States Medicare data showed that the median age of patients with achalasia was 52.70 years, and 56% of patients with achalasia cardia were female[13]. According to a recent large multi-center database study conducted in Japan, male sex and family history may be risk factors for achalasia[14]. One study found that socioeconomic status and lifestyle factors were associated with achalasia, in addition to the highest risk of developing achalasia in individuals with low-level occupations (OR = 1.88, 95%CI: 1.02-3.45)[15]. Foreign travel history and the presence of pets in the household also increased the risk of achalasia[16].

PATHOGENESIS OF ACHALASIA

Currently, the etiology and pathogenesis of achalasia cardia remain unclear; however, it is generally

believed that the histological changes of the esophageal mucosa caused by the loss of esophageal nerve cell function play a key role in its pathophysiology. Autoimmune attack of esophageal myenteric nerves through cell-mediated and possibly antibody-mediated mechanisms may lead to the inhibition of esophageal smooth muscles, resulting in loss of nerve function and nerve fiber degeneration[2,16].

In addition, several pathological mechanisms have been proposed as possible triggers for this immune disruption process, including underlying viral infections, idiopathic autoimmune triggers, and genetic predisposition[17,18]. Enteric herpes zoster virus, herpes simplex virus, measles, and human papillomavirus can impair the regulation of functional esophageal movement and LES control in patients with achalasia, but not in all patients with viral infections[19]. According to a case-control study by Naik *et al*[20], 80% of patients with achalasia had varicella-zoster virus DNA present in their saliva. A small amount of data suggests that eosinophils and mast cells may play a role in the development of achalasia and esophageal obstructive motility disorders. The aggregation of eosinophils and mast cells in the esophagus causes an increased concentration of inflammatory cytokines; this leads to fibrosis remodeling of the esophageal wall, ultimately causing esophageal dysfunction and related symptoms [21,22]. In 2013, Cools-Lartigue *et al*[23] enrolled 96 patients with achalasia who underwent laparoscopic Heller myotomy (LHM) and found that many patients with achalasia had esophageal eosinophilic infiltration. However, other studies have not found a cause–effect relationship between eosinophils and achalasia[24].

Sara *et al*[25] found a two-fold increase in the prevalence of autoimmune diseases in patients with achalasia cardia, which is often associated with type I diabetes (47.80%) and thyroid diseases (19.60%). In addition, patients with Sjogren's syndrome, psoriasis, autoimmune uveitis, rheumatoid arthritis, and Crohn's disease are more prone to achalasia. In addition, autoantibodies against sarcomeres are present in serum samples from patients with achalasia cardia, particularly in carriers of the HLA DQA1*0103 and DQB1*0603 alleles[16]. Of the comorbidities identified in this study, thyroid disease and Down syndrome were the most common autoimmune and hereditary conditions, respectively. Familial achalasia, achalasia with hereditary disease, and achalasia with autoimmune disease were present in 0.63%, 0.99%, and 2.40% of cases, respectively[14].

CLASSIFICATION OF ACHALASIA

Achalasia can be divided into three subtypes according to the Chicago classification criteria: Type I achalasia accounts for 20%-40% of cases; type II achalasia, the most common, accounts for 50%-70% of cases and has the highest levels of interleukin 4; type III achalasia, the rarest and most difficult to treat, accounts for 10% of cases[26] (Table 1). Compared with types II and III, type I is associated with lower concentrations of regulatory cells, pro-inflammatory cytokines, extracellular matrix converting proteins, and Fas receptors and higher levels of transforming growth factor-β[7]. Achalasia can progress from one type to another; this mainly relates to the pathological transition from ganglion inflammation to fibrosis [27,28].

Pseudoachalasia, also known as secondary achalasia, refers to the esophageal motility disorder caused by dysphagia and weight loss due to gastric cardia tumors or infiltrating intestinal plexus tumors (gastroesophageal junction adenocarcinoma, pancreatic cancer, breast cancer, lung cancer, or hepatocellular carcinoma)[29]. Pseudoachalasia is characterized by symptoms as well as manometry, endoscopy, and barium swallow findings similar to those of achalasia. This condition is often caused by tumors[30]. Moreover, in esophageal manometry, pseudoachalasia exhibits a lower incidence of complete peristalsis loss, combined relaxation pressure, and EGJ systolic scores compared with those observed in primary achalasia. Furthermore, invasive malignancies can be rapidly assessed using endoscopy and endoscopic ultrasonography or cross-sectional imaging[7,31].

Notably, in addition to the Chicago classification for esophageal achalasia - regarded as the international standard - there is also a Japanese classification system for this condition. In addition, three endoscopic structures have been identified based on the Ling classification, including polycyclic, crescent, and diverticular structures. The new Japanese Classification system for esophageal achalasia aims for a more practical classification based on clinicopathology, and cases are divided into three types based on their X-ray results: Straight (St), S-shaped (Sg), and advanced sigmoid (aSg)[32]. However, this system has not been widely used in Japan and has not been fully validated in terms of its demographic significance and ability to predict postoperative outcomes. The Ling classification system is a new type of endoscopic classification of achalasia cardia used to select patients who are suitable for transoral endoscopic myotomy [peroral endoscopic myotomy (POEM)] (Table 2). According to the Ling classification criteria, there are three types: Type I, smooth and without polycyclic, crescentic, or diverticular structures; type II, with polycyclic or crescent structures; and type III, with diverticular structures. Type II has three subtypes: Ling IIa, Ling IIb, and Ling IIc. Type III also has three subtypes: Ling III_l, Ling IIIr, and Ling IIIlr[33].

Table 1 Classification of achalasia in the Chicago classification system

Type	Feature
I	All failed without PEP
II	All failed ≥ 20%with PEP
III	≥ 20% premature ± PEP

PEP: Pan-esophageal pressurization.

Table 2 Ling classification of achalasia cardia

Type	Endoscopic presentation
I	The lumen was slightly dilated and smooth without polyring, crescent-shaped structures, or diverticular structures
II	The lumen was dilated and polycyclic or crescent-shaped structures appeared after inflation
II_a	A thin ring, no crescent structure
II_b	Crescent structure, not more than 1/3 of the lumen
II_c	Crescent structure, more than 1/3 of the lumen
III	The lumen was significantly dilated, with the diverticular structure-like structures
III_l	Diverticulum structure in the left wall of esophagus
III_r	Diverticulum structure in the right wall of esophagus
III_{lr}	Diverticulum structure in both the left and right walls of esophagus

CLINICAL PRESENTATION OF ACHALASIA

Dysphagia (solid or liquid) is a common symptom in patients with achalasia. This symptom is initially intermittent; however, as the disease advances, it progresses along with significant dilation of the esophagus, leading to burns and decompensation of the sigmoid esophagus with corresponding clinical symptoms[34]. Notably, approximately 90% of people with achalasia experience the main symptoms of progressive difficulty in swallowing liquids and solids[30].

Studies have shown that 70% of patients also experience reflux, which is the second most common symptom of achalasia; in turn, this causes corresponding respiratory symptoms such as coughing and burping, wheezing, hoarseness, and bronchitis[35,36].

In addition, patients with achalasia may experience chest pain[5]. There is also a risk of long-term aspiration pneumonia and esophageal squamous cell carcinoma[17]. A study conducted using data from a United Kingdom hospital and primary care database found that patients with achalasia had a high incidence of, and mortality from, esophageal cancer, aspiration pneumonia, and lower respiratory tract infections[37]. In addition, other studies have found that patients with achalasia have acute respiratory failure and hemodynamic instability. End-stage achalasia with thoracoesophageal enlargement may manifest as an acute disease[38].

Studies have found that achalasia often has an insidious onset with many subclinical features before definitive diagnosis, which can lead to a delay between symptom onset and diagnosis[31,38]. The Eckardt score can be used to assess the symptoms of achalasia (Table 3). This is a standardized and verified scoring system that rates four symptoms of achalasia (dysphagia, reflux, chest pain, and weight loss) based on severity, each on a scale of 0 to 3 on a final 12-point scale, where higher scores indicate more severe symptoms. A score < 3 is used to define symptom remission or successful remission[39]. Studies have shown that an Eckardt score ≥ 9 before treatment can predict the success of endoscopic myotomy in patients with achalasia cardia[40]. There is also evidence that genetic susceptibility, environmental triggers, and autoimmune enteromyelitis determine clinical phenotypes[41].

DIAGNOSIS OF ACHALASIA

Currently, achalasia cardia is mainly diagnosed using high-resolution manometry (HRM), endoscopy, and barium meal examination[42]. A timed barium meal esophagogram or functional lumen imaging probe (FLIP) is used only when achalasia cannot be diagnosed[43].

Table 3 Eckardt rating table

Score	Symptom			
	Weight loss	Dysphagia	Retrosternal pain	Palirrhea
0	-	-	-	-
1	< 5	Occasional	Occasional	Occasional
2	5-10	Daily	Daily	Daily
3	> 10	Every meal	Every meal	Every meal

HRM

Manometry plays an important role in the differential diagnosis of dynamic esophageal disorders. HRM is the gold standard for diagnosing achalasia cardia. HRM usually refers to performing a manometry test with at least 21 pressure sensors scattered across the catheter. Each pressure sensor is spaced 1 cm apart to record baseline resting measurements. The probe enters from the nose and passes through the esophagus to the LES, allowing for the examination of the entire esophagus[3,34,44].

The essential condition for HRM diagnosis of achalasia cardia is a comprehensive relaxation pressure (IRP) > 15 mmHg, which is defined as "impaired LES relaxation". A resting pressure > 45 mmHg is defined as a high-pressure LES[45,46]. The IRP is the most important parameter for the assessment of LES relaxation using HRM, which is measured after the relaxation of the EGJ in anticipation of the arrival of peristaltic waves after upper sphincter relaxation[45]. Clinical studies have shown that when LES-IRP is > 10 mmHg after treatment, repeated treatment is required[47].

In fact, HRM may not only confirm the diagnosis of achalasia but also identify specific subtypes that have significantly different treatment outcomes[39]. An appropriate intraoperative HRM diagnosis can help determine therapeutic approaches and predict therapeutic outcomes[42].

Endoscopy

Endoscopy is crucial for patients with digestive disorders although it is not very sensitive for achalasia. Studies have shown that only one-third of patients can be diagnosed with achalasia using endoscopy [48]. Typically, endoscopy is used to screen patients with gastrointestinal symptoms and to rule out luminal malignancies in the esophagus and proximal stomach[49]. Endoscopy may be normal in patients with early achalasia as curvatures or rose-like structures at the EGJ are characteristic of patients with more advanced achalasia. In addition, Gomi *et al*[50] found that the Champagne glass sign displayed by the endoscope could indicate achalasia. Notably, in 2020, Hoshikawa *et al*[51] found that all patients with achalasia with "esophageal rota" had the "ginkgo leaf sign." This is a new finding regarding the diagnosis of achalasia. Therefore, further research is needed to confirm its sensitivity, specificity, and interobserver consistency.

Barium meal esophagogram

Barium contrast is usually used to evaluate esophageal morphology before surgery. In patients with achalasia cardia, barium meal esophagogram reveals esophageal dilation, EGJ stenosis, beak formation, intestinal peristalsis, and delayed barium emptiness[5] (Figure 1). Studies have shown that four stages of achalasia cardia can be distinguished according to the maximum barium diameter and shape in the esophagus (Table 4): Stage 1, ≤ 4 cm; stage 2, 4-6 cm; stage 3, ≥ 6 cm, with a straight esophagus; stage 4, ≥ 6 cm, with a sigmoid tube (end-stage disease)[5,48].

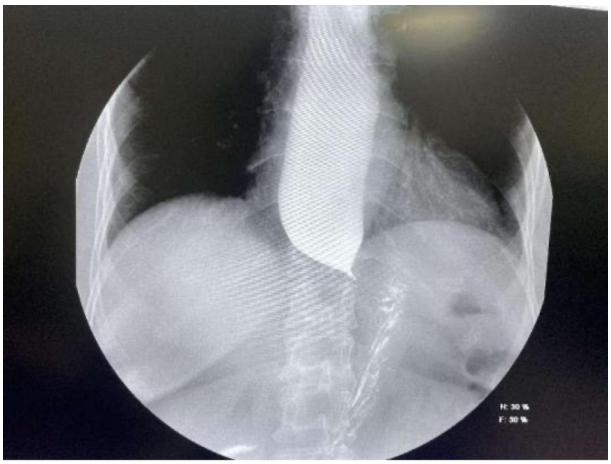
Timed barium ingestion (TBS) refers to the acquisition of static images of the esophagus at predetermined time intervals after the ingestion of a fixed amount of barium sulfate. It is an improved esophagography technique that can assess esophageal emptying more objectively[52]. TBS can be used to evaluate treatment success. It is simple, economical, non-invasive, repeatable, and well-tolerated by patients[45]. Notably, TBS is widely used for the preliminary evaluation of patients with suspected type I, II, or III achalasia.

FLIP

FLIP is a novel catheter-based device that can be used to analyze the relationship between cross-sectional area and pressure of the lumen, measure the EGJ and dilatation index (DI) in real time, and provide supplementary information for HRM of EMDs, especially for achalasia cardia. FLIP has become a potential tool for the diagnosis and real-time calibration of achalasia cardia[53,54]. This device is generally suitable for patients with suspected achalasia but normal combined relaxation pressure, non-diagnostic HRM results, and those who cannot tolerate HRM testing[55]. Ren *et al*[56] and Carlson *et al* [57] found that FLIP could detect esophageal contractility in patients with achalasia that was not observed using manometry. In addition, FLIP can accurately predict the immediate outcome of balloon dilation and be used to guide the selection of balloon size for a single endoscopic balloon dilation.

Table 4 Radiological stages of achalasia

Radiological stage	Esophageal diameter	Esophageal shape
I	≤ 4 cm	-
II	4-6 cm	-
III	≥ 6 cm	-
IV (End-stage disease)	≥ 6 cm	Sigmoid



DOI: 10.12998/wjcc.v11.i8.1741 **Copyright** ©The Author(s) 2023.

Figure 1 Impaired relaxation of the lower esophageal sphincter is usually characterized by "beak" narrowing at the lower esophageal sphincter.

Other investigations

Studies have shown that chest computed tomography (CT), radiography, and ultrasound can also detect achalasia cardia[58,59]. Imaging is often used in the diagnosis of achalasia. Most patients with achalasia have esophageal dilation and mild symmetrical wall thickening on CT. Additionally, chest CT can be used to distinguish between primary and secondary achalasia cardia. Distal esophageal wall thickening (nodular/Lobular and asymmetrical); soft tissue masses at the gastroesophageal junction; mediastinal lymph node enlargement; and lung, liver, or bone metastases are suggestive of secondary achalasia[60]. Currently, imaging is mainly used for auxiliary examinations.

TREATMENT OF ACHALASIA

Treatment of achalasia cardia involves drugs, endoscopic Botox injections, and surgery to reduce LES pressure, relieve the patient's symptoms, and improve esophageal emptying; however, the condition cannot be cured. Surgical treatment for this disease is controversial as the related procedures may lead to gastroesophageal reflux; moreover, each treatment has particular limitations.

Medication

Medication is usually adopted in patients who cannot, or refuse to, undergo endoscopic or surgical treatment and in those for whom endoscopic or surgical treatment has failed (Table 5). Calcium channel blockers, nitrates, and proton pump inhibitors are commonly used to control acid reflux; however, they provide only short-term relief and are less effective[49].

Endoscopic treatment

Traditional endoscopic treatment of achalasia involves injections of botulinum toxin type A, pneumatic dilation (PD), and sclerotherapy.

Botulinum toxin type A: Botulinum toxin type A originated in 1980. It is a biological neurotoxin released by *Clostridium botulinum* that can prevent the release of acetylcholine from voluntary and involuntary muscle nerve endings[61]. It is considered an effective treatment for short-term symptomatic relief in patients with esophageal achalasia. This treatment is initially effective, but the

Table 5 Pharmacotherapy for achalasia

Type	On behalf of drugs	Mechanism of action
Calcium channel blockers	Nifedipine	Inhibit L - type calcium channel, relax smooth muscle and empty esophagus
Nitrates	Carvasin	Increase NO in tissue and relax smooth muscle
Anticholinergic	Ceto bromide ammonium bromide	Relax smooth muscle
Phosphodiesterase inhibitors	Silaenafil	Prevent the degradation of NO and prolong the relaxation of esophageal smooth muscle

outcome of repeated usage is poor, and the maintenance time is short (approximately 6-9 mo). Yamaguchi *et al*[61] found a high degree of remission of dysphagia after 1 wk of botulinum toxin treatment; however, 50% of patients relapsed 3-24 mo after treatment.

PD: Originating in 1674, PD is the earliest form of treatment for types I and II achalasia cardia. This method involves the use of an inflated balloon with a strong stretch to destroy the LES. The diameter of the balloon can range from 30 to 40 mm. Although short-term results of PD are adequate, the long-term outcomes are poor, requiring multiple treatments[39]. The most commonly used expander is the Rigiflex, which is usually ≥ 3 cm in diameter when fully inflated[62,63]. However, the effectiveness of the treatment decreases over time, and repeated treatment is required. A multicenter randomized controlled trial that compared aerated dilation with LHM indicated that 25% of patients with achalasia who received PD required retreatment[64]. Similarly, Jung *et al*[65] conducted a 1-year follow-up study of 73 Korean patients with achalasia cardia and found that balloon dilation was more effective than botulinum toxin in providing long-term relief.

Endoscopic sclerotherapy: Currently, the commonly used hardener ethanolamine oleate can induce an inflammatory response and fibrosis, thus causing excitatory neuronal damage and reducing LES pressure[66]. However, this method can cause patients to develop esophageal wall fibrosis; therefore, it is not recommended for routine use[7].

Operative treatment

Surgical treatments for achalasia include POEM, LHM, stent implantation, and esophagectomy (Table 6).

LHM: LHM is a common clinical treatment for achalasia, especially in adolescents and young adults, with a success rate of approximately 90%; however, the adverse outcome of gastroesophageal reflux disease (GERD) can occur in 55%-100% of cases. Subsequently, to compensate for the damage caused by esophageal reflux disease, LHM combined with anterior Dor fundoplication or posterior Toupet fundoplication was introduced[42,47,67]. Access to acid-lowering medication is required, and trauma, scars, and complications of esophageal or gastric perforation may occur[62]. Studies have shown that robot-assisted Heller myotomy (RAHM) is safer than LHM and can significantly reduce the incidence of esophageal perforation[63]. A recent review suggested that RAHM is safe and effective for the treatment of achalasia cardia and for that of esophageal dyskinesia, owing to its low incidence of technical complications compared to that for LHM[68].

POEM: Recently, POEM has emerged as an alternative to LHM. Introduced in 2008, this technique is a new minimally invasive therapeutic endoscopic surgical technique that is especially suitable for patients with type III achalasia cardia[47]. This operation involves establishing a submucosal tunnel in the lower esophagus to reach the LES' inner ring muscle bundle for myotomy while preserving the external longitudinal muscle bundle; this can prevent body wall trauma and preserve the external esophageal anatomy, while being precise and minimally invasive[46,62]. One advantage of POEM over LHM is that it can adjust the proximal myotomy range[69]. A recent study reported a 19-fold increase in the use of POEM. In addition, POEM can be used to perform a real-time direct biopsy of muscle layers and easily control the length and location of the myotomy[70]. Wang *et al*[71] conducted a multicenter, randomized controlled trial to follow-up patients with type II achalasia who underwent POEM and PD for 5 years and found that transoral endoscopic myotomy was superior to PD, with fewer complications, and should be recommended as the initial treatment option for patients with achalasia cardia. In addition, a meta-analysis indicated that the 2-year success rate of POEM treatment was significantly improved compared with that of inflatable dilation in first-time patients; however, reflux esophagitis was more common in the POEM group than in the inflatable dilation group[72].

A study comparing POEM with LHM found that POEM was safer and even superior to LHM in terms of cost-effectiveness, length of hospital stay, and dysphagia relief[28,46]. One study showed an early success rate of 89%-100% for POEM and that it is highly effective in the management of type III

Table 6 Surgical treatment of achalasia

Procedure	Indication	Complication
Peroral endoscopic myotomy	Advanced sigmoidocardia achalasia; surgical myotomy failed; patients with achalasia cardia who have previously received endoscopic treatment; spastic esophageal dyskinesia, such as jackhammer esophagus; diffuse esophageal spasm; hypertensive lower esophageal sphincter; nutcracker esophageal dyskinesia	Mucosal perforation; subcutaneous emphysema; pneumoperitoneum; pneumothorax; mediastinal emphysema; pleural effusion and pneumonia; delayed bleeding; infection; gastroesophageal reflux disease
Laparoscopic Heller myotomy	Drug treatment if symptomatic improvement is not obvious	Gastroesophageal reflux disease; punch
Stent implantation	Patients who are not candidates for surgery	Mucosal hyperplasia; local esophageal stenosis; scaffold migration
Esophagectomy	A zigzag giant esophagus; esophageal stenosis caused by reflux	Leakage

achalasia cardia[73]. Schlottmann *et al*[35] conducted a meta-analysis of 2000 cases of POEM reported in 21 articles worldwide and found that POEM is a relatively safe procedure with low morbidity and mortality rates.

Studies have shown that the POEM technique has certain drawbacks that can lead to GERD because POEM is not combined with anti-reflux surgery[39]. One study indicated that 41% of patients developed reflux esophagitis after POEM[74]. Similarly, a 2-year follow-up study showed that POEM was not inferior to LHM combined with Dor fundoplication in controlling the symptoms of 2-year achalasia cardia; however, compared with LHM patients, POEM patients were more prone to GERD. Nabi *et al*[75] found that GERD is very common after POEM; moreover, Barrett's esophagus - a potential long-term sequela of postoperative reflux - may also occur if the reflux persists long term. In addition, studies have shown that although POEM is a promising new therapy, most endoscopists worldwide have not yet mastered this technique owing to its high technical requirements and steep learning curve. POEM can also be challenging[63].

It is important to note that long-term follow-up is necessary for patients with achalasia cardia who undergo POEM, which can be used to monitor clinical, radiological, and manometry therapy success; functional changes in GEJ; and pathological gastroesophageal reflux. The follow-up duration is usually 3-6 mo after discharge. The Eckardt score should be assessed, and endoscopy, manometry, and timed barium meal examinations should be performed. If necessary, esophageal dilation and a 24-h esophageal pH test may be performed[76].

Stent implantation: Self-expanding metal stents (SEMS) have long been used in the management of both benign and malignant diseases of the esophagus. Esophageal stent implantation is a technique that slowly expands the stent to a predetermined diameter, breaks the LES muscle fibers, and reshapes them to reduce LES pressure. Currently, temporary SEMS are mostly used for treatment[77].

Stenting therapy has been effective in nearly 100% of patients with achalasia for more than 8 years [78]. Stents are considered a safe and effective treatment because of their uniform dilating tension; however, they do not provide sustained symptom relief and are prone to complications, such as stent displacement, regurgitation, perforation, bleeding, and, most importantly, stent-induced tissue proliferation leading to new stenosis[27,78,79]. Currently, a biodegradable scaffold exists that can be used in the elderly; however, its efficacy requires further investigation.

Esophagectomy: Owing to the development of endoscopic technology and the maturity of minimally invasive surgical operations, esophagectomy has rarely been used. Patients with surgical failure and end-stage achalasia cardia can undergo esophagectomy. In 2018, the International Society for Esophageal Diseases guidelines recommended esophagectomy for patients with persistent or recurrent achalasia after minor invasive treatment failure and disease progression[7].

CONCLUSION

Achalasia is a relatively rare disease of esophageal motility. Its main clinical manifestations are dysphagia, reflux, chest pain, and weight loss; these may significantly reduce a patient's quality of life. The treatment of achalasia cardia mainly aims to relieve symptoms since the disease is incurable. POEM is expected to become the optimal means of treating achalasia cardia owing to its effectiveness and safety. Personalized treatment should be provided according to the clinical characteristics of each patient. Currently, clinical research on achalasia cardia suggests the possibility of infectious events related to certain genetic factors that trigger the autoimmune mechanism. However, further research is necessary in the related fields to explore optimal treatment plans.

FOOTNOTES

Author contributions: Li MY and Wang QH contribute equally to this work; Li MY, Wang QY, and Wang DY performed the majority of the writing, prepared the figures and tables; Chen RP performed data accusation and writing; Su XF provided the input in writing the paper; Wang QH and Wang DY designed the outline and coordinated the writing of the paper.

Conflict-of-interest statement: The authors declared that no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Ming-Yue Li 0000-0002-3585-6795; Qing-Hua Wang 0000-0003-4000-5415; Run-Peng Chen 0000-0003-3607-9892; Xiao-Fang Su 0000-0003-2436-7635; Dong-Yang Wang 0000-0001-5549-3437.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

REFERENCES

1 **Montoro-Huguet MA**. Dietary and Nutritional Support in Gastrointestinal Diseases of the Upper Gastrointestinal Tract (I): Esophagus. *Nutrients* 2022; **14** [PMID: 36432505 DOI: 10.3390/nu14224819]
2 **Savarino E**, Bhatia S, Roman S, Sifrim D, Tack J, Thompson SK, Gyawali CP. Achalasia. *Nat Rev Dis Primers* 2022; **8**: 28 [PMID: 35513420 DOI: 10.1038/s41572-022-00356-8]
3 **Oude Nijhuis RAB**, Zaninotto G, Roman S, Boeckxstaens GE, Fockens P, Langendam MW, Plumb AA, Smout A, Targarona EM, Trukhmanov AS, Weusten B, Bredenoord AJ. European guidelines on achalasia: United European Gastroenterology and European Society of Neurogastroenterology and Motility recommendations. *United European Gastroenterol J* 2020; **8**: 13-33 [PMID: 32213062 DOI: 10.1177/2050640620903213]
4 **Patel CK**, Kahrilas PJ, Hodge NB, Tsikretsis LE, Carlson DA, Pandolfino JE, Tétreault MP. RNA-sequencing reveals molecular and regional differences in the esophageal mucosa of achalasia patients. *Sci Rep* 2022; **12**: 20616 [PMID: 36450816 DOI: 10.1038/s41598-022-25103-7]
5 **Pomenti S**, Blackett JW, Jodorkovsky D. Achalasia: Diagnosis, Management and Surveillance. *Gastroenterol Clin North Am* 2021; **50**: 721-736 [PMID: 34717867 DOI: 10.1016/j.gtc.2021.07.001]
6 **Geiculescu I**, Dranove J, Cosper G, Edmondson AC, Morava-Kozicz E, Carter LB. A rare cause of infantile achalasia: GMPPA-congenital disorder of glycosylation with two novel compound heterozygous variants. *Am J Med Genet A* 2022; **188**: 2438-2442 [PMID: 35665995 DOI: 10.1002/ajmg.a.62859]
7 **Tustumi F**, de Sousa JHB, Dornelas NM, Rosa GM, Steinman M, Bianchi ET. The Mechanisms for the Association of Cancer and Esophageal Dysmotility Disorders. *Med Sci (Basel)* 2021; **9** [PMID: 34064058 DOI: 10.3390/medsci9020032]
8 **Gass JM**, Cron L, Mongelli F, Tartanus J, Angehrn FV, Neuschütz K, von Flüe M, Fourie L, Steinemann D, Bolli M. From laparoscopic to robotic-assisted Heller myotomy for achalasia in a single high-volume visceral surgery center: postoperative outcomes and quality of life. *BMC Surg* 2022; **22**: 391 [PMID: 36369034 DOI: 10.1186/s12893-022-01818-2]
9 **Jung HK**, Hong SJ, Lee OY, Pandolfino J, Park H, Miwa H, Ghoshal UC, Mahadeva S, Oshima T, Chen M, Chua ASB, Cho YK, Lee TH, Min YW, Park CH, Kwon JG, Park MI, Jung K, Park JK, Jung KW, Lim HC, Jung DH, Kim DH, Lim CH, Moon HS, Park JH, Choi SC, Suzuki H, Patcharatrakul T, Wu JCY, Lee KJ, Tanaka S, Siah KTH, Park KS, Kim SE; Korean Society of Neurogastroenterology and Motility. 2019 Seoul Consensus on Esophageal Achalasia Guidelines. *J Neurogastroenterol Motil* 2020; **26**: 180-203 [PMID: 32235027 DOI: 10.5056/jnm20014]
10 **Swanström LL**. Achalasia: treatment, current status and future advances. *Korean J Intern Med* 2019; **34**: 1173-1180 [PMID: 30866609 DOI: 10.3904/kjim.2018.439]
11 **van Hoeij FB**, Ponds FA, Smout AJ, Bredenoord AJ. Incidence and costs of achalasia in The Netherlands. *Neurogastroenterol Motil* 2018; **30** [PMID: 28836740 DOI: 10.1111/nmo.13195]
12 **Tebaibia A**, Boudjella MA, Boutarene D, Benmediouni F, Brahimi H, Oumnia N. Incidence, clinical features and para-clinical findings of achalasia in Algeria: Experience of 25 years. *World J Gastroenterol* 2016; **22**: 8615-8623 [PMID: 27784974 DOI: 10.3748/wjg.v22.i38.8615]
13 **Gaber CE**, Eluri S, Cotton CC, Strassle PD, Farrell TM, Lund JL, Dellon ES. Epidemiologic and Economic Burden of Achalasia in the United States. *Clin Gastroenterol Hepatol* 2022; **20**: 342-352.e5 [PMID: 33652152 DOI: 10.1016/j.cgh.2021.02.035]
14 **Tanaka S**, Abe H, Sato H, Shiwaku H, Minami H, Sato C, Ogawa R, Shimamura Y, Yokomichi H, Inoue H. Frequency and clinical characteristics of special types of achalasia in Japan: A large-scale, multicenter database study. *J Gastroenterol Hepatol* 2021; **36**: 2828-2833 [PMID: 34032322 DOI: 10.1111/jgh.15557]
15 **Coleman HG**, Gray RT, Lau KW, McCaughey C, Coyle PV, Murray LJ, Johnston BT. Socio-economic status and lifestyle

factors are associated with achalasia risk: A population-based case-control study. *World J Gastroenterol* 2016; **22**: 4002-4008 [PMID: 27099443 DOI: 10.3748/wjg.v22.i15.4002]

16 **Romero-Hernández F**, Furuzawa-Carballeda J, Hernández-Molina G, Alejandro-Medrano E, Núñez-Álvarez CA, Hernández-Ramírez DF, Azamar-Llamas D, Olivares-Martínez E, Breña B, Palacios A, Valdovinos MA, Coss-Adame E, Ramos-Ávalos B, Torres-Landa S, Hernández-Ávila AA, Flores-Nájera A, Torres-Villalobos G. Autoimmune comorbidity in achalasia patients. *J Gastroenterol Hepatol* 2018; **33**: 203-208 [PMID: 28568312 DOI: 10.1111/jgh.13839]

17 **Mota RCL**, de Moura EGH, de Moura DTH, Bernardo WM, de Moura ETH, Brunaldi VO, Sakai P, Thompson CC. Risk factors for gastroesophageal reflux after POEM for achalasia: a systematic review and meta-analysis. *Surg Endosc* 2021; **35**: 383-397 [PMID: 32206921 DOI: 10.1007/s00464-020-07412-y]

18 **de Moura ETH**, Jukemura J, Ribeiro IB, Farias GFA, de Almeida Delgado AA, Coutinho LMA, de Moura DTH, Aissar Sallum RA, Nasi A, Sánchez-Luna SA, Sakai P, de Moura EGH. Peroral endoscopic myotomy *vs* laparoscopic myotomy and partial fundoplication for esophageal achalasia: A single-center randomized controlled trial. *World J Gastroenterol* 2022; **28**: 4875-4889 [PMID: 36156932 DOI: 10.3748/wjg.v28.i33.4875]

19 **Hernández-Ramírez DF**, Olivares-Martínez E, Nuñez-Álvarez CA, Coss-Adame E, Valdovinos MA, López-Verdugo F, Furuzawa-Carballeda J, Torres-Villalobos G. Triosephosphate isomerase, carbonic anhydrase, and creatinine kinase-brain isoform are possible antigen targets in patients with achalasia. *Neurogastroenterol Motil* 2020; **32**: e13804 [PMID: 31991059 DOI: 10.1111/nmo.13804]

20 **Naik RD**, Vaezi MF, Gershon AA, Higginbotham T, Chen JJ, Flores E, Holzman M, Patel D, Gershon MD. Association of Achalasia With Active Varicella Zoster Virus Infection of the Esophagus. *Gastroenterology* 2021; **161**: 719-721.e2 [PMID: 33932481 DOI: 10.1053/j.gastro.2021.04.057]

21 **Ghisa M**, Laserra G, Marabotto E, Ziola S, Tolone S, de Bortoli N, Frazzoni M, Mauro A, Penagini R, Savarino V, Barberio B, Giannini EG, Zentilin P, Gyawali CP, Savarino E. Achalasia and Obstructive Motor Disorders Are Not Uncommon in Patients With Eosinophilic Esophagitis. *Clin Gastroenterol Hepatol* 2021; **19**: 1554-1563 [PMID: 32763482 DOI: 10.1016/j.cgh.2020.07.056]

22 **Nelson M**, Zhang X, Genta RM, Turner K, Podgaetz E, Paris S, Cardenas J, Gu J, Leeds S, Ward M, Nguyen A, Konda V, Furuta GT, Pan Z, Souza RF, Spechler SJ. Lower esophageal sphincter muscle of patients with achalasia exhibits profound mast cell degranulation. *Neurogastroenterol Motil* 2021; **33**: e14055 [PMID: 33280206 DOI: 10.1111/nmo.14055]

23 **Cools-Lartigue J**, Chang SY, Mckendy K, Mayrand S, Marcus V, Fried GM, Ferri LE. Pattern of esophageal eosinophilic infiltration in patients with achalasia and response to Heller myotomy and Dor fundoplication. *Dis Esophagus* 2013; **26**: 766-775 [PMID: 22891632 DOI: 10.1111/j.1442-2050.2012.01385.x]

24 **Schizas D**, Syllaios A, Vailas M, Sotiropoulou M, Triantafyllou T, Tsapralis D, Papanikolaou IS, Theodorou D. Eosinophilic Esophagitis and Achalasia: Two Distinct Nosologic Entities or a Possible Etiopathogenic Association? *Dig Dis* 2021; **39**: 553-560 [PMID: 33647902 DOI: 10.1159/000515520]

25 **Sara C**, Marcella P, Martina C, Marta A, Eleonora E, Giovanni A, Marco M, Paola DV, Domenico PG, Giovanni S. Clinical correlation and disease phenotype in patients with esophageal achalasia and comorbid autoimmune diseases. *Dis Esophagus* 2021; **34** [PMID: 32766709 DOI: 10.1093/dote/doaa072]

26 **Sudarshan M**, Raja S, Adhikari S, Murthy S, Thota P, Gabbard S, Ray M, Ahmad U, Sanaka M. Peroral endoscopic myotomy provides effective palliation in type III achalasia. *J Thorac Cardiovasc Surg* 2022; **163**: 512-519.e1 [PMID: 33741133 DOI: 10.1016/j.jtcvs.2021.01.128]

27 **Cappell MS**, Stavropoulos SN, Friedel D. Updated Systematic Review of Achalasia, with a Focus on POEM Therapy. *Dig Dis Sci* 2020; **65**: 38-65 [PMID: 31451984 DOI: 10.1007/s10620-019-05784-3]

28 **Arcerito M**, Jamal MM, Perez MG, Kaur H, Sundahl A, Moon JT. Esophageal Achalasia: From Laparoscopic to Robotic Heller Myotomy and Dor Fundoplication. *JSLS* 2022; **26** [PMID: 35967962 DOI: 10.4293/JSLS.2022.00027]

29 **Ates F**, Vaezi MF. The Pathogenesis and Management of Achalasia: Current Status and Future Directions. *Gut Liver* 2015; **9**: 449-463 [PMID: 26087861 DOI: 10.5009/gnl14446]

30 **Fabian E**, Eherer AJ, Lackner C, Urban C, Smolle-Juettner FM, Krejs GJ. Pseudoachalasia as First Manifestation of a Malignancy. *Dig Dis* 2019; **37**: 347-354 [PMID: 30602160 DOI: 10.1159/000495758]

31 **Uppal DS**, Wang AY. Update on the endoscopic treatments for achalasia. *World J Gastroenterol* 2016; **22**: 8670-8683 [PMID: 27818585 DOI: 10.3748/wjg.v22.i39.8670]

32 **Kato R**, Nakajima K, Takahashi T, Tanaka K, Miyazaki Y, Makino T, Kurokawa Y, Yamasaki M, Mori M, Doki Y. Validation of new Japanese classification system for esophageal achalasia. *Esophagus* 2019; **16**: 252-257 [PMID: 30771041 DOI: 10.1007/s10388-019-00658-z]

33 **Li HK**, Linghu EQ. New endoscopic classification of achalasia for selection of candidates for peroral endoscopic myotomy. *World J Gastroenterol* 2013; **19**: 556-560 [PMID: 23382636 DOI: 10.3748/wjg.v19.i4.556]

34 **Mari A**, Abu Baker F, Pellicano R, Khoury T. Diagnosis and Management of Achalasia: Updates of the Last Two Years. *J Clin Med* 2021; **10** [PMID: 34441901 DOI: 10.3390/jcm10163607]

35 **Schlottmann F**, Herbella F, Allaix ME, Patti MG. Modern management of esophageal achalasia: From pathophysiology to treatment. *Curr Probl Surg* 2018; **55**: 10-37 [PMID: 29548347 DOI: 10.1067/j.cpsurg.2018.01.001]

36 **Harvey PR**, Thomas T, Chandan JS, Mytton J, Coupland B, Bhala N, Evison F, Patel P, Nirantharakumar K, Trudgill NJ. Incidence, morbidity and mortality of patients with achalasia in England: findings from a study of nationwide hospital and primary care data. *Gut* 2019; **68**: 790-795 [PMID: 29925629 DOI: 10.1136/gutjnl-2018-316089]

37 **Blaney H**, Agrawal N, Ashfaq S, Naumann C. Achalasia Revealed by Respiratory Failure and Hemodynamic Instability. *ACG Case Rep J* 2020; **7**: e00298 [PMID: 32309492 DOI: 10.14309/crj.0000000000000298]

38 **Tashiro J**, Petrosyan M, Kane TD. Current management of pediatric achalasia. *Transl Gastroenterol Hepatol* 2021; **6**: 33 [PMID: 34423154 DOI: 10.21037/tgh-20-215]

39 **Chadalavada P**, Thota PN, Raja S, Sanaka MR. Peroral Endoscopic Myotomy as a Novel Treatment for Achalasia: Patient Selection and Perspectives. *Clin Exp Gastroenterol* 2020; **13**: 485-495 [PMID: 33173323 DOI: 10.2147/CEG.S230436]

40 **Ren Y**, Tang X, Chen Y, Chen F, Zou Y, Deng Z, Wu J, Li Y, Huang S, Jiang B, Gong W. Pre-treatment Eckardt score is a

simple factor for predicting one-year peroral endoscopic myotomy failure in patients with achalasia. *Surg Endosc* 2017; **31**: 3234-3241 [PMID: 27864723 DOI: 10.1007/s00464-016-5352-5]

41 **Tuason J**, Inoue H. Current status of achalasia management: a review on diagnosis and treatment. *J Gastroenterol* 2017; **52**: 401-406 [PMID: 28188367 DOI: 10.1007/s00535-017-1314-5]

42 **Feng J**, Ali RW, Hao JY, Kong GX, Yang LH, Huang XJ. Peroral endoscopic myotomy for esophageal motility disorders. *Esophagus* 2020; **17**: 11-18 [PMID: 31606768 DOI: 10.1007/s10388-019-00693-w]

43 **Jung KW**. [Chicago Classification ver. 4.0: Diagnosis of Achalasia and Esophagogastric Junction Outflow Obstruction]. *Korean J Gastroenterol* 2022; **79**: 61-65 [PMID: 35232920 DOI: 10.4166/kjg.2022.017]

44 **Gyawali CP**, Penagini R. Clinical usefulness of esophageal high resolution manometry and adjunctive tests: An update. *Dig Liver Dis* 2021; **53**: 1373-1380 [PMID: 33994122 DOI: 10.1016/j.dld.2021.04.007]

45 **Sato H**, Takahashi K, Mizuno KI, Hashimoto S, Yokoyama J, Terai S. A clinical study of peroral endoscopic myotomy reveals that impaired lower esophageal sphincter relaxation in achalasia is not only defined by high-resolution manometry. *PLoS One* 2018; **13**: e0195423 [PMID: 29608597 DOI: 10.1371/journal.pone.0195423]

46 **Rassoul Abu-Nuwar M**, Eriksson SE, Sarici IS, Zheng P, Hoppo T, Jobe BA, Ayazi S. GERD after Peroral Endoscopic Myotomy: Assessment of Incidence and Predisposing Factors. *J Am Coll Surg* 2023; **236**: 58-70 [PMID: 36519909 DOI: 10.1097/XCS.0000000000000448]

47 **Sanaka MR**, Hayat U, Thota PN, Jegadeesan R, Ray M, Gabbard SL, Wadhwa N, Lopez R, Baker ME, Murthy S, Raja S. Efficacy of peroral endoscopic myotomy *vs* other achalasia treatments in improving esophageal function. *World J Gastroenterol* 2016; **22**: 4918-4925 [PMID: 27239118 DOI: 10.3748/wjg.v22.i20.4918]

48 **Riccio F**, Costantini M, Salvador R. Esophageal Achalasia: Diagnostic Evaluation. *World J Surg* 2022; **46**: 1516-1521 [PMID: 35195753 DOI: 10.1007/s00268-022-06483-3]

49 **Ochuba O**, Ruo SW, Alkayyali T, Sandhu JK, Waqar A, Jain A, Joseph C, Srivastava K, Poudel S. Endoscopic Surveillance in Idiopathic Achalasia. *Cureus* 2021; **13**: e17436 [PMID: 34513522 DOI: 10.7759/cureus.17436]

50 **Gomi K**, Inoue H, Ikeda H, Bechara R, Sato C, Ito H, Onimaru M, Kitamura Y, Suzuki M, Nakamura J, Hata Y, Maruyama S, Sumi K, Takahashi H. New endoscopic classification of the cardiac orifice in esophageal achalasia: Champagne glass sign. *Dig Endosc* 2016; **28**: 645-649 [PMID: 26969481 DOI: 10.1111/den.12642]

51 **Hoshikawa Y**, Hoshino S, Kawami N, Tanabe T, Hanada Y, Takenouchi N, Goto O, Kaise M, Iwakiri K. Possible new endoscopic finding in patients with achalasia: "Gingko leaf sign". *Esophagus* 2020; **17**: 208-213 [PMID: 31227944 DOI: 10.1007/s10388-019-00684-x]

52 **Sanagapalli S**, Plumb A, Sweis R. Timed barium swallow: Esophageal stasis varies markedly across subtypes of esophagogastric junction obstruction. *Neurogastroenterol Motil* 2022; **34**: e14322 [PMID: 35072303 DOI: 10.1111/nmo.14322]

53 **Holmstrom AL**, Campagna RJ, Carlson DA, Pandolfino JE, Soper NJ, Hungness ES, Teitelbaum EN. Comparison of preoperative, intraoperative, and follow-up functional luminal imaging probe measurements in patients undergoing myotomy for achalasia. *Gastrointest Endosc* 2021; **94**: 509-514 [PMID: 33662363 DOI: 10.1016/j.gie.2021.02.031]

54 **Pannala R**, Krishnan K, Watson RR, Vela MF, Abu Dayyeh BK, Bhatt A, Bhutani MS, Bucobo JC, Chandrasekhara V, Copland AP, Jirapinyo P, Kumta NA, Law RJ, Maple JT, Melson J, Parsi MA, Rahimi EF, Saumoy M, Sethi A, Trikudanathan G, Trindade AJ, Yang J, Lichtenstein DR. Devices for esophageal function testing. *VideoGIE* 2022; **7**: 1-20 [PMID: 35059533 DOI: 10.1016/j.vgie.2021.08.012]

55 **Jacobs JW Jr**, Richter JE. Functional lumen imaging probe and Heller myotomy: solves the dysphagia issue, but the resulting GERD is still a mystery. *Gastrointest Endosc* 2021; **94**: 515-516 [PMID: 34412826 DOI: 10.1016/j.gie.2021.03.931]

56 **Ren Z**, Zhong Y, Zhou P, Xu M, Cai M, Li L, Shi Q, Yao L. Perioperative management and treatment for complications during and after peroral endoscopic myotomy (POEM) for esophageal achalasia (EA) (data from 119 cases). *Surg Endosc* 2012; **26**: 3267-3272 [PMID: 22609984 DOI: 10.1007/s00464-012-2336-y]

57 **Carlson DA**, Lin Z, Kahrilas PJ, Sternbach J, Donnan EN, Friesen L, Listernick Z, Mogni B, Pandolfino JE. The Functional Lumen Imaging Probe Detects Esophageal Contractility Not Observed With Manometry in Patients With Achalasia. *Gastroenterology* 2015; **149**: 1742-1751 [PMID: 26278501 DOI: 10.1053/j.gastro.2015.08.005]

58 **Jovanovic S**, Djuric-Stefanovic A, Simić A, Skrobic O, Pesko P. Value of Multidetector Computed Tomography in the Assessment of Achalasia Subtypes and Detection of Pulmonary and Thoracic Complications. *Med Princ Pract* 2019; **28**: 539-546 [PMID: 31112951 DOI: 10.1159/000501057]

59 **Chou DW**, Wu MH. Early detection of recent onset achalasia from a chest radiograph. *Intern Emerg Med* 2017; **12**: 407-408 [PMID: 27283407 DOI: 10.1007/s11739-016-1485-8]

60 **Licurse MY**, Levine MS, Torigian DA, Barbosa EM Jr. Utility of chest CT for differentiating primary and secondary achalasia. *Clin Radiol* 2014; **69**: 1019-1026 [PMID: 24957858 DOI: 10.1016/j.crad.2014.05.005]

61 **Yamaguchi D**, Tsuruoka N, Sakata Y, Shimoda R, Fujimoto K, Iwakiri R. Safety and efficacy of botulinum toxin injection therapy for esophageal achalasia in Japan. *J Clin Biochem Nutr* 2015; **57**: 239-243 [PMID: 26566311 DOI: 10.3164/jcbn.15-47]

62 **Tang YF**, Jin P, Tao YR, Xie H, Wang X, Yu D, Tang S, Sheng JQ. Comparison of fully coated anti-reflux metal stenting and per-oral endoscopic myotomy in patients with achalasia: a propensity score-matched retrospective study. *BMC Gastroenterol* 2022; **22**: 253 [PMID: 35585499 DOI: 10.1186/s12876-022-02282-1]

63 **Chuah SK**, Chiu CH, Tai WC, Lee JH, Lu HI, Changchien CS, Tseng PH, Wu KL. Current status in the treatment options for esophageal achalasia. *World J Gastroenterol* 2013; **19**: 5421-5429 [PMID: 24023484 DOI: 10.3748/wjg.v19.i33.5421]

64 **Moonen A**, Annese V, Belmans A, Bredenoord AJ, Bruley des Varannes S, Costantini M, Dousset B, Elizalde JI, Fumagalli U, Gaudric M, Merla A, Smout AJ, Tack J, Zaninotto G, Busch OR, Boeckxstaens GE. Long-term results of the European achalasia trial: a multicentre randomised controlled trial comparing pneumatic dilation versus laparoscopic Heller myotomy. *Gut* 2016; **65**: 732-739 [PMID: 26614104 DOI: 10.1136/gutjnl-2015-310602]

65 **Jung HE**, Lee JS, Lee TH, Kim JN, Hong SJ, Kim JO, Kim HG, Jeon SR, Cho JY. Long-term outcomes of balloon dilation versus botulinum toxin injection in patients with primary achalasia. *Korean J Intern Med* 2014; **29**: 738-745 [PMID:

25378972 DOI: 10.3904/kjim.2014.29.6.738]
66 **Arora Z**, Thota PN, Sanaka MR. Achalasia: current therapeutic options. *Ther Adv Chronic Dis* 2017; **8**: 101-108 [PMID: 28717439 DOI: 10.1177/2040622317710010]
67 **Richter JE**, Boeckxstaens GE. Management of achalasia: surgery or pneumatic dilation. *Gut* 2011; **60**: 869-876 [PMID: 21303915 DOI: 10.1136/gut.2010.212423]
68 **Ali AB**, Khan NA, Nguyen DT, Chihara R, Chan EY, Graviss EA, Dunkin BJ, Kim MP. Robotic and per-oral endoscopic myotomy have fewer technical complications compared to laparoscopic Heller myotomy. *Surg Endosc* 2020; **34**: 3191-3196 [PMID: 31482358 DOI: 10.1007/s00464-019-07093-2]
69 **Abbas AE**. Commentary: Peroral endoscopic myotomy, the poetic remedy for type III achalasia. *J Thorac Cardiovasc Surg* 2022; **163**: 522-523 [PMID: 33838912 DOI: 10.1016/j.jtcvs.2021.03.038]
70 **Chen H**, Calderon LF, Shah R, Zheng W, Xia L, Wang W, Li L, Li B, Xue Y, Keilin S, Cai Q. Simultaneous Examination of Eosinophil Infiltration in Esophageal Mucosa and Muscle in Patients with Achalasia: Direct Biopsy of the Esophageal Muscle at Per-oral Endoscopic Myotomy. *Dig Dis Sci* 2022; **67**: 170-176 [PMID: 33502676 DOI: 10.1007/s10620-021-06827-4]
71 **Wang X**, Tan Y, Lv L, Zhu H, Chu Y, Li C, Liu D. Peroral endoscopic myotomy versus pneumatic dilation for achalasia in patients aged ≥ 65 years. *Rev Esp Enferm Dig* 2016; **108**: 637-641 [PMID: 27649684 DOI: 10.17235/reed.2016.4488/2016]
72 **Ponds FA**, Fockens P, Lei A, Neuhaus H, Beyna T, Kandler J, Frieling T, Chiu PWY, Wu JCY, Wong VWY, Costamagna G, Familiari P, Kahrilas PJ, Pandolfino JE, Smout AJPM, Bredenoord AJ. Effect of Peroral Endoscopic Myotomy vs Pneumatic Dilation on Symptom Severity and Treatment Outcomes Among Treatment-Naive Patients With Achalasia: A Randomized Clinical Trial. *JAMA* 2019; **322**: 134-144 [PMID: 31287522 DOI: 10.1001/jama.2019.8859]
73 **Markar S**, Zaninotto G. Management of oesophageal achalasia in POEM (and GOOGLE) times. *Br J Surg* 2022; **109**: 150-151 [PMID: 34910114 DOI: 10.1093/bjs/znab420]
74 **Raja S**, Murthy SC, Tang A, Siddiqui HU, Parikh MP, Ahmad U, Gabbard S, Thota P, Ray MN, Wadhwa N, Sanaka MR. Per oral endoscopic myotomy: Another tool in the toolbox. *J Thorac Cardiovasc Surg* 2019; **158**: 945-951 [PMID: 31213374 DOI: 10.1016/j.jtcvs.2018.11.132]
75 **Nabi Z**, Chavan R, Basha J, Sekharan A, Reddy DN. Peroral endoscopic myotomy and gastroesophageal reflux: A word of caution! *Gastrointest Endosc* 2021; **94**: 1009-1010 [PMID: 34242643 DOI: 10.1016/j.gie.2021.07.001]
76 **Bechara R**, Ikeda H, Inoue H. Peroral endoscopic myotomy: an evolving treatment for achalasia. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 410-426 [PMID: 26035678 DOI: 10.1038/nrgastro.2015.87]
77 **Law R**, Prabhu A, Fujii-Lau L, Shannon C, Singh S. Stent migration following endoscopic suture fixation of esophageal self-expandable metal stents: a systematic review and meta-analysis. *Surg Endosc* 2018; **32**: 675-681 [PMID: 28726147 DOI: 10.1007/s00464-017-5720-9]
78 **Cheng YS**, Ma F, Li YD, Chen NW, Chen WX, Zhao JG, Wu CG. Temporary self-expanding metallic stents for achalasia: a prospective study with a long-term follow-up. *World J Gastroenterol* 2010; **16**: 5111-5117 [PMID: 20976849 DOI: 10.3748/wjg.v16.i40.5111]
79 **El Abiad R**, Khashab MA. Role of biodegradable stents in octogenarians with achalasia. *Endosc Int Open* 2021; **9**: E767-E769 [PMID: 34080587 DOI: 10.1055/a-1393-5665]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1753-1760

DOI: 10.12998/wjcc.v11.i8.1753

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Patients with hepatocellular carcinoma that die during the first year of liver transplantation have high blood sFasL concentrations

Leonardo Lorente, Sergio T Rodriguez, Pablo Sanz, Agustín F González-Rivero, Antonia Pérez-Cejas, Javier Padilla, Dácil Díaz, Antonio González, María M Martín, Alejandro Jiménez, Purificación Cerro, Julián Portero, Manuel A Barrera

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Cheng HW, China; Li ZZ, China

Received: December 13, 2022
Peer-review started: December 13, 2022
First decision: January 19, 2023
Revised: January 20, 2023
Accepted: February 21, 2023
Article in press: February 21, 2023
Published online: March 16, 2023

Leonardo Lorente, Intensive Care Unit, Hospital Universitario de Canarias, La Laguna 38320, Spain

Sergio T Rodriguez, María M Martín, Intensive Care Unit, Hospital Universitario Nuestra Señora Candelaria, Santa Cruz Tenerife 38010, Spain

Pablo Sanz, Javier Padilla, Manuel A Barrera, Department of Surgery, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz Tenerife 38010, Spain

Agustín F González-Rivero, Antonia Pérez-Cejas, Department of Laboratory, Hospital Universitario de Canarias, La Laguna 38320, Spain

Dácil Díaz, Antonio González, Department of Digestive, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz Tenerife 38010, Spain

Alejandro Jiménez, Research Unit, Hospital Universitario de Canarias, La Laguna 38320, Spain

Purificación Cerro, Transplant Unit, Hospital Universitario Nuestra Señora Candelaria, Santa Cruz Tenerife 38010, Spain

Julián Portero, Department of Radiology, Hospital Universitario Nuestra Señora Candelaria, Santa Cruz Tenerife 38010, Spain

Corresponding author: Leonardo Lorente, MD, PhD, Attending Doctor, Medical Assistant, Intensive Care Unit, Hospital Universitario de Canarias, Ofra, La Laguna 38320, Spain.
lorentemartin@msn.com

Abstract

BACKGROUND

Fas ligand (FasL) is one ligand that activates extrinsic apoptosis pathway. High expression in lymphocytes of FasL have been found in patients with acute rejection of liver transplantation (LT). No high blood concentrations of soluble FasL (sFasL) have been found in patients with acute LT rejection; however, the samples size of those studies was small.

AIM

To determine whether patients with hepatocellular carcinoma (HCC) that dead during the first year of LT have higher blood sFasL concentrations previously to LT that those who that remain alive in a study of higher sample size.

METHODS

Patients underwent LT due to HCC were included in this retrospective study. Serum sFasL levels prior to LT were measured and one-year LT mortality was registered.

RESULTS

Non-surviving patients (n = 14) showed higher serum sFasL levels [477 (269-496) *vs* 85 (44-382) pg/mL; P < 0.001] than surviving patients (n = 113). Serum sFasL levels (pg/mL) were associated with mortality (OR = 1.006; 95%CI = 1.003-1.010; P = 0.001) independently of age of LT donor in the logistic regression analysis.

CONCLUSION

We report for the first time that HCC patients who die within the first year of HT have higher blood sFasL concentrations prior to HT than those who remain alive.

Key Words: sFasL; Hepatocellular carcinoma; Liver transplantation; Mortality; Outcome

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Fas ligand (FasL) is one of the main ligands that activate apoptosis *via* the extrinsic pathway. Elevated blood concentrations of soluble FasL (sFasL) have not been found in patients with acute liver transplant (LT) rejection; however, the sample sizes of those studies were small. We found in this retrospective study of 127 patients with hepatocellular carcinoma underwent to LT that patients that die during the first year of LT have higher blood sFasL concentrations previously to LT than those who that remain alive. The beneficial results of blockade of the Fas system in animal models could motivate its investigation in these patients.

Citation: Lorente L, Rodriguez ST, Sanz P, González-Rivero AF, Pérez-Cejas A, Padilla J, Díaz D, González A, Martín MM, Jiménez A, Cerro P, Portero J, Barrera MA. Patients with hepatocellular carcinoma that die during the first year of liver transplantation have high blood sFasL concentrations. *World J Clin Cases* 2023; 11(8): 1753-1760

URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1753.htm

DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1753

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies with the highest attributable mortality[1-4]. Liver transplantation (LT) in some HCC patients is the treatment of choice, as it removes the liver tumour and treats liver failure[5-8].

Apoptotic cell death occurs in healthy subjects (for morphogenesis and tissue remodelling) and in different diseases such as liver diseases[9-13]. Apoptosis can be activated by so-called extrinsic and intrinsic pathways. Extrinsic apoptosis pathway is activated when binding a protein of ligands superfamily of the tumour necrosis factor (TNFSF) to its receptor of membrane receptors superfamily of the tumour necrosis factor (TNFRSF). Fas ligand (FasL) is a major ligand for TNFSF, and Fas is a major receptor for TNFRSF. Upon binding of FasL to Fas, a death signal appears that will activate caspase 8. Subsequently, caspase 8 will produce caspase-3 activation, leading to cell death[9-13].

Little data has been reported on the FasL/Fas system in LT patients. Higher lymphocyte expression of Fas[14,15] and FasL[15] has been found in patients with acute LT rejection than in patients without rejection. In addition, higher blood sFas levels have been found in patients with acute LT rejection than in patients without rejection[16-18]; however, two of these studies found no difference in blood sFasL levels between patients with and without LT rejection[16,17] and one study did not report blood sFasL levels[18]. Finally, another study found no differences in sFas and sFasL blood levels between patients with and without LT rejection[19]. However, the sample size in all these studies was small (less than 70 patients undergoing LT). Therefore, we aimed to determine whether HCC patients who die during the first year of LT have higher pre-LT blood sFasL concentrations than those who remain alive in a larger sample size study.

MATERIALS AND METHODS

Design and patients

Inclusion criteria were the following: Patients undergoing donor LT in brain death by HCC. Patients were recluted at the Hospital Universitario Nuestra Señora de Candelaria (Santa Cruz de Tenerife, Spain). Recruitment period was from January 1996 to May 2017 by HCC. No exclusion criteria were considered. This retrospective study was performed with Institutional Ethic Review Board approval and with informed (and written) consent of patients (or a legal guardian). Formently, we determined DNA and RNA oxidative damage[20] in some of those LT patients. Now, in this research, we have measured serum levels of sFasL concentrations.

Variables recorded

Variables recorded for each patient were serum alpha-fetoprotein (AFP) levels, Child-Pugh score[21], nodule size, within Milan criteria[22] pre- and post-LT, degree of tumour differentiation, age of liver donor, model for end-stage liver disease (MELD) score[23] by liver function, liver recipient age, sex, infiltration, macrovascular and microvascular invasion, LT technique, portal hypertension, multinodular tumour, pre-LT treatment and 1-year survival from LT (our endpoint study).

Determination of serum levels of sFasL

Analyses to measure serum FasL concentrations were performed at the Laboratory Department of the Hospital Universitario de Canarias (Tenerife, Spain) by enzyme-linked immunosorbent assay. The human FasL ELISA kit (Elabscience, Houston, TX, United States) with intra-assay and inter-assay coefficients of variation of less than 6% and a limit of detection of 15.6 pg/mL was used.

Statistical methods

We employed χ^2 test to compare categorical variables (reported as frequencies and percentages) and Mann-Whitney test to compare continuous variables (reported as medians and interquartile ranges). Areceiver operating characteristic (ROC) curve was employed to test the predictive capability of LT 1-year mortality with pre-LT serum sFasL levels. Kaplan-Meier survival curves were constructed using 1-year LT survival and pre-LT serum sFasL levels below/above 190 pg/mL (this cut-off point was selected based on Youden-Jindex). We employed logistic regression analysis to determine a possible association between pre-LT serum sFasL levels and mortality at 1-year post-LT, controlling for LT donor age. Statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL, United States) and MedCal 15.2.1 (Ostend, Belgium).

RESULTS

A total of 127 patients were included in the study, 113 (89.0%) of them remain alive at one year post-LT and 14 (11.0%) dead during the first year of LT. Their mean age was 51 ± 17 years, 109 (85.8%) were males and 18 (14.2%) were females. Of them, 121 (95.3%) were inside Milan criteria previously to LT and 107 (84.3%) after LT, 41 had (32.3%) infiltration, 29 (22.8%) microvascular invasion, 87 (68.5%) portal hypertension, 44 (34.6%) multinodular tumor, and 7 (5.5%) macrovascular invasion.

We found that 1-year LT survivors revealed younger LT donors (P = 0.049) and lower serum sFasL levels (P < 0.001) than non-surviving ones (Table 1). However, serum AFP levels, Child-Pugh score, nodule size, fulfilment of Milan criteria before and after HT, degree of tumour differentiation, MELD score by liver function, age of the liver recipient, sex, infiltration, macrovascular invasion, microvascular invasion, HT technique, portal hypertension, multinodular tumour and pre-HT treatment showed no statistical difference in the comparison between surviving and non-surviving patients (Table 1).

Serum sFasL levels (pg/mL) were associated mortality (Odds Ratio = 1.006; 95%CI = 1.003-1.010; P = 0.001) independently of LT donor age in logistic regression analysis (Table 2). We found an area under the curve of 84% (95%CI = 75%-93%; P < 0.001) for prediction of mortality by serum sFasL levels (Figure 1). Kaplan-Meier analysis showed that patients with serum sFasL concentrations higher than 190 pg/mL had an increased risk of death (Hazard ratio = 13.5; 95%CI = 4.5-40.7); P < 0.001) (Figure 2).

We found a positive correlation between serum levels of sFasL and AFP (rho = 0.73; P < 0.001). However, we no found significant differences in serum sFasL levels related to LT recipient age (P = 0.36), sex (P = 0.27), MELD score (P = 0.12), Child–Pugh score (P = 0.48), portal hypertension (P = 0.82), multinodular tumor (P = 0.16), macrovascular invasion (P = 0.48), degree of tumor differentiation (P = 0.22), microvascular invasion (P = 0.19), serun protein concentration (P = 0.67), serum albumin concentration (P = 0.07) and serum creatinine concentration (P = 0.96).

Table 1 Clinical and biochemical characteristics of one-year liver transplantation survivor and non-survivor patients

	1 yr survivor patients, (*n* = 113)	1 yr non-survivor patients, (*n* = 14)	*P* value
Serum sFasL (pg/mL) - median (p 25-75)	85 (44-382)	477 (269-496)	< 0.001
Age of liver donor (yr) - median (p 25-75)	52 (35-64)	62 (49-73)	0.049
Age of liver recipient (yr) - median (p 25-75)	59 (52-62)	56 (53-62)	0.88
Serum alpha-fetoprotein (ng/dL) - median (p 25-75)	8 (4-37)	13 (5-180)	0.36
MELD score - median (p 25-75)	15 (12-18)	16 (14-18)	0.78
Nodules size (cm) - median (p 25-75)	3.0 (2.0-3.5)	2.8 (1.6-4.3)	0.94
Protein (g/dL) - median (p 25-75)	6.7 (6.0-7.1)	6.7 (5.7-7.7)	0.83
Leukocytes (count/mm^3) - median (p 25-75)	4800 (3590-6200)	4940 (3490-7920)	0.60
Albumin (g/dL) - median (p 25-75)	3.3 (2.9-4.1)	3.3 (2.9-4.2)	0.91
Creatinine (mg/dL) - median (p 25-75)	0.9 (0.8-1.1)	1.0 (0.8-1.1)	0.43
BMI (kg/m^2) - median (p 25-75)	27.6 (24.5-30.0)	28.1 (23.1-31.1)	0.80
Gender female - *n* (%)	18 (15.9)	0	0.11
Portal hypertension - *n* (%)	77 (68.1)	10 (71.4)	0.80
Child-Pugh score - *n* (%)			0.47
A	53 (46.9)	9 (64.3)	
B	34 (30.1)	3 (21.4)	
C	26 (23.0)	2 (14.3)	
Multinodular tumor- *n* (%)	33 (29.2)	5 (35.7)	0.62
Macrovascular invasion - *n* (%)	7 (6.2)	0	0.34
Microvascular invasion - *n* (%)	26 (23.0)	3 (21.4)	0.89
Infiltration - *n* (%)	38 (33.6)	3 (21.4)	0.36
Inside Milan criteria previously to LT - *n* (%)	108 (95.6)	13 (92.9)	0.65
Inside Milan criteria after LT - *n* (%)	97 (85.8)	10 (71.4)	0.16
Treatment previously to LT - *n* (%)	62 (54.9)	10 (71.4)	0.24
Transplantation technique – *n* (%)			0.63
By-pass	41 (36.3)	6 (42.9)	
Piggy back	72 (63.7)	8 (57.1)	
Degree of tumor differentiation – *n* (%)			0.51
Well	83 (73.5)	11 (78.6)	
Moderate	27 (23.9)	2 (14.3)	
Poor	3 (2.7)	1 (7.1)	

MELD: Model for end-stage liver disease; BMI: Body mass index; sFasL: Soluble FasL.

DISCUSSION

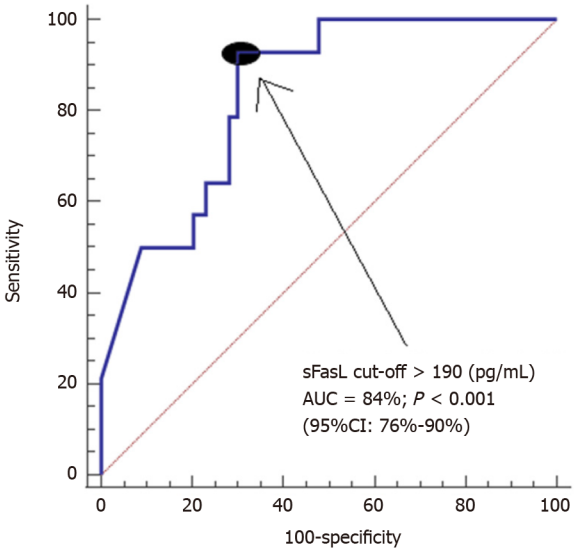
The main novel finding that showed our study was that association between elevated serum sFasL levels prior to LT and increased risk of death during the first year after LT. The 1-year survival rate from LT in our series (89%) is similar to those reported in other series (75%-95%)[24-28]. Several factors associated with worse prognosis in HCC patients undergoing LT have been reported (tumour size, outside Milan criteria, hepatic microinvasion, tumour number, degree of differentiation, vascular infiltration, serum AFP levels, and invasion)[29]; however, only higher serum sFasL levels and age of the LT donor were factors associated with worse prognosis in our series.

Previously, higher lymphocyte expression of FasL[15] has been found in patients with acute LT rejection than in patients without rejection. Furthermore, three studies found no difference in blood sFasL levels between patients with and without LT rejection[16,17,19]. Therefore, the association

Table 2 Logistic regression analysis for the variables associated with one-year liver transplantation mortality

	Odds ratio	95% confidence interval	*P* value
Age of liver donor (age)	1.044	1.001-1.088	0.045
Serum sFasL levels (pg/mL)	1.006	1.003-1.010	0.001

sFasL: Soluble FasL.



DOI: 10.12998/wjcc.v11.i8.1753 **Copyright** ©The Author(s) 2023.

Figure 1 Receiver operation characteristic of serum soluble FasL levels previously to liver transplantation due to hepatocellular carcinoma for the prediction of one-year liver transplantation mortality. Area under curve of serum soluble FasL (sFasL) levels and sensitivity/specificity of serum sFasL levels > 190 pg/mL are reported. AUC: Area under curve; sFasL: Soluble FasL.

between elevated serum sFasL levels before LT and death is a new finding of our study. Possibly the larger sample size (127 patients) of our study compared to that of previous studies (less than 70 patients) contributes to this new finding.

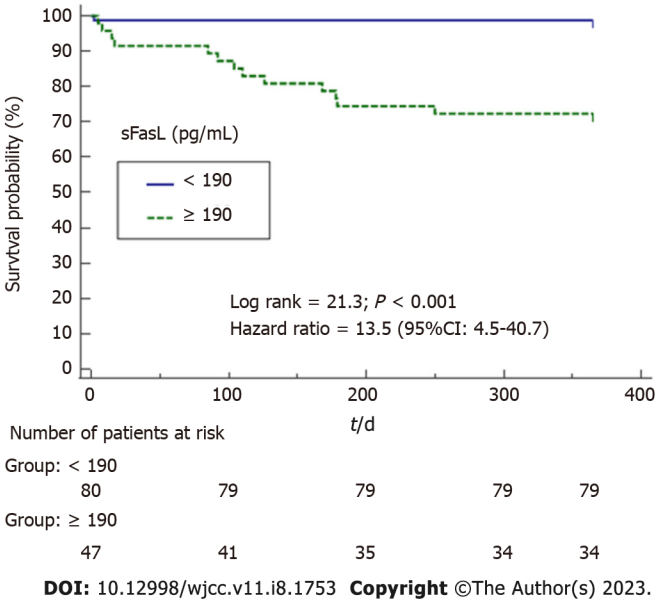
In addition, we also found a positive association between serum levels of sFasL and AFP, and that association is according to the findings of one previous study[30]; however, we did not found an association between serum sFasL levels and other variables.

FasL is one of TNFSF that activates apoptosis extrinsic pathway when binding to its receptor Fas. Due to this binding, a death signal is generated (which will activate caspase 8). Subsequently, caspase 8 will lead to the activation of caspase 3 (responsible for cell death)[9-13]. Therefore, we think that the findings of our study that non-surviving patients showed higher serum sFasL levels compared to surviving ones could be related to a higher activation of apoptosis. Although limitations of our study were the absence of data on apoptosis in liver tissue and data on blood sFasL levels during patient follow-up. Another limitation was the relatively low sample size of our study to include more variables in the regression model.

In rodent animal models of hepatic ischaemia-reperfusion injury, administration of Fas and/or FasL-blocking agents reduced hepatic caspase-3 activity and hepatocyte apoptosis, and increased animal survival[31-33]. We think that the findings from our study with patients undergoing HT due to HCC could encourage research to clarify the potential role of serum sFasL levels in estimating the prognosis of HT patients in a larger series. In addition, the findings from rodent animal models could encourage research to clarify the potential role of administration of Fas/FasL-blocking agents in improving the prognosis of these patients.

CONCLUSION

We report for the first time that HCC patients who die during the first year of LT have higher blood sFasL concentrations prior to LT than those who remain alive.



DOI: 10.12998/wjcc.v11.i8.1753 **Copyright** ©The Author(s) 2023.

Figure 2 Kaplan-Meier survival analysis using mortality (as dependent variable) during first year of liver transplantation due to hepatocellular carcinoma and serum soluble FasL levels previously to liver transplantation lower/higher than 190 pg/mL (as independent variable). Both survival curves were compared by log rank and hazard ratio. sFasL: Soluble FasL.

ARTICLE HIGHLIGHTS

Research background

Fas ligand (FasL) is one ligands that activates extrinsic apoptosis pathway. High expression in lymphocytes of FasL have been found in patients with acute rejection of liver transplantation (LT).

Research motivation

No high blood concentrations of soluble FasL (sFasL) have been found in patients with acute LT rejection; however, the samples size of those studies was small.

Research objectives

To determine whether patients with hepatocellular carcinoma (HCC) that dead during the first year of LT have higher blood sFasL concentrations previously to LT that those who that remain alive in a study of higher sample size.

Research methods

Patients underwent LT due to HCC were included in this retrospective study. Serum sFasL levels prior to LT were measured and one-year LT mortality was registered.

Research results

Non-surviving patients (n = 14) showed higher serum sFasL levels [477 (269-496) *vs* 85 (44-382) pg/mL; P < 0.001] than surviving patients (n = 113). Serum sFasL levels (pg/mL) were associated with mortality (OR = 1.006; 95%CI = 1.003-1.010; P = 0.001) independently of LT donor in the logistic regression analysis.

Research conclusions

We report for the first time that HCC patients who die within the first year of HT have higher blood sFasL concentrations prior to HT than those who remain alive.

Research perspectives

The beneficial results of blockade of the Fas system in animal models could motivate its investigation in these patients.

FOOTNOTES

Author contributions: Lorente L was responsible of conceive, design and coordinate the study, made substantial contributions to acquisition of data, analysis and interpretation of data, and drafted the manuscript; Rodriguez ST, Sanz P, Padilla J, Díaz D, González A, Martín MM, Cerro P, Portero J and Barrera MA have made substantial contributions to acquisition of data and provided useful suggestions; González-Rivero AF and Pérez-Cejas A participated in blood determination levels; Jiménez A have made substantial contributions to analysis and interpretation of data; All authors read critically and approved the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Institutional review board statement: The Institutional Board of the Hospital Universitario Nuestra Señora de Candelaria (Santa Cruz de Tenerife, Spain) approved the study protocol.

Informed consent statement: The informed consent to participate in the study was signed by the patient or a family member.

Conflict-of-interest statement: There are no conflicts of interest to declare.

Data sharing statement: The datasets generated during the current study are available from the corresponding author on reasonable request.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Spain

ORCID number: Leonardo Lorente 0000-0003-4902-4065; Sergio T Rodriguez 0000-0003-1635-3604; Pablo Sanz 0000-0003-4770-0111; Agustín F González-Rivero 0000-0002-9712-6990; Antonia Pérez-Cejas 0000-0002-8267-4556; Javier Padilla 0000-0001-8103-7267; Dácil Díaz 0000-0002-8836-9771; Antonio González 0000-0002-4180-0376; María M Martín 0000-0003-0239-873X; Alejandro Jiménez 0000-0001-8732-2616; Purificación Cerro 0000-0002-1270-5046; Julián Portero 0000-0001-9619-197X; Manuel A Barrera 0000-0001-8216-6212.

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

REFERENCES

1 **Tümen D**, Heumann P, Gülow K, Demirci CN, Cosma LS, Müller M, Kandulski A. Pathogenesis and Current Treatment Strategies of Hepatocellular Carcinoma. *Biomedicines* 2022; **10** [PMID: 36551958 DOI: 10.3390/biomedicines10123202]
2 **Ince V**, Sahin TT, Akbulut S, Yilmaz S. Liver transplantation for hepatocellular carcinoma: Historical evolution of transplantation criteria. *World J Clin Cases* 2022; **10**: 10413-10427 [PMID: 36312504 DOI: 10.12998/wjcc.v10.i29.10413]
3 **Bzeizi KI**, Abdullah M, Vidyasagar K, Alqahthani SA, Broering D. Hepatocellular Carcinoma Recurrence and Mortality Rate Post Liver Transplantation: Meta-Analysis and Systematic Review of Real-World Evidence. *Cancers (Basel)* 2022; **14** [PMID: 36291898 DOI: 10.3390/cancers14205114]
4 **Vogel A**, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. *Lancet* 2022; **400**: 1345-1362 [PMID: 36084663 DOI: 10.1016/S0140-6736(22)01200-4]
5 **Bodzin AS**, Busuttil RW. Hepatocellular carcinoma: Advances in diagnosis, management, and long term outcome. *World J Hepatol* 2015; **7**: 1157-1167 [PMID: 26019732 DOI: 10.4254/wjh.v7.i9.1157]
6 **Toyoda H**, Kumada T, Tada T, Sone Y, Kaneoka Y, Maeda A. Tumor Markers for Hepatocellular Carcinoma: Simple and Significant Predictors of Outcome in Patients with HCC. *Liver Cancer* 2015; **4**: 126-136 [PMID: 26020034 DOI: 10.1159/000367735]
7 **Guerrero-Misas M**, Rodríguez-Perálvarez M, De la Mata M. Strategies to improve outcome of patients with hepatocellular carcinoma receiving a liver transplantation. *World J Hepatol* 2015; **7**: 649-661 [PMID: 25866602 DOI: 10.4254/wjh.v7.i4.649]
8 **Slotta JE**, Kollmar O, Ellenrieder V, Ghadimi BM, Homayounfar K. Hepatocellular carcinoma: Surgeon's view on latest findings and future perspectives. *World J Hepatol* 2015; **7**: 1168-1183 [PMID: 26019733 DOI: 10.4254/wjh.v7.i9.1168]
9 **Shojaie L**, Iorga A, Dara L. Cell Death in Liver Diseases: A Review. *Int J Mol Sci* 2020; **21** [PMID: 33353156 DOI: 10.3390/ijms21249682]
10 **Magusto J**, Majdi A, Gautheron J. [Cell death mechanisms in non-alcoholic steatohepatitis]. *Biol Aujourdhui* 2020; **214**: 1-13 [PMID: 32773025 DOI: 10.1051/jbio/2020002]
11 **García-Pras E**, Fernández-Iglesias A, Gracia-Sancho J, Pérez-Del-Pulgar S. Cell Death in Hepatocellular Carcinoma: Pathogenesis and Therapeutic Opportunities. *Cancers (Basel)* 2021; **14** [PMID: 35008212 DOI: 10.3390/cancers14010048]

12 **Chu Q**, Gu X, Zheng Q, Wang J, Zhu H. Mitochondrial Mechanisms of Apoptosis and Necroptosis in Liver Diseases. *Anal Cell Pathol (Amst)* 2021; **2021**: 8900122 [PMID: 34804779 DOI: 10.1155/2021/8900122]

13 **Gruevska A**, Moragrega ÁB, Cossarizza A, Esplugues JV, Blas-García A, Apostolova N. Apoptosis of Hepatocytes: Relevance for HIV-Infected Patients under Treatment. *Cells* 2021; **10** [PMID: 33669403 DOI: 10.3390/cells10020410]

14 **Boix F**, Millan O, San Segundo D, Mancebo E, Rimola A, Fabrega E, Fortuna V, Mrowiec A, Castro-Panete MJ, Peña Jde L, Llorente S, Minguela A, Bolarin JM, Paz-Artal E, Lopez-Hoyos M, Brunet M, Muro M. High expression of CD38, CD69, CD95 and CD154 biomarkers in cultured peripheral T lymphocytes correlates with an increased risk of acute rejection in liver allograft recipients. *Immunobiology* 2016; **221**: 595-603 [PMID: 26850323 DOI: 10.1016/j.imbio.2016.01.008]

15 **Yu LX**, Han SL, Miao Y. [Detection of CD95 and CD95L mRNA expression after liver transplantation using SYBR real-time PCR during acute rejection]. *Nan Fang Yi Ke Da Xue Xue Bao* 2006; **26**: 185-188 [PMID: 16503525]

16 **Seino K**, Kayagaki N, Yamaguchi N, Takada Y, Uyama S, Kiuchi T, Tanaka K, Yagita H, Okumura K, Fukao K. Soluble forms of CD95 and CD95 ligand after living related liver transplantation. *Transplantation* 1999; **67**: 634-636 [PMID: 10071041 DOI: 10.1097/00007890-199902270-00026]

17 **Wang YL**, Zhang YY, Li G, Tang ZQ, Zhou YL, Zhu ZJ, Yao Z. Correlation of CD95 and soluble CD95 expression with acute rejection status of liver transplantation. *World J Gastroenterol* 2005; **11**: 1700-1704 [PMID: 15786554 DOI: 10.3748/wjg.v11.i11.1700]

18 **Rivero M**, Crespo J, Mayorga M, Fábrega E, Casafont F, Pons-Romero F. Involvement of the Fas system in liver allograft rejection. *Am J Gastroenterol* 2002; **97**: 1501-1506 [PMID: 12094873 DOI: 10.1111/j.1572-0241.2002.05797.x]

19 **Marín LA**, Moya-Quiles MR, Miras M, Minguela A, Bermejo J, Ramírez P, García-Alonso AM, Parrilla P, Alvarez-López MR, Muro M. Evolution of soluble forms of CD86, CD95 and CD95L molecules in liver transplant recipients. *Transpl Immunol* 2012; **26**: 94-100 [PMID: 22182632 DOI: 10.1016/j.trim.2011.12.001]

20 **Lorente L**, Rodriguez ST, Sanz P, González-Rivero AF, Pérez-Cejas A, Padilla J, Díaz D, González A, Martín MM, Jiménez A, Cerro P, Portero J, Barrera MA. DNA and RNA oxidative damage in hepatocellular carcinoma patients and mortality during the first year of liver transplantation. *World J Hepatol* 2022; **14**: 1182-1189 [PMID: 35978670 DOI: 10.4254/wjh.v14.i6.1182]

21 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649 [PMID: 4541913 DOI: 10.1002/bjs.1800600817]

22 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]

23 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]

24 **Gelson W**, Hoare M, Dawwas MF, Vowler S, Gibbs P, Alexander G. The pattern of late mortality in liver transplant recipients in the United Kingdom. *Transplantation* 2011; **91**: 1240-1244 [PMID: 21516069 DOI: 10.1097/TP.0b013e31821841ba]

25 **Doyle MB**, Vachharajani N, Maynard E, Shenoy S, Anderson C, Wellen JR, Lowell JA, Chapman WC. Liver transplantation for hepatocellular carcinoma: long-term results suggest excellent outcomes. *J Am Coll Surg* 2012; **215**: 19-28; discussion 28 [PMID: 22608403 DOI: 10.1016/j.jamcollsurg.2012.02.022]

26 **Dumitra S**, Alabbad SI, Barkun JS, Dumitra TC, Coutsinos D, Metrakos PP, Hassanain M, Paraskevas S, Chaudhury P, Tchervenkov JI. Hepatitis C infection and hepatocellular carcinoma in liver transplantation: a 20-year experience. *HPB (Oxford)* 2013; **15**: 724-731 [PMID: 23490176 DOI: 10.1111/hpb.12041]

27 **Teng F**, Wang GH, Tao YF, Guo WY, Wang ZX, Ding GS, Shi XM, Fu ZR. Criteria-specific long-term survival prediction model for hepatocellular carcinoma patients after liver transplantation. *World J Gastroenterol* 2014; **20**: 10900-10907 [PMID: 25152592 DOI: 10.3748/wjg.v20.i31.10900]

28 **Ninomiya M**, Shirabe K, Facciuto ME, Schwartz ME, Florman SS, Yoshizumi T, Harimoto N, Ikegami T, Uchiyama H, Maehara Y. Comparative study of living and deceased donor liver transplantation as a treatment for hepatocellular carcinoma. *J Am Coll Surg* 2015; **220**: 297-304.e3 [PMID: 25617912 DOI: 10.1016/j.jamcollsurg.2014.12.009]

29 **Lorente L**. New prognostic biomarkers of mortality in patients undergoing liver transplantation for hepatocellular carcinoma. *World J Gastroenterol* 2018; **24**: 4230-4242 [PMID: 30310256 DOI: 10.3748/wjg.v24.i37.4230]

30 **Song le H**, Binh VQ, Duy DN, Bock TC, Kremsner PG, Luty AJ, Mavoungou E. Variations in the serum concentrations of soluble Fas and soluble Fas ligand in Vietnamese patients infected with hepatitis B virus. *J Med Virol* 2004; **73**: 244-249 [PMID: 15122799 DOI: 10.1002/jmv.20082]

31 **Al-Saeedi M**, Steinebrunner N, Kudsi H, Halama N, Mogler C, Büchler MW, Krammer PH, Schemmer P, Müller M. Neutralization of CD95 ligand protects the liver against ischemia-reperfusion injury and prevents acute liver failure. *Cell Death Dis* 2018; **9**: 132 [PMID: 29374146 DOI: 10.1038/s41419-017-0150-0]

32 **Nakajima H**, Mizuta N, Fujiwara I, Sakaguchi K, Ogata H, Magae J, Yagita H, Koji T. Blockade of the Fas/Fas ligand interaction suppresses hepatocyte apoptosis in ischemia-reperfusion rat liver. *Apoptosis* 2008; **13**: 1013-1021 [PMID: 18561025 DOI: 10.1007/s10495-008-0234-5]

33 **Wang J**, Li W, Min J, Ou Q, Chen J. Fas siRNA reduces apoptotic cell death of allogeneic-transplanted hepatocytes in mouse spleen. *Transplant Proc* 2003; **35**: 1594-1595 [PMID: 12826229 DOI: 10.1016/S0041-1345(03)00438-X]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1761-1770

DOI: 10.12998/wjcc.v11.i8.1761

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Prospective Study

Epidemiological and clinical characteristics of COVID-19 in a Brazilian public hospital

Fillipe Dantas Pinheiro, Luana Weber Lopes, Rafael Santos Dantas Miranda Dórea, Glauber Rocha Lima Araújo, Filipe Antônio França da Silva, Breno Bittencourt de Brito, Maria Luísa Cordeiro Santos, Geovani Moreno Santos Júnior, Maria Teresa Araújo de Lorenzo Barcia, Renata de Amorim Marques, André Bezerra Botelho, Anna Carolina Saúde Dantas, Davi Tanajura Costa, Adriano Fernandes Teixeira, Cláudio Lima Souza, Lucas Miranda Marques, Guilherme Barretos Campos, Márcio Vasconcelos Oliveira, Dulciene Maria de Magalhães Queiroz, Fabrício Freire de Melo

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: Ganguli S, Bangladesh; Su C, China

Received: October 9, 2022
Peer-review started: October 9, 2022
First decision: October 24, 2022
Revised: November 19, 2022
Accepted: January 28, 2023
Article in press: January 28, 2023
Published online: March 16, 2023

Fillipe Dantas Pinheiro, Luana Weber Lopes, Rafael Santos Dantas Miranda Dórea, Glauber Rocha Lima Araújo, Filipe Antônio França da Silva, Breno Bittencourt de Brito, Maria Luísa Cordeiro Santos, André Bezerra Botelho, Anna Carolina Saúde Dantas, Davi Tanajura Costa, Adriano Fernandes Teixeira, Cláudio Lima Souza, Lucas Miranda Marques, Guilherme Barretos Campos, Márcio Vasconcelos Oliveira, Fabrício Freire de Melo, Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Vitória da Conquista 45029-094, Bahia, Brazil

Geovani Moreno Santos Júnior, Maria Teresa Araújo de Lorenzo Barcia, Renata de Amorim Marques, Hospital Geral de Vitória da Conquista, Vitória da Conquista 45030-160, Bahia, Brazil

Davi Tanajura Costa, Departamento de Ciências da Saúde, Universidade Estadual do Sudoeste da Bahia (UESB), Vitória da Conquista 45083-900, Bahia, Brazil

Dulciene Maria de Magalhães Queiroz, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte 31270-901, Minas Gerais, Brazil

Corresponding author: Fabrício Freire de Melo, MSc, PhD, Postdoc, Professor, Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Rua Hormínio Barros, 58, Candeias, Vitória da Conquista 45029-094, Bahia, Brazil. freiremelo@yahoo.com.br

Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic has become a major health concern worldwide. In that context, the understanding of epidemiological and clinical features associated with the disease and its severity is crucial for the establishment of strategies aimed at disease control and remedy.

AIM

To describe epidemiological features, signs, symptoms, and laboratory findings among severely ill COVID-19 patients from an inten-sive care unit in northeastern

Brazil as well as to evaluate predictor factors for disease outcomes.

METHODS
This is a prospective single-center study that evaluated 115 patients admitted to the intensive care unit in a northeastern Brazilian hospital.

RESULTS
The patients had a median age of 65.60 ± 15.78 years. Dyspnea was the most frequent symptom, affecting 73.9% of the patients, followed by cough (54.7%). Fever was reported in approximately one-third of patients and myalgia in 20.8% of the patients. At least two comorbidities were found in 41.7% of the patients, and hypertension was the most prevalent (57.3%). In addition, having two or more comorbidities was a predictor of mortality, and lower platelet count was positively associated with death. Nausea and vomiting were two symptoms that were predictors of death, and the presence of a cough was a protective factor.

CONCLUSION
This is the first report of a negative correlation between cough and death in severely ill severe acute respiratory syndrome coronavirus 2-infected individuals. The associations between comorbidities, advanced age, and low platelet count and the outcomes of the infection were similar to the results of previous studies, highlighting the relevance of these features.

Key Words: COVID-19; Epidemiology; Symptoms; Comorbidities; Laboratory parameters

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This is a prospective study carried out in a hospital in Brazil with 115 patients admitted to the intensive care unit with a positive diagnosis for severe acute respiratory syndrome coronavirus 2. The epidemiological features, signs, symptoms, and laboratory findings among severely ill coronavirus disease 2019 patients and the predictive factors for disease outcomes were evaluated. This is the first report of a negative correlation between cough and death in severely ill severe acute respiratory syndrome coronavirus 2-infected individuals.

Citation: Pinheiro FD, Lopes LW, Dórea RSDM, Araújo GRL, Silva FAFD, de Brito BB, Cordeiro Santos ML, Júnior GMS, de Lorenzo Barcia MTA, Marques RA, Botelho AB, Dantas ACS, Costa DT, Teixeira AF, Souza CL, Marques LM, Campos GB, Oliveira MV, de Magalhães Queiroz DM, Freire de Melo F. Epidemiological and clinical characteristics of COVID-19 in a Brazilian public hospital. *World J Clin Cases* 2023; 11(8): 1761-1770
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1761.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1761

INTRODUCTION

Since its first records at the end of 2019 in Wuhan, capital city of Hubei province, China, the coronavirus disease 2019 (COVID-19) has caused numerous challenges with regard to a better understanding of its immunology, pathophysiology, clinical manifestations, diagnosis, and treatment[1]. The pathogen was identified as a novel enveloped RNA betacoronavirus that has a phylogenetic similarity to the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1). In that context, the so-called SARS-CoV-2 has become a global health concern, and on March 11, 2020 the World Health Organization declared the COVID-19 outbreak a pandemic[2].

The incubation period for COVID-19 is generally within 14 d following exposure, and the onset of symptoms occurs 4-5 d after inoculation[3]. In a study including 1084 COVID-19 patients from China, the median period of incubation was 7.8 d, with 5% to 10% of patients experiencing the first symptoms after 14 d of exposure[3]. Recent meta-analyses about the topic corroborate this finding, highlighting averages of 5.1 and 5.6 d for disease incubation[4,5]. Among those affected by the disease, about 17.9% to 33.3% remain asymptomatic, highlighting the difficult control of the transmission of the disease[6].

Pneumonia is the most frequent serious finding, and it usually occurs with fever, cough, expectoration, and dyspnea. Other common symptoms are myalgia, diarrhea, anosmia and dysgeusia, and upper respiratory tract symptoms[7-9]. Of note, dysgeusia and anosmia disorders are more common in COVID-19 than in other viral infections[10]. The prevalence of SARS-CoV-2 infection-related manifestations can vary depending on the level of severity of the illness. In this sense, the prevalence of fever was higher among hospitalized patients in a trial with 1099 patients when compared to non-hospit-

alized COVID-19 patients. Only 44% of the patients had fever at admission, whereas 89% were febrile during hospitalization[11]. When compared to severe and mild disease groups, patients with moderate involvement had higher rates of dysgeusia and anosmia (88.70% among patients with moderate disease and 45.83% in severely ill individuals)[12].

As prognostic markers of the disease, clinical and epidemiological features have been reported as predictors of severity among patients in hospital care. While dyspnea is also an important finding for a poor prognosis, studies suggest that peripheral oxygen saturation is the respiratory factor to be assessed, as it excludes the subjective factor from the assessment. These studies suggest that an oxygen saturation below 92% was associated with a poor prognosis. Furthermore, it takes about 5 d for the patient to develop dyspnea after the first symptoms, and it can be quickly followed by acute respiratory distress syndrome. In this sense, adequate monitoring of saturation levels in COVID-19 patients is indicated[13].

Efforts have been directed towards the understanding of the relationship between comorbidities and the severity and mortality in SARS-CoV-2 infection. In this sense, studies have shown that diabetes, hypertension, obesity, and cardiovascular disease are important risk factors for severity and mortality [14-16]. In addition, various abnormalities in serum laboratory parameters have been associated with COVID-19, and some of them have been related to an increased risk of mortality[17,18].

To date, SARS-CoV-2 has infected almost 200 million people worldwide, from which 4 million died [2]. In Brazil, 30639130 cases of the disease have been registered so far, with 664641 deaths associated with the disease. The northeast region of Brazil, in which the current study was carried out, has reported 6256874 cases, with the occurrence of 128829 deaths among them[19]. The aim of this study was to describe epidemiological features, signs, symptoms, and laboratory findings at the moment of intensive care unit (ICU) admission among severely ill COVID-19 patients in a city from northeastern Brazil. We also evaluated predictive factors for disease outcomes in the study sample. This study showed some differences in the clinical and epidemiological profiles of COVID-19 patients when compared with previous studies, mainly regarding the frequency of symptoms. We report, for the first time, a negative association between cough and death among severely ill SARS-CoV-2-infected patients.

MATERIALS AND METHODS

Study design and participants

This single-center prospective study included 225 consecutive COVID-19 patients admitted to the ICU, General Hospital of Vitória da Conquista city, Bahia State, Brazil, from July 30, 2020 to August 28, 2021. The Vitória da Conquista General Hospital is a regional hospital in the third largest city in the Bahia State, providing an extensive multidisciplinary teaching service and attends to a large number of highly complex cases from more than 70 surrounding cities. All included patients had SARS-CoV-2 infection confirmed by real-time (RT-) PCR of nasopharyngeal swab specimens. Subjects were selected according to the criteria for ICU admission recommended by the Bahia State Department of Health. This study was approved by the Ethics Committee of the Brazilian National Research Ethics Commission (No. 4.155.234), with an informed consent form obtained from the relatives responsible for the enrolled patients.

Data collection

Epidemiological, clinical, and laboratory data of the included patients were obtained both at admission and during hospitalization. Clinical outcomes were monitored in the inpatient system, which indicated discharge, transfer, or death. Data collection comprised clinical, epidemiological, and demographic data as well as exposure history to infected individuals, date of symptom onset, RT-PCR result, and presence of comorbidities. Comorbidities included: (1) Hypertension; (2) Diabetes; (3) Cardiovascular disease; (4) Chronic kidney disease; (5) Obesity; (6) Chronic obstructive pulmonary disease; and (7) Autoimmune diseases.

Blood samples were obtained from the patients for assessment of white blood cell [reference values: (4-10) × 10^3 mm^3] and platelet [reference values: (150-450) × 10^3 g/L] count, hemoglobin levels [reference values 11.5-18.0 mg/dL (female) or 13.0-18.0 mg/dL (male)], C-reactive protein (reference value: ≤ 6 g/L), serum sodium (reference values: 130-150 mEq/L), aspartate aminotransferase (reference values: 10-37 U/I), alanine aminotransferase (reference values: 10-45 U/I), and lactic dehydrogenase (reference values: 120-246 U/I). All laboratory evaluations were completed by conventional methods.

Statistical analysis

Statistical analysis data were analyzed by the public domain statistical software Epi Info 7 and the SPSS statistical software package version 26.0 (SPSS Inc., Chicago, IL, United States). For the comparisons, Kolgomorov-Smirnov or Shapiro-Wilk test were used to assess the normality of the data as indicated. Two-tailed student's t test or Mann-Whitney U test as well as χ^2 test with Yates' correction or Fisher's exact test were employed as indicated. The level of significance was set at $P \leq 0.05$. Forward binary logistic regression was performed during analysis.

RESULTS

Demographic data

All subjects were positive for SARS-CoV-2 RNA detected by RT-PCR. Their mean age [standard deviation (SD)] was 65.60 ± 15.78 years. Patients included 69 (60%) males (mean age = 67.09, SD = 14.09) and 46 (40%) females (mean age = 63.37, SD = 17.96). A total of 38 patients (33.1%) were from Vitória da Conquista and 36 from adjacent cities (Figure 1).

Clinical features

The most frequent clinical symptom was dyspnea, present in more than two-thirds of the included patients (85 patients, 73.9%). Cough was the second most frequent symptom (63 patients, 54.7%) followed by fever (38 patients, 33.0%), myalgia (24 patients, 20.8%), diarrhea (9 patients, 7.8%), nausea (8 patients, 6.9%), vomiting (7 patients, 6.0%), headache, dysgeusia, and anosmia (5 patients, 4.3% for each symptom). Regarding comorbidities, 66 patients (57.3%) had hypertension, 32 patients (27.8%) had diabetes, 23 patients (20.0%) had cardiovascular disease, 15 patients (13.0%) had obesity, 12 patients (10.4%) had chronic kidney disease, 4 patients (3.4%) had chronic obstructive pulmonary disease, and 1 patient (0.8%) had an autoimmune disease. In the group of patients from whom the information was obtained, no comorbidities were present in 15 patients, whereas 36 and 29 patients had one and two comorbidities, respectively. The others had either three (n = 13) or four (n = 5) comorbidities.

Vital signs and laboratory data

Respiratory rate was increased in the majority of patients (n = 39; 52.0%), whereas 2 patients (2.7%) presented with bradypnea and 34 patients (45.3%) were eupneic. The white blood cell count was elevated in 61.9% of the patients (n = 60), and leukopenia was observed in 5 patients (5.2%) (reference value = 5000-11000 leukocytes/mm^3). The inflammatory marker C-reactive protein was found to be altered in 74 patients (96.10%; reference value ≤ 3 mg/L). Regarding hepatic lesion markers, aspartate aminotransferase and alanine aminotransferase levels were elevated in 13 patients (54.2%) and 15 patients (68.2%), respectively.

When the group of patients who died were compared with those who had a favorable disease outcome, increasing age was significantly associated with death (69.28 ± 15.16 *vs* 61.54 ± 17.08, P = 0.02). The presence of two or more comorbidities was a positive predictor of mortality (P = 0.01). The presence of at least two concomitant illnesses was observed in 60.9% of the patients who died compared with the other group (39.1%). No association was observed for gender (female, male, P = 0.16) and a plethora of patient factors including demographic, clinical, immunologic, hematological, biochemical, and radiographic findings, may be of utility to clinicians to predict COVID-19 severity and mortality. In addition, the mean platelet count among patients who died was 141.49 × 10^3 g/L. A statistically significant relationship was observed between the lower platelet count and death (P ≤ 0.001). No statistically significant results were obtained when other comorbidities and laboratory results were assessed.

When evaluating the main outcomes and the symptoms of the patients in the ICU, we found that nausea (P = 0.02) and vomiting (P = 0.05) were predictors of death, and the presence of a cough was a protective factor. There was no statistically significant association between other symptoms and the evaluated outcomes. Tables 1-4 summarize the findings of this study.

DISCUSSION

This study evaluated the clinical and epidemiological profiles of hospitalized individuals from an ICU in a Brazilian public hospital. Some symptom data found in this investigation diverge from the pattern observed in previous studies. In an investigation in China, fever was the most prevalent symptom among the 1099 laboratory-confirmed COVID-19 patients at admission (43.8%) or during hospitalization (88.7%)[20], in contrast to the approximately one-third of patients observed in this study. Furthermore, a high prevalence of fever (88.7% of the 656 patients) was also identified in a meta-analysis study[21].

Notably, cough was not associated with poor outcomes among the severely ill COVID-19 patients we evaluated. To the best of our knowledge, this is the first study to demonstrate a negative association between cough and death in patients infected with SARS-CoV-2 in the ICU, in contrast a meta-analysis study evaluating 10014 patients with COVID-19[22]. In addition, a high prevalence of this symptom was observed in the present study, corroborating an investigation from the Center for Disease Control and Prevention, which evaluated 373883 individuals and found that the aforementioned symptom was the most common manifestation in COVID-19 (50%)[23].

Seeking explanations for this finding, the hypothesis of coughing as an alarm signal was raised. This sign would make patients seek emergency care earlier when compared to critically ill patients without cough. It is plausible that the patients without cough but desaturation and severe condition did not understand that they should be evaluated by a doctor. During the peak of the epidemic, health systems were overcrowded, and government entities were oriented on a national network to seek assistance only in a serious condition. Faced with these situations, we may be dealing with a needy population with a

Table 1 Prevalence of outcomes/destinations in the studied population, *n* = 101

Prevalence of outcomes/destinations	*n* (%)
Discharge or transfer from the ICU	48 (47.5)
Death	47 (46.5)
Transfer	6 (5.9)

ICU: Intensive care unit.

Table 2 Hematologic risk factors associated with death in the patients

Hematologic values	With death, mean ± SD	Without death, mean ± SD	*P* value
Hemoglobin, mg/dL	11.31 ± 2.96	11.70 ± 2.79	0.55
Leukocytes, mm³	14.45 ± 6.88	14.29 ± 8.71	0.92
CRP, g/L	143.46 ± 150.76	147.53 ± 201.60	0.77
Platelets, g/L	141.49 ± 9.55	154.88 ± 72.91	< 0.001

CRP: C-reactive protein; SD: Standard deviation.

Table 3 Age, sex, comorbidities, and laboratory tests associated with the main outcomes, *n* (%)

Comorbidities	Death, *n*	Discharged, *n*	*P* value	Death, mean ± SD	Discharged median ± SD
Hypertension	33 (53.2)	29 (46.8)	0.15		
Diabetes	18 (58.1)	13 (41.9)	0.14		
Cardiovascular disease	11 (50.0)	11 (50.0)	0.54		
Obesity	6 (50.0)	6 (50.0)	0.58		
Chronic kidney disease	8 (66.7)	4 (33.3)	0.15		
Chronic obstructive pulmonary disease	2 (50.0)	2 (50.0)	0.67		
Autoimmune diseases	0 (0)	1 (100)	0.51		
At least 2 comorbidities	28 (60.9)	18 (39.1)	0.01		
Laboratory tests					
Hemoglobin, mg/dL			0.55	11.31 ± 2.96	11.70 ± 2.79
Leukogram, mm³			0.93	14.448 ± 6.878	14.292 ± 8.705
CRP, g/L			0.18	143.46 ± 150.76	147.53 ± 201.60
Platelets, g/L			< 0.001	141.49 ± 9.55	154.88 ± 72.91
Serum sodium, mEq/L			0.35	143.00 ± 9.79	140.62 ± 10.70
AST, U/L			0.22	54.20 ± 32.41	92.83 ± 24.10
ALT, U/L			0.7	26.00 ± 13.78	81.90 ± 90.50
Lactic dehydrogenase, U/L	486.00 ± 48.08	274	0.17		

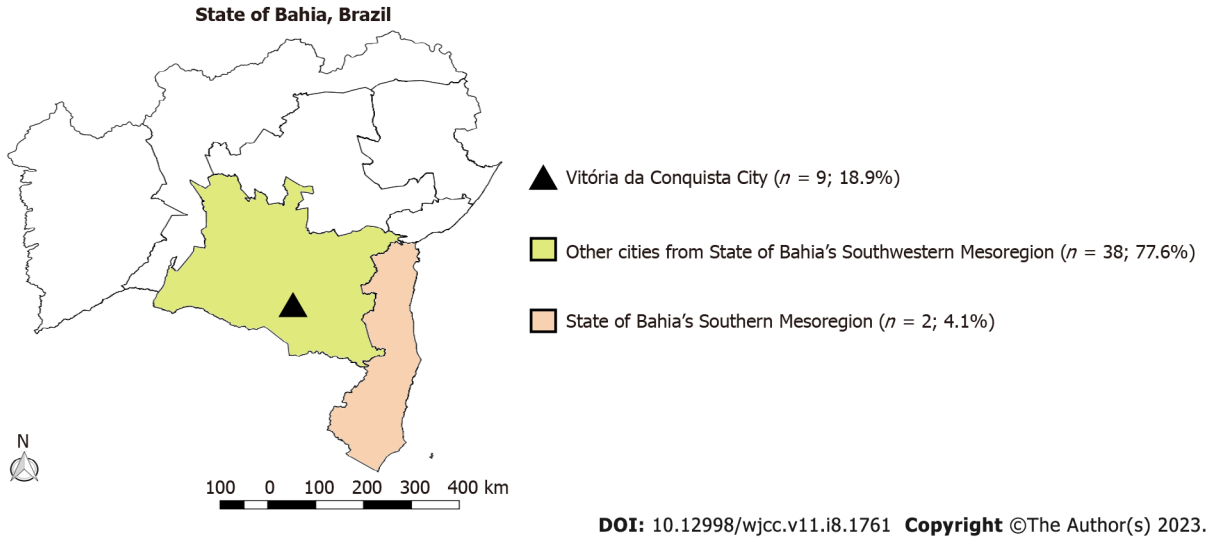
CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; SD: Standard deviation.

low availability of health services and with government guidelines to avoid emergency services. This culminates in critically ill patients staying at home for too long and arriving at hospitals in very serious conditions. This could also explain the high mortality rates in the study.

Nausea and vomiting were positively associated with death in the present study in contrast to previous investigations that have associated gastrointestinal symptoms with milder SARS-CoV-2 infections. The frequency of gastrointestinal symptoms found here was lower than in other surveys. In a systematic review performed by our group that included 43 studies and 18246 COVID-19 patients, the

Table 4 Relationship between symptoms and the main clinical outcomes, *n* (%)

Symptom	Death	Discharged	*P* value
Dyspnea	36 (46.8)	41 (53.2)	0.09
Cough	23 (40.4)	34 (59.6)	0.01
Fever	14 (41.2)	20 (58.8)	0.15
Myalgia	9 (42.9)	12 (57.1)	0.30
Diarrhea	6 (66.6)	3 (33.3)	0.24
Headache	4 (44.0)	5 (55.0)	0.02
Nausea	7 (87.5)	1 (12.5)	0.02
Vomiting	6 (85.7)	1 (14.3)	0.05
Chills	1 (20.0)	4 (80.0)	0.18
Taste changes	1 (50.0)	1 (50.0)	0.75
Anosmia	1 (50.0)	1 (50.0)	0.75



DOI: 10.12998/wjcc.v11.i8.1761 **Copyright** ©The Author(s) 2023.

Figure 1 Map of the study region with the number of patients (*n*) from each mesoregion.

prevalence of diarrhea was higher than in this investigation[8]. The most common symptom in our investigation was dyspnea, a pivotal finding among severely ill COVID-19 patients. In a meta-analysis study evaluating 1813 patients, only dyspnea was able to predict severe disease and ICU admission[24]. Headache was more infrequent in our patients than in the aforementioned investigation by Center for Disease Control and Prevention[23], likely due to the administration of analgesics in the emergency room or in other hospitals before admission to the ICU. Similarly, there was a low prevalence of anosmia and taste change, which was expected because these symptoms have been observed in better prognoses[21].

Leukocytosis was found in most individuals included in this investigation, which was in agreement with the higher frequencies of this manifestation reported among critically ill individuals[25,26]. Red blood cell count abnormality was another relevant laboratory finding in this study, with the detection of hemoglobin levels below 11 g/dL in 38.7% of the patients, also in accordance with previous studies showing reduced levels of serum hemoglobin in SARS-CoV-2-infected individuals with severe disease [21]. The levels of serum lactate dehydrogenase were found to be increased in our samples, a common finding among COVID-19 patients[27]. Moreover, serum sodium levels were increased in the patients we evaluated. This was similar to the increased odds of in-hospital death among hypernatremic individuals compared to normonatremic persons[28].

Furthermore, a decreased platelet count was positively associated with mortality in our investigation. Previous studies suggested that the occurrence of thrombocytopenia in SARS-CoV-2 infection can be associated with serious conditions such as intravascular coagulation and sepsis[29]. Another cause of low platelet count in patients with COVID-19 may be drug-induced[3].

This study demonstrated a higher mortality rate among critically ill SARS-CoV-2-infected individuals than most studies have. Of note, ICU mortality due to COVID-19 around the world has ranged from 20% to 62%[30-32]. The difficulties faced by the Brazilian public health system to make enough ICU beds available for COVID-19 patients during the pandemics should be emphasized. In the period from 2020 to 2021, there were approximately 70 ICU beds in the study city, which is the main healthcare center in a region that embraces 2 million inhabitants[33]. This scenario contributed to the occurrence of delays in providing adequate life support for critically ill individuals, which potentially contributed to the high mortality rate observed in this study.

A high prevalence of comorbidities was observed in our patients. Hypertension was the most prevalent comorbidity, which was in agreement with a meta-analysis study. Moreover, the presence of two or more comorbidities as well as older age were associated with higher mortality in our study, similarly to a previous study[34]. The circulating variants of SARS-CoV-2 is an important issue to be accounted for when considering the clinical manifestations of COVID-19 among individuals from a given geographical area[35]. Although the differentiation of the SARS-CoV-2 strains that infected the patients could not be performed in this study, the co-circulation of 13 different strains has been reported to date in the Brazilian state where the study was carried out. The first subline identified was B.1.1.162 [36]. Of note, the variants P.1 and P.2, which have been identified in the Brazilian cities Manaus and Rio de Janeiro, respectively, have been detected in the aforementioned state as well[37,38]. Lastly, the Peruvian lineage C.14 was also detected in the study region after its introduction through a ship traveler. Until February 2021, the variants circulating in Bahia state were limited to the A, B, C and P types[39,40].

There are a few limitations to this study. This was an epidemiological investigation conducted at a single health care system with a limited number of participants and in a confined geographic area, thus limiting the generalizability of the results. Future research should be made to identify and predict further factors associated with mortality in COVID-19 populations admitted to the ICU.

CONCLUSION

This study revealed differences in the clinical profile of COVID-19 patients when compared with previous studies, such as the observation of a negative association between cough and death in severely ill individuals. On the other hand, the associations between comorbidities, advanced age, and low platelet count and the outcomes of the infection were similar to the results of previous studies, highlighting the relevance of these features. Further investigations are needed in order to better characterize risks of poor outcomes among severely ill COVID-19 patients.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) has been a health concern around the world since it was first identified in 2019. An understanding of the epidemiological and clinical features related to the infection is very important for the development of prevention and treatment of the disease.

Research motivation

There is a lack of studies evaluating the clinical and epidemiological characteristics of patients with severe COVID-19 in the study region. Moreover, the data regarding the infection features in that population can contribute to the understanding of the disease.

Research objectives

The objectives were to describe epidemiological characteristics, signs, symptoms, and laboratory findings in individuals with severe COVID-19 from an intensive care unit in the state of Bahia in northeastern Brazil and to analyze predictive features for the disease outcomes.

Research methods

In this prospective, single-center study, 115 patients with severe COVID-19 admitted to an intensive care unit in northeastern Brazil were evaluated. Epidemiological, clinical, and laboratory data of the included patients were obtained. Clinical outcomes were monitored in the inpatient system.

Research results

The patients had a median age of 65.60 ± 15.78 years. Dyspnea was the most frequent symptom, affecting 73.9% of the patients, followed by cough (54.7%). Fever was reported in approximately one-third of patients and myalgia in 20.8% of patients. At least two comorbidities were found in 41.7% of the

patients, and hypertension was the most prevalent one (57.3%). In addition, having two or more comorbidities was a predictor of mortality, and lower platelet count was positively associated with death as well. Nausea and vomiting were predictors of death, and the presence of a cough was a protective factor.

Research conclusions

This is the first report of a negative correlation between cough and death in severely ill severe acute respiratory syndrome coronavirus 2-infected individuals. The associations between comorbidities, advanced age, low platelet count, and the outcomes of the infection were similar to the results of previous studies, highlighting the relevance of these features.

Research perspectives

In future analyses, we will evaluate the role of various cytokine profiles in the inflammatory response in the population of this study. Moreover, the relationship between comorbidities and infection outcomes might be further explored in the next steps of the research.

FOOTNOTES

Author contributions: Lopes LW, Dórea RSDM, Araújo GRL, Silva FAFD, de Brito BB, and Cordeiro Santos ML contributed to laboratory processing of samples and data collection; Souza CL, Oliveira MV, Magalhães Queiroz DM, and Freire de Melo F contributed to development, supervision, and analysis of project stages; Lopes LW, Dórea RSDM, Araújo GRL, Silva FAFD, de Brito BB, Cordeiro Santos ML, Magalhães Queiroz DM, and Freire de Melo F contributed to project submission to the ethics committee and/or financial support; Silva FAFD, de Brito BB, and Cordeiro Santos ML wrote the article; Pinheiro FD, Júnior GMS, de Lorenzo Barcia MTA, Marques RA, Botelho AB, Dantas ACS, Costa DT, Teixeira AF, Marques LM, Campos GB contributed to reviewing and data analysis.

Supported by FAPEMIG Edital 001/2020 - Programa Emergencial de Apoio a Ações de Enfrentamento da Pandemia Causada pelo Novo Coronavírus. FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DA BAHIA – FAPESB, PPSUS - Programa Pesquisa para o SUS - Headline 02/2020, Term of Grant nº SUS0025/2021. Magalhães Queiroz DM, Freire de Melo F, are research fellows of the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq-) – Brazil. Programa Permanecer da Universidade Federal da Bahia. Programa Institucional de Bolsas de Iniciação Científica da Universidade Federal da Bahia (PIBIC-UFBA).

Institutional review board statement: This study was approved by the Ethics Committee from the Brazilian National Commission of Research Ethics (N. 4155234).

Clinical trial registration statement: We declare that this manuscript is not a clinical trial, and therefore a clinical trial registration is not needed.

Informed consent statement: The informed consent form was obtained from the relatives responsible for the enrolled patients.

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

Data sharing statement: All the data related to the research is available in the manuscript.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Brazil

ORCID number: Fillipe Dantas Pinheiro 0000-0002-3489-4853; Luana Weber Lopes 0000-0002-7771-2650; Rafael Santos Dantas Miranda Dórea 0000-0002-5347-6913; Glauber Rocha Lima Araújo 0000-0002-5195-3632; Filipe Antônio França da Silva 0000-0002-0550-1109; Breno Bittencourt de Brito 0000-0002-1831-7909; Maria Luísa Cordeiro Santos 0000-0001-7078-9789; Adriano Fernandes Teixeira 0000-0001-9193-2628; Cláudio Lima Souza 0000-0002-8094-8357; Lucas Miranda Marques 0000-0002-8276-8149; Márcio Vasconcelos Oliveira 0000-0002-8959-0478; Dulciene Maria de Magalhães Queiroz 0000-0003-1334-9423; Fabrício Freire de Melo 0000-0002-5680-2753.

S-Editor: Wang JJ
L-Editor: Filipodia

P-Editor: Wang JJ

REFERENCES

1 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

2 **World Health Organization**. WHO Director-General's opening remarks at the media briefing on COVID-19. [cited 16 July 2022]. Available from: https://vietnam.un.org/en/38806-who-director-generals-opening-remarks-media-briefing-covid-19

3 **Qin J**, You C, Lin Q, Hu T, Yu S, Zhou XH. Estimation of incubation period distribution of COVID-19 using disease onset forward time: a novel cross-sectional and forward follow-up study. *medRxiv* 2020 [PMID: 32511426 DOI: 10.1101/2020.03.06.20032417]

4 **Alene M**, Yismaw L, Assemie MA, Ketema DB, Gietaneh W, Birhan TY. Serial interval and incubation period of COVID-19: a systematic review and meta-analysis. *BMC Infect Dis* 2021; **21**: 257 [PMID: 33706702 DOI: 10.1186/s12879-021-05950-x]

5 **McAloon C**, Collins Á, Hunt K, Barber A, Byrne AW, Butler F, Casey M, Griffin J, Lane E, McEvoy D, Wall P, Green M, O'Grady L, More SJ. Incubation period of COVID-19: a rapid systematic review and meta-analysis of observational research. *BMJ Open* 2020; **10**: e039652 [PMID: 32801208 DOI: 10.1136/bmjopen-2020-039652]

6 **Quesada JA**, López-Pineda A, Gil-Guillén VF, Arriero-Marín JM, Gutiérrez F, Carratala-Munuera C. [Incubation period of COVID-19: A systematic review and meta-analysis]. *Rev Clin Esp (Barc)* 2021; **221**: 109-117 [PMID: 33024342 DOI: 10.1016/j.rce.2020.08.005]

7 **Cascella M**, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation, and Treatment of Coronavirus (COVID-19). 2022 Oct 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan- [PMID: 32150360]

8 **Li LQ**, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, Zhang HY, Sun W, Wang Y. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol* 2020; **92**: 577-583 [PMID: 32162702 DOI: 10.1002/jmv.25757]

9 **Silva FAFD**, Brito BB, Santos MLC, Marques HS, Silva Júnior RTD, Carvalho LS, Vieira ES, Oliveira MV, Melo FF. COVID-19 gastrointestinal manifestations: a systematic review. *Rev Soc Bras Med Trop* 2020; **53**: e20200714 [PMID: 33263693 DOI: 10.1590/0037-8682-0714-2020]

10 **Mao L**, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol* 2020; **77**: 683-690 [PMID: 32275288 DOI: 10.1001/jamaneurol.2020.1127]

11 **Mullol J**, Alobid I, Mariño-Sánchez F, Izquierdo-Domínguez A, Marin C, Klimek L, Wang DY, Liu Z. The Loss of Smell and Taste in the COVID-19 Outbreak: a Tale of Many Countries. *Curr Allergy Asthma Rep* 2020; **20**: 61 [PMID: 32748211 DOI: 10.1007/s11882-020-00961-1]

12 **Eastin C**, Eastin T. Clinical Characteristics of Coronavirus Disease 2019 in China. *J Emerg Med* 2020; **58**: 711-712 [DOI: 10.1016/j.jemermed.2020.04.004]

13 **Mendonça CV**, Mendes Neto JA, Suzuki FA, Orth MS, Machado Neto H, Nacif SR. Olfactory dysfunction in COVID-19: a marker of good prognosis? *Braz J Otorhinolaryngol* 2022; **88**: 439-444 [PMID: 33441276 DOI: 10.1016/j.bjorl.2020.12.002]

14 **Jang JG**, Hur J, Choi EY, Hong KS, Lee W, Ahn JH. Prognostic Factors for Severe Coronavirus Disease 2019 in Daegu, Korea. *J Korean Med Sci* 2020; **35**: e209 [PMID: 32537954 DOI: 10.3346/jkms.2020.35.e209]

15 **Cai Z**, Yang Y, Zhang J. Obesity is associated with severe disease and mortality in patients with coronavirus disease 2019 (COVID-19): a meta-analysis. *BMC Public Health* 2021; **21**: 1505 [PMID: 34348687 DOI: 10.1186/s12889-021-11546-6]

16 **Mahamat-Saleh Y**, Fiolet T, Rebeaud ME, Mulot M, Guihur A, El Fatouhi D, Laouali N, Peiffer-Smadja N, Aune D, Severi G. Diabetes, hypertension, body mass index, smoking and COVID-19-related mortality: a systematic review and meta-analysis of observational studies. *BMJ Open* 2021; **11**: e052777 [PMID: 34697120 DOI: 10.1136/bmjopen-2021-052777]

17 **de Almeida-Pititto B**, Dualib PM, Zajdenverg L, Dantas JR, de Souza FD, Rodacki M, Bertoluci MC; Brazilian Diabetes Society Study Group (SBD). Severity and mortality of COVID 19 in patients with diabetes, hypertension and cardiovascular disease: a meta-analysis. *Diabetol Metab Syndr* 2020; **12**: 75 [PMID: 32874207 DOI: 10.1186/s13098-020-00586-4]

18 **Velavan TP**, Meyer CG. Mild *vs* severe COVID-19: Laboratory markers. *Int J Infect Dis* 2020; **95**: 304-307 [PMID: 32344011 DOI: 10.1016/j.ijid.2020.04.061]

19 **Tjendra Y**, Al Mana AF, Espejo AP, Akgun Y, Millan NC, Gomez-Fernandez C, Cray C. Predicting Disease Severity and Outcome in COVID-19 Patients: A Review of Multiple Biomarkers. *Arch Pathol Lab Med* 2020; **144**: 1465-1474 [PMID: 32818235 DOI: 10.5858/arpa.2020-0471-SA]

20 **Coronavírus Brasil**. Painel Coronavirus - Brasil. [cited 20 July 2022]. Available from: https://covid.saude.gov.br

21 **Guan W**, Ni Z, Yu Hu, Liang W, Ou C, He J, Liu L, Shan H, Lei C, Hui DSC, Du B, Li L, Zeng G, Yuen KY, Chen R, Tang C, Wang T, Chen P, Xiang J, Li S, Wang J, Liang Z, Peng Y, Wei L, Liu Y, Hu Y, Peng P, Liu J, Chen Z, Li G, Zheng Z, Qiu S, Luo J, Ye C, Zhu S, Zhong N. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [DOI: 10.1056/NEJMoa2002032]

22 **Rodriguez-Morales AJ**, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, Alvarado-Arnez LE, Bonilla-Aldana DK, Franco-Paredes C, Henao-Martinez AF, Paniz-Mondolfi A, Lagos-

Grisales GJ, Ramírez-Vallejo E, Suárez JA, Zambrano LI, Villamil-Gómez WE, Balbin-Ramon GJ, Rabaan AA, Harapan H, Dhama K, Nishiura H, Kataoka H, Ahmad T, Sah R; Latin American Network of Coronavirus Disease 2019-COVID-19 Research (LANCOVID-19). Electronic address: https://www.lancovid.org. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis* 2020; **34**: 101623 [PMID: 32179124 DOI: 10.1016/j.tmaid.2020.101623]

23 **Barek MA**, Aziz MA, Islam MS. Impact of age, sex, comorbidities and clinical symptoms on the severity of COVID-19 cases: A meta-analysis with 55 studies and 10014 cases. *Heliyon* 2020; **6**: e05684 [PMID: 33344791 DOI: 10.1016/j.heliyon.2020.e05684]

24 **Czeisler MÉ**, Marynak K, Clarke KEN, Salah Z, Shakya I, Thierry JM, Ali N, McMillan H, Wiley JF, Weaver MD, Czeisler CA, Rajaratnam SMW, Howard ME. Delay or Avoidance of Medical Care Because of COVID-19-Related Concerns - United States, June 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 1250-1257 [DOI: 10.15585/mmwr.mm6936a4]

25 **Jain V**, Yuan JM. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. *Int J Public Health* 2020; **65**: 533-546 [PMID: 32451563 DOI: 10.1007/s00038-020-01390-7]

26 **Sayad B**, Afshar ZM, Mansouri F, Rahimi Z. Leukocytosis and alteration of hemoglobin level in patients with severe COVID-19: Association of leukocytosis with mortality. *Health Sci Rep* 2020; **3**: e194 [PMID: 33083572 DOI: 10.1002/hsr2.194]

27 **Yamada T**, Wakabayashi M, Yamaji T, Chopra N, Mikami T, Miyashita H, Miyashita S. Value of leukocytosis and elevated C-reactive protein in predicting severe coronavirus 2019 (COVID-19): A systematic review and meta-analysis. *Clin Chim Acta* 2020; **509**: 235-243 [PMID: 32533986 DOI: 10.1016/j.cca.2020.06.008]

28 **Hirsch JS**, Uppal NN, Sharma P, Khanin Y, Shah HH, Malieckal DA, Bellucci A, Sachdeva M, Rondon-Berrios H, Jhaveri KD, Fishbane S, Ng JH; Northwell Nephrology COVID-19 Research Consortium. Prevalence and outcomes of hyponatremia and hypernatremia in patients hospitalized with COVID-19. *Nephrol Dial Transplant* 2021; **36**: 1135-1138 [PMID: 33724428 DOI: 10.1093/ndt/gfab067]

29 **Asakura H**, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. *Int J Hematol* 2021; **113**: 45-57 [PMID: 33161508 DOI: 10.1007/s12185-020-03029-y]

30 **Bomhof G**, Mutsaers PGNJ, Leebeek FWG, Te Boekhorst PAW, Hofland J, Croles FN, Jansen AJG. COVID-19-associated immune thrombocytopenia. *Br J Haematol* 2020; **190**: e61-e64 [PMID: 32420612 DOI: 10.1111/bjh.16850]

31 **Stokes EK**, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, Tie Y, Fullerton KE. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 759-765 [PMID: 32555134 DOI: 10.15585/mmwr.mm6924e2]

32 **Arentz M**, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA* 2020; **323**: 1612-1614 [PMID: 32191259 DOI: 10.1001/jama.2020.4326]

33 **Ganesan R**, Mahajan V, Singla K, Konar S, Samra T, Sundaram SK, Suri V, Garg M, Kalra N, Puri GD. Mortality Prediction of COVID-19 Patients at Intensive Care Unit Admission. *Cureus* 2021; **13**: e19690 [PMID: 34976472 DOI: 10.7759/cureus.19690]

34 **Thakur B**, Dubey P, Benitez J, Torres JP, Reddy S, Shokar N, Aung K, Mukherjee D, Dwivedi AK. A systematic review and meta-analysis of geographic differences in comorbidities and associated severity and mortality among individuals with COVID-19. *Sci Rep* 2021; **11**: 8562 [PMID: 33879826 DOI: 10.1038/s41598-021-88130-w]

35 **Tegally H**, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, Doolabh D, Pillay S, San EJ, Msomi N, Mlisana K, von Gottberg A, Walaza S, Allam M, Ismail A, Mohale T, Glass AJ, Engelbrecht S, Van Zyl G, Preiser W, Petruccione F, Sigal A, Hardie D, Marais G, Hsiao NY, Korsman S, Davies MA, Tyers L, Mudau I, York D, Maslo C, Goedhals D, Abrahams S, Laguda-Akingba O, Alisoltani-Dehkordi A, Godzik A, Wibmer CK, Sewell BT, Lourenço J, Alcantara LCJ, Kosakovsky Pond SL, Weaver S, Martin D, Lessells RJ, Bhiman JN, Williamson C, de Oliveira T. Detection of a SARS-CoV-2 variant of concern in South Africa. *Nature* 2021; **592**: 438-443 [PMID: 33690265 DOI: 10.1038/s41586-021-03402-9]

36 **Fundação Ezequiel Dias**. Boletim Informativo - Vigilância Laboratorial dos Vírus Respiratórios. Fundação Ezequiel Dias, 2021 [cited 30 July 2022]. Available from: http://www.funed.mg.gov.br/wp-content/uploads/2021/12/Informe-Virus-Respiratorios.pdf/

37 **Hitchings MDT**, Ranzani OT, Torres MSS, de Oliveira SB, Almiron M, Said R, Borg R, Schulz WL, de Oliveira RD, da Silva PV, de Castro DB, Sampaio VS, de Albuquerque BC, Ramos TCA, Fraxe SHH, da Costa CF, Naveca FG, Siqueira AM, de Araújo WN, Andrews JR, Cummings DAT, Ko AI, Croda J. Effectiveness of CoronaVac among healthcare workers in the setting of high SARS-CoV-2 Gamma variant transmission in Manaus, Brazil: A test-negative case-control study. *Lancet Reg Health Am* 2021; **1**: 100025 [PMID: 34386791 DOI: 10.1016/j.lana.2021.100025]

38 **Moreira FRR**, D'arc M, Mariani D, Herlinger AL, Schiffler FB, Rossi ÁD, Leitão IC, Miranda TDS, Cosentino MAC, Tôrres MCP, da Costa RMDSC, Gonçalves CCA, Faffe DS, Galliez RM, Junior ODCF, Aguiar RS, Dos Santos AFA, Voloch CM, Castiñeiras TMPP, Tanuri A. Epidemiological dynamics of SARS-CoV-2 VOC Gamma in Rio de Janeiro, Brazil. *Virus Evol* 2021; **7**: veab087 [PMID: 34725568 DOI: 10.1093/ve/veab087]

39 **Laboratório Central de Saúde Pública - Bahia**. Relatório dos resultados parciais referente ao sequenciamento de nova geração das amostras de SARS-CoV-2 positivas realizado no Laboratório Central de Saúde Pública Profº Gonçalo Moniz. Secretaria Estadual de Saúde. [cited 1 August 2022]. Available from: http://www.saude.ba.gov.br/wp-content/uploads/2021/05/11.05-BOLETIM-INFORMATIVO-SEQUENCIAMENTO-LACEN-EDICAO-05.pdf/

40 **Padilla-Rojas C**, Barcena-Flores L, Vega-Chozo K, Galarza-Perez M, Bailon-Calderon H, Lope-Pari P, Balbuena-Torres J, Huaringa-Nuñez M, Caceres-Rey O, Rojas-Serrano N. Near-Complete Genome Sequence of a SARS-CoV-2 VOC 202012/01 Strain in Peru. *Microbiol Resour Announc* 2021; **10** [PMID: 33766897 DOI: 10.1128/MRA.00069-21]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1771-1781

DOI: 10.12998/wjcc.v11.i8.1771

ISSN 2307-8960 (online)

CASE REPORT

Pediatric acute heart failure caused by endocardial fibroelastosis mimicking dilated cardiomyopathy: A case report

Yao-Ying Xie, Qiu-Li Li, Xin-Le Li, Fan 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): B, B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Batta A, India; Gupta P, United States; Ong H, Malaysia

Received: August 10, 2022
Peer-review started: August 10, 2022
First decision: October 21, 2022
Revised: October 26, 2022
Accepted: January 9, 2023
Article in press: January 9, 2023
Published online: March 16, 2023

Yao-Ying Xie, Xin-Le Li, College of Clinical Medicine, Inner Mongolia Minzu University, Tongliao 028000, Inner Mongolia Autonomous Region, China

Yao-Ying Xie, Fan Yang, Department of Pediatric Medical Center, Soochow University, Affiliated Hulunbuir Hospital, Hulunbuir 021000, Inner Mongolia Autonomous Region, China

Qiu-Li Li, College of Medicine, Shantou University, Shantou 515063, Guangdong Province, China

Fan Yang, School of Medicine, Shihezi University, Shihezi 832000, Xinjiang Uygur Autonomous Region, China

Corresponding author: Yao-Ying Xie, MD, MSc, PhD, Research Fellow, College of Clinical Medicine, Inner Mongolia Minzu University, No. 536 Huolinhe Street (West), Tongliao 028000, Inner Mongolia Autonomous Region, China. xieyaoying@vip.qq.com

Abstract

BACKGROUND

Endocardial fibroelastosis (EFE) is a diffuse endocardial collagen and elastin hyperplasia disease of unknown etiology, which may be accompanied by myocardial degenerative changes leading to acute or chronic heart failure. However, acute heart failure (AHF) without obvious associated triggers is rare. Prior to the report of endomyocardial biopsy, the diagnosis and treatment of EFE are highly susceptible to being confounded with other primary cardiomyopathies. Here, we report a case of pediatric AHF caused by EFE mimicking dilated cardiomyopathy (DCM), with the aim of providing a valuable reference for clinicians to early identify and diagnose EFE-induced AHF.

CASE SUMMARY

A 13-mo-old female child was admitted to hospital with retching. Chest X-ray demonstrated enhanced texture in both lungs and an enlarged heart shadow. Color doppler echocardiography showed an enlarged left heart with ventricular wall hypokinesis and decreased left heart function. Abdominal color ultrasonography revealed a markedly enlarged liver. Pending the result of the endomyocardial biopsy report, the child was treated with a variety of resuscitative measures including nasal cannula for oxygen, intramuscular sedation with chlorpromazine and promethazine, cedilanid for cardiac contractility enhancement, and diuretic treatment with furosemide. Subsequently, the child's endomyocardial biopsy report result was confirmed as EFE. After the above early

interventions, the child's condition gradually stabilized and improved. One week later, the child was discharged. During a 9-mo follow-up period, the child took intermittent low-dose oral digoxin with no signs of recurrence or exacerbation of the heart failure.

CONCLUSION

Our report suggests that EFE-induced pediatric AHF may present in children over 1 year of age without any apparent precipitants, and that the associated clinical presentations are grossly similar to that of pediatric DCM. Nonetheless, it is still possible to be diagnosed effectively on the basis of the comprehensive analysis of auxiliary inspection findings before the result of the endomyocardial biopsy is reported.

Key Words: Endocardial fibroelastosis; Dilated cardiomyopathy; Pediatric; Acute heart failure; Early identification and diagnosis

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Prior to the report of endomyocardial biopsy, the diagnosis and treatment of endocardial fibroelastosis (EFE) is highly susceptible to be confounded with other primary cardiomyopathies. Herein, we report a case of pediatric acute heart failure (AHF) caused by EFE mimicking dilated cardiomyopathy, aiming to provide a valuable reference for clinicians to early identify and diagnose EFE-induced AHF.

Citation: Xie YY, Li QL, Li XL, Yang F. Pediatric acute heart failure caused by endocardial fibroelastosis mimicking dilated cardiomyopathy: A case report. *World J Clin Cases* 2023; 11(8): 1771-1781
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1771.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1771

INTRODUCTION

Pediatric endocardial fibroelastosis (EFE) is a kind of primary infantile cardiomyopathy, also known as endocardial sclerosis[1]. While various theories have been proposed in recent years in relation to the pathogenesis of EFE, the exact etiology of EFE remains unknown[2]. At present, most scholars believe that it is associated with the immune inflammatory response caused by viral infection[3]. More than 60% of children with onset are younger than 1 year of age[4]. The clinical manifestations of infants under 6 mo of age are principally acute heart failure (AHF), while the clinical manifestations of infants 6 to 12 mo of age are principally chronic heart failure (CHF), and often occurs after respiratory infections [5]. The symptoms and signs of AHF caused by EFE greatly resemble those of the acute exacerbations of dilated cardiomyopathy (DCM) in pediatric patients[5]. However, the treatment options for these two conditions clinically are not exactly identical, and early misdiagnosis may have potentially unintended consequences for the subsequent therapy of the children[6]. More importantly, it is relatively rare for children with EFE over 1 year of age to develop AHF suddenly without any notable triggers or other directly related underlying diseases[7].

Here, we report a case of pediatric AHF caused by EFE mimicking DCM, in which the child was preliminarily diagnosed with EFE based on critical auxiliary examinations encompassing chest radiography, electrocardiography and echocardiography alone before the result of the endomyocardial biopsy was available, and complete clinical remission was achieved with early and correct interventions. By reporting this case, we hope to provide clinicians who are under-resourced for specific subspecialty pathological biopsies with additional empiric references in terms of early screening and differentiating when encountering children with EFE confused with DCM, and to remain vigilant for those children's clinical manifestations.

CASE PRESENTATION

Chief complaints

A 13-mo-old female child was admitted to our hospital with retching for 1 wk and worsening condition for 2 d.

History of present illness

The child had experienced retching without apparent triggers for 1 wk prior to presentation at our hospital, but no vomiting. The child's family denied that the child had a history of fever, rash, cough and expectoration, jaundice, diarrhea, and trauma. Outpatient blood assays revealed hemoglobin (HGB) 84.00 g/L, C-reactive protein (CRP) 0.30 mg/L, and carbon dioxide combining power (CO_2CP) 15.70 mmol/L. During the course of the illness, the child had poor appetite, poor sleep, fair mental status, and reduced urine output, but there was no abnormal exhaust and defecation. The child had no other concomitant symptoms, including any signs of upper respiratory tract infection.

History of past illness

The child was hospitalized in our neonatology unit 1 year ago with a diagnosis of neonatal hyperbilirubinemia (NHB), neonatal bilirubin encephalopathy (NBE), congenital hepatic cyst (CHC), and congenital bilateral renal multiple cysts (CRMCs). NHB and NBE recovered favorably after active treatment. CHC and CRMC were treated with conservative observation, and color ultrasonography of the liver and kidneys were conducted every other year. Anemia was detected at 8 mo of age, with a minimum HGB of about 34 g/L. After treatment with oral medication and dietary therapy, the maximum HGB was about 80 g/L. The child had no previous history of surgery or blood transfusion.

Personal and family history

The child was born of a gravida 1, parity 1 mother. She was delivered vaginally at 38^{+2} wk of gestation, with a birth weight of 2750 g. She was breastfed, with normal growth and developmental milestones and no significant history of medication or food allergies. The child's parents were healthy, and there was no abnormality in the family history.

Physical examination

The child was 74 cm tall and weighed 9.5 kg, with body temperature 36.4 °C, pulse rate 150/min, respiration rate 68/min, blood pressure 77/64 mmHg, and poor general status, tachypnea, anemic appearance. Physical examination showed coarse breath sounds in both lungs, low and dull heart sounds, heart rate 150/min, galloping rhythm, a pansystolic grade 3 murmur in the precardiac area, and the lower border of the liver reaching the right pelvic inlet.

Laboratory examinations

The relevant blood tests of the child after admission are illustrated in Table 1. A number of laboratory test indicators, including HGB, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and ferritin concentration, were decreased. Biomarkers of heart failure such as N-Terminal pro-brain natriuretic peptide were remarkably elevated. No abnormal results were found in urine and stool analyses.

Imaging examinations

Chest X-ray demonstrated enhanced texture in both lungs and enlarged heart shadow, with a cardiothoracic ratio of about 0.62 (Figure 1A). Electrocardiogram (ECG) suggested left axis deviation, paroxysmal supraventricular tachycardia with a heart rate of 150/min and ST-T segment changes. Color doppler echocardiography (CDE) displayed enlarged left heart, thickening of the posterior wall of the left ventricle, minor amounts of mitral regurgitation, ventricular wall hypokinesis and decreased left heart function (Figure 1B-D). Cardiac magnetic resonance (CMR) revealed slight endocardial thickening of the left ventricle, minor thickening of the myocardium, and diffuse motion reduction of the ventricular wall with no apparent delayed enhancement abnormalities (Figure 1E and F). Color ultrasonography of the abdomen showed hepatic cyst (size: 0.93 cm × 0.75 cm), bilateral renal multiple cysts (the largest one size: 1.1 cm × 1.7 cm) and a markedly enlarged liver with a right oblique diameter of 8.25 cm and an inferior hepatic border 6.32 cm from the right inferior costal arch border of the midclavicular line (Figure 2A and B).

FINAL DIAGNOSIS

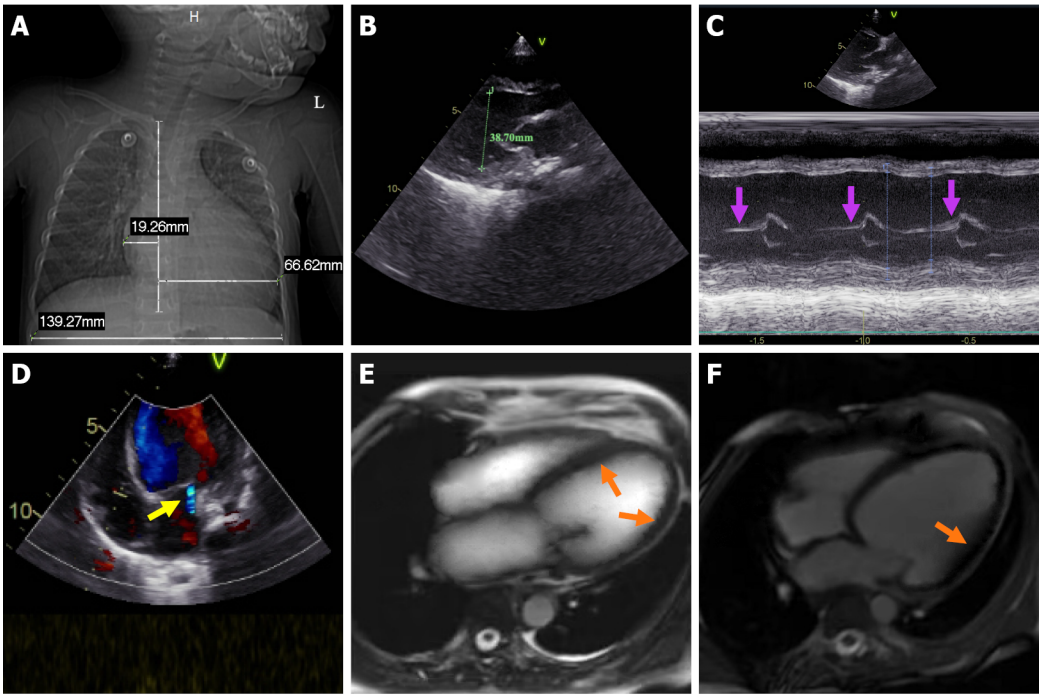
We arranged emergency consultations with multiple disciplines encompassing respiratory medicine, cardiology, hematology, and nursing. According to the clinical symptoms, signs, laboratory examinations, imaging examinations, relevant medical history, age of onset, and rapid development of the condition, the child was preliminarily diagnosed with pediatric AHF caused by EFE. And the result of the final endomyocardial biopsy report also confirmed our diagnosis (Figure 2C and D).

Table 1 Some blood routine and blood biochemistry tests of the child

Test item	Day 1	Day 3	Day 7
WBC	10.11 × 10^9/L (4.4-11.0)	9.32 × 10^9/L (4.4-11.0)	8.68 × 10^9/L (4.4-11.0)
RBC	4.84 × 10^{12}/L (4.0-5.5)	4.77 × 10^{12}/L (4.0-5.5)	4.82 × 10^{12}/L (4.0-5.5)
HGB	84 g/L (112-149)	82 g/L (112-149)	83 g/L (112-149)
HCT	30.7% (34-43)	33.5% (34-43)	38.1% (34-43)
MCV	63.4 fL (76-88)	62.8 fL (76-88)	63.0 fL (76-88)
MCH	17.4 pg (24-30)	16.9 pg (24-30)	17.2 pg (24-30)
MCHC	274 g/L (310-355)	271 g/L (310-355)	273 g/L (310-355)
PLT	522 × 10^9/L (188-472)	487 × 10^9/L (188-472)	445 × 10^9/L (188-472)
LYMPH%	56.3% (23-69)	44.1% (23-69)	40.7% (23-69)
MONO%	7.2% (2-11)	8.1% (2-11)	8.6% (2-11)
NEUT%	34.0% (22-65)	36.7% (22-65)	33.15% (22-65)
LYMPH#	5.69 × 10^9/L (1.8-6.3)	4.42 × 10^9/L (1.8-6.3)	4.05 × 10^9/L (1.8-6.3)
MONO#	0.73 × 10^9/L (0.12-0.80)	0.80 × 10^9/L (0.12-0.80)	0.87 × 10^9/L (0.12-0.80)
NEUT#	3.44 × 10^9/L (1.2-7.0)	3.65 × 10^9/L (1.2-7.0)	3.34 × 10^9/L (1.2-7.0)
RDW-CV	20.4% (10.9-15.0)	19.4% (10.9-15.0)	17.6% (10.9-15.0)
FER	8.11 ng/mL (15.0-150.0)	8.10 ng/mL (15.0-150.0)	8.10 ng/mL (15.0-150.0)
VB_{12}	362.40 pg/mL (197.00-771.00)	348.67 pg/mL (197.00-771.00)	384.22 pg/mL (197.00-771.00)
Folate	18.77 ng/mL (3.89-26.80)	18.03 ng/mL (3.89-26.80)	19.55 ng/mL (3.89-26.80)
CRP	0.3 mg/L (0.0-1.0)	0.2 mg/L (0.0-1.0)	0.05 mg/L (0.0-1.0)
IgG	10.43 g/L (7.00-16.00)	8.27 g/L (7.00-16.00)	9.01 g/L (7.00-16.00)
IgA	1.30 g/L (0.70-4.00)	1.55 g/L (0.70-4.00)	1.41 g/L (0.70-4.00)
IgM	1.73 g/L (0.40-2.30)	1.66 g/L (0.40-2.30)	1.80 g/L (0.40-2.30)
C3	1.56 g/L (0.90-1.80)	1.31 g/L (0.90-1.80)	1.45 g/L (0.90-1.80)
C4	0.32 g/L (0.10-0.40)	0.30 g/L (0.10-0.40)	0.29 g/L (0.10-0.40)
ASO	96 IU/mL (0-170)	83 IU/mL (0-170)	79 IU/mL (0-170)
ESR	16 mm/h (0-20)	14 mm/h (0-20)	12 mm/h (0-20)
PCT	0.12 ng/mL (< 0.05)	0.07 ng/mL (< 0.05)	0.03 ng/mL (< 0.05)
NT-proBNP	893.15 ng/L	517.40 ng/L	190.64 ng/L
Ca	2.65 mmol/L (2.10-2.80)	2.50 mmol/L (2.10-2.80)	2.69 mmol/L (2.10-2.80)
K	4.36 mmol/L (3.70-5.20)	4.62 mmol/L (3.70-5.20)	4.57 mmol/L (3.70-5.20)
Na	139.70 mmol/L (135.00-145.00)	142.74 mmol/L (135.00-145.00)	140.32 mmol/L (135.00-145.00)
Cl	102.80 mmol/L (96.00-108.00)	105.71 mmol/L (96.00-108.00)	103.40 mmol/L (96.00-108.00)
AMY	50.0 U/L (35.0-135.0)	62.0 U/L (35.0-135.0)	57.0 U/L (35.0-135.0)
CO_2CP	15.7 mmol/L (22.0-29.0)	21.1 mmol/L (22.0-29.0)	25.8 mmol/L (22.0-29.0)
ALT	11.0 U/L (7.0-30.0)	10.3 U/L (7.0-30.0)	9.0 U/L (7.0-30.0)
AST	39.0 U/L (15.0-40.0)	36.7 U/L (15.0-40.0)	29.4 U/L (15.0-40.0)
AST/ALT	3.55	3.56	3.27
LDH	394.0 U/L (120.0-250.0)	376.0 U/L (120.0-250.0)	285.0 U/L (120.0-250.0)
CK	100.0 U/L (50.0-310.0)	84.0 U/L (50.0-310.0)	77.0 U/L (50.0-310.0)
CK-MB	23.5 U/L (0.0-25.0)	20.9 U/L (0.0-25.0)	18.4 U/L (0.0-25.0)
α-HBDH	331.0 U/L (72.0-182.0)	255.4 U/L (72.0-182.0)	191.1 U/L (72.0-182.0)

GLU	5.35 mmol/L (3.90-6.10)	5.62 mmol/L (3.90-6.10)	5.05 mmol/L (3.90-6.10)
BUN	3.2 mmol/L (2.7-7.0)	2.9 mmol/L (2.7-7.0)	2.7 mmol/L (2.7-7.0)
CREA	22.2 μmol/L (19.0-44.0)	21.4 μmol/L (19.0-44.0)	20.1 μmol/L (19.0-44.0)

α-HBDH: α-hydroxybutyrate dehydrogenase; ALT: Alanine aminotransferase; AMY: Amylase; ASO: Anti-streptolysin O; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; C3: Complement C3; C4: Complement C4; Ca: Calcium; CO_2CP: Carbon dioxide combining power; CK: Creatine kinase; CK-MB: Creatine kinase MB isoenzyme; Cl: Chlorine; CREA: Creatinine; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; FER: Ferritin; GLU: Glucose; HCT: Hematocrit; HGB: Hemoglobin; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; K: Kalium; LDH: Lactate dehydrogenase; LYMPH%: Lymphocyte ratio; LYMPH#: Lymphocyte count; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; MCV: Mean corpuscular volume; MONO%: Monocyte ratio; Na: Natrium; NEUT%: Neutrophil ratio; NEUT#: Neutrophil count; PCT: Procalcitonin; NT-proBNP: N-terminal pro-brain natriuretic peptide; PLT: Platelet; MONO#: Monocyte count; RBC: Red blood cell; RDW-CV: Red cell distribution width-coefficient of variation; VB_{12}: Vitamin B_{12}; WBC: White blood cell.

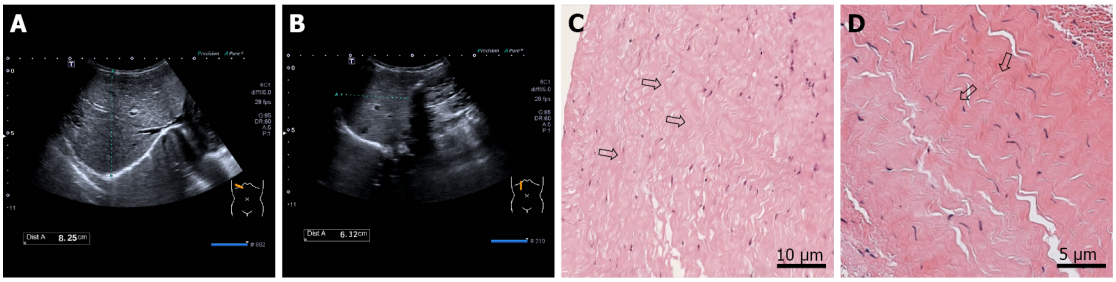


DOI: 10.12998/wjcc.v11.i8.1771 **Copyright** ©The Author(s) 2023.

Figure 1 Chest radiograph, color doppler echocardiography, and cardiac magnetic resonance of the child. A: Prominently enlarged heart with a high cardiothoracic ratio; B: Marked enlargement of the left ventricle (inner diameter 38.70 mm) with diffuse slight thickening of the endocardium; C: Thickening of the posterior wall of the left ventricle (purple arrow); D: A small amount of mitral regurgitation (yellow arrow); E: Bright-blood T_1-weighted image shows slight endocardial thickening of the left ventricle and slight thickening of the myocardium (orange arrow); F: Dark-blood T_2-weighted image shows diffuse ventricular wall hypokinesis without visible delayed enhancement abnormalities (orange arrow).

TREATMENT

As per the standard pediatric advanced life support guidelines, the child was immediately resuscitated and monitored for vital signs, and administered oxygen by nasal cannula (oxygen flow rate: 6 L/min), sedated with chlorpromazine 1 mg/kg and promethazine 1 mg/kg by intramuscular (i.m.) injection, enhanced cardiac contractility with 10 μg/kg cedilanid by intravenous (i.v.) push (half of the total amount given for the first time and the remaining amount given in two divided doses, every 6 h), prompted diuresis with 0.1 mg/kg furosemide by i.v. push (given every 6 h), and relieved bronchospasm and reduced myocardial edema with 0.5 mg/kg dexamethasone by i.v. drip[8]. After the above resuscitation measures, the child fell asleep quietly with heart rate 147/min, respiration rate 43/min, and percutaneous oxygen saturation 95%-99%, under the bedside monitor. In view of the potential for adverse reactions of either oral or i.v. iron supplementation to adversely affect the child's rescue, we managed her anemia with regular dietary iron supplementation during hospitalization. Day 2 ward rounds, the child was in poor general condition with coarse breath sounds in both lungs, low and dull heart sounds, but stable breathing, and a heart rate of 140/min after activity. Cedilanid was given as a maintenance dose for consolidation therapy, vitamin C was administered intravenously for nourishing the myocardium, and changes in the condition were closely observed. Day 3 ward rounds, the child's



DOI: 10.12998/wjcc.v11.i8.1771 **Copyright** ©The Author(s) 2023.

Figure 2 Abdominal color ultrasonography and endomyocardial biopsy for the child. A and B: Congestive hepatomegaly with a right oblique diameter of 8.25 cm and an inferior hepatic border 6.32 cm from the right inferior costal arch border of the midclavicular line; C and D: Endomyocardial biopsy shows diffuse elastin and collagen hyperplasia (black arrow).

general condition improved with stable respiration, breathing rate 45/min, strong and rhythmic heart sounds, and heart rate 120/min. The inferior hepatic border was located approximately 3 cm at the inferior costal arch border of the right midclavicular line, and the hepatomegaly was visibly retracted. Bedside CDE demonstrated that the enlarged left heart began to shrink. After that, low-dose cedilanid was continued for maintenance therapy, and the heart rate status was monitored. Day 4 ward rounds, the child's condition was relatively stable, with heart rate 105-120/min at rest and percutaneous oxygen saturation above 95%. The relevant blood tests were reexamined and all laboratory indicators gradually returned to normal. The maintained dose of cedilanid was given again to continue the treatment, and subtle changes in the condition were monitored. Day 7 ward rounds, the vital signs of the child were stable and the breath was slightly tachypnea, with heart rate 116/min and respiration rate 41/min, under the bedside monitor. The inferior hepatic border was located about 2 cm at the inferior costal arch border of the right midclavicular line, and the spleen was not palpated under the left rib. There was no edema in both lower extremities of the child post treatment and the capillary refill time was around 2 s. On the same day, the relevant blood tests were reexamined again and a number of laboratory test indicators, encompassing hematocrit, CRP and CO_2CP, returned to normal.

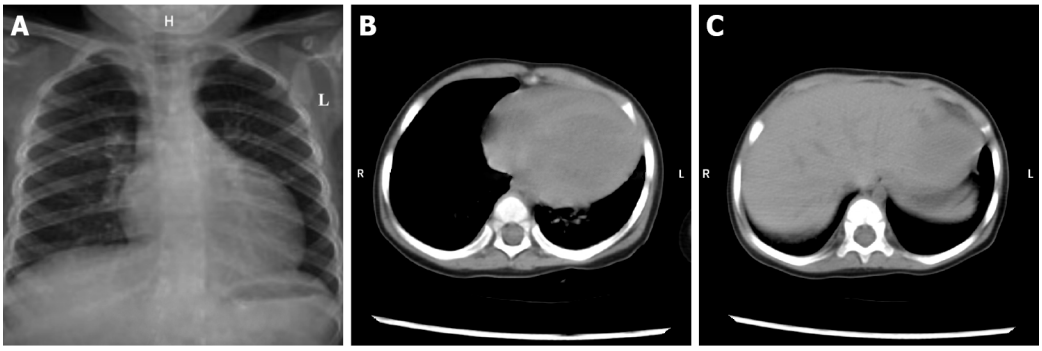
OUTCOME AND FOLLOW-UP

After correct, timely, and effective treatment, the child was discharged on day 7 after admission without any complications. The reexamination result of chest X-ray showed that the enlarged heart shadow was slightly retracted (Figure 3A). Similarly, the computed tomography (CT) reexamination results of thorax and abdomen revealed that the size of enlarged heart was marginally retracted, and the hepatomegaly was visibly retracted (Figure 3B and C). After the child was discharged from our hospital, her anemia improved dramatically with a combination of oral drug (ferrous gluconate: 3 mg per time, three times 1 d) and dietary iron supplementation manners. Except for this, the child took intermittent low-dose oral digoxin (0.05 mg per time, once every 12 h) with no signs of recurrence or exacerbation of the heart failure, within a 9-mo follow-up period. The timeline of the child's visit is illustrated in Figure 4.

DISCUSSION

EFE is one of the important causes of heart failure in infants and toddlers. It occurs in 1/5000 live births and accounts for 1% to 2% of congenital heart disease, which has an unknown etiology and genetic characteristics, can occur in the absence of cardiac malformations[6,9]. The younger the age of onset of the children with EFE, the worse the prognosis and the higher the mortality[10]. Due to the lack of specificity in the presentation of this disease, it is prone to be confounded with pneumonia and myocarditis and other diseases, so the clinical diagnosis before the result of the endomyocardial biopsy report is difficult, especially when combined with other primary cardiomyopathies that can cause left ventricular enlargement, the clinical presentation of EFE may be masked, with a high risk of missed diagnosis and misdiagnosis[10].

Evidence-based medicine has indicated that AHF caused by EFE has a devastating course and severe prognosis[11]. The gold standard for the diagnosis and differential diagnosis of EFE is the endomyocardial biopsy; however, the biopsy result requires a long waiting time[12]. During this time window, clinicians often first need to refer to chest radiographs, ECGs, CDEs and related laboratory examinations for initial diagnosis and early patient management, which is a great test of clinicians' personal competences and experience levels. Currently, no practical guidelines on the diagnosis and treatment of EFE prior to the tissue biopsy result have been released internationally by national heart associations



DOI: 10.12998/wjcc.v11.i8.1771 **Copyright** ©The Author(s) 2023.

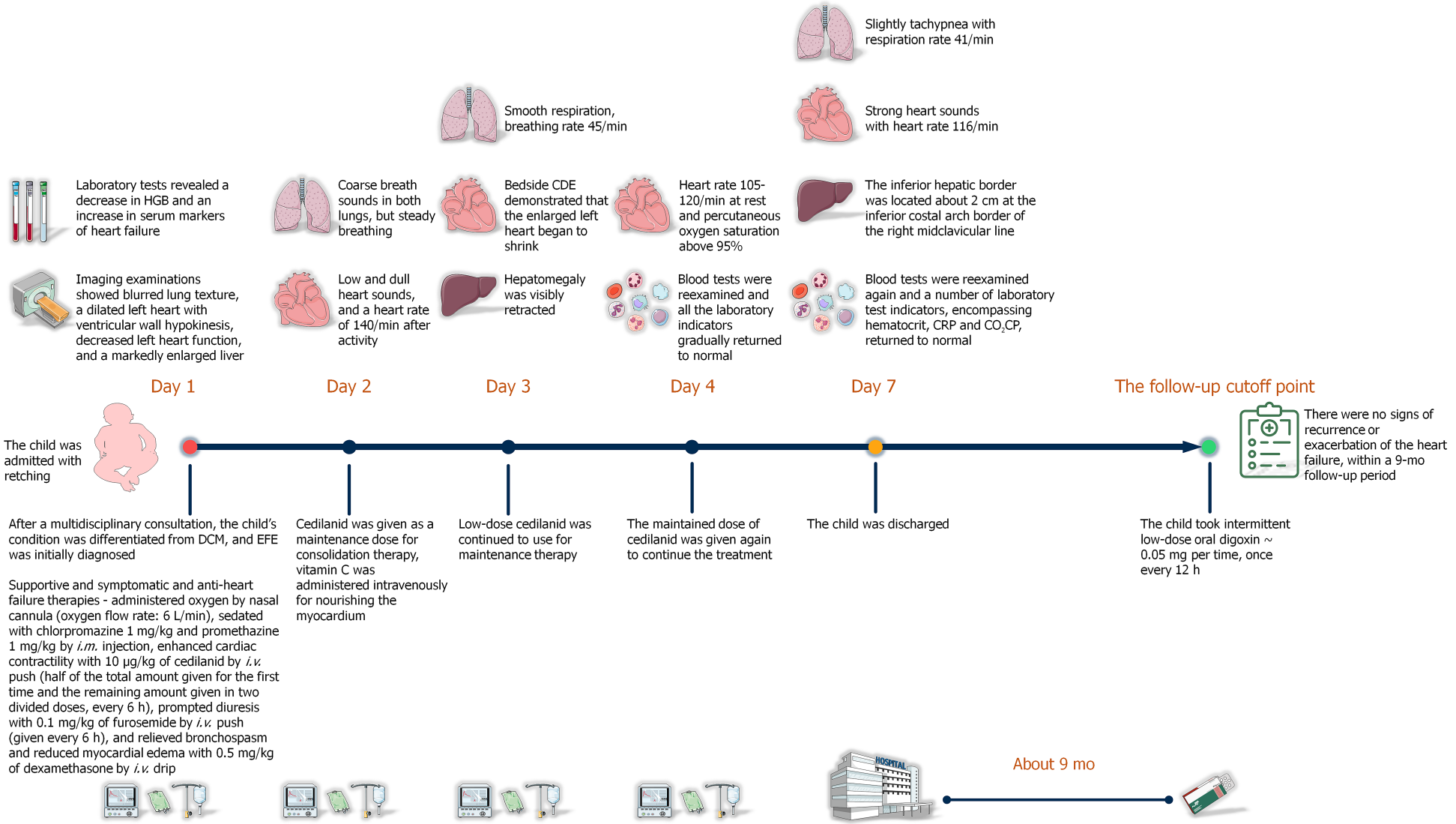
Figure 3 Chest X-ray and thoracic and abdominal computed tomography re-examination results of the child before discharge. A and B: Mild cardiac retraction; C: Remarkable retraction of the previously enlarged liver.

worldwide. The discrimination of pediatric AHF caused by EFE from other diseases with similar clinical symptoms and manifestations is therefore very challenging, especially for DCM in infants and young children[13].

Children younger than 1 year of age or even younger with primary EFE are more likely to be exactly diagnosed according to the age distribution of the onset of pediatric heart diseases[14-16]. Yet, in rare-onset children older than 1 year of age, the manifestation of EFE's cardiac imaging examinations are almost identical to those of early onset DCM in infants and toddlers[17]. Both show a sudden dilatation of a single heart cavity (*e.g.*, the left ventricle) on chest X-ray or chest CT. On a more accurate CDE inspection, both also exhibit the same ventricular wall hypokinesis, varying degrees of ventricular wall thickening, cardiac valve regurgitation, and left heart dysfunction. And more important, the blood-related tests of both present with assay indicators of AHF without any specificity. These things together make it easy for pediatric AHF caused by EFE to be masqueraded as DCM[10].

In our case, this 13-mo-old female child suddenly developed AHR without any triggers and without any history of infection, cardiac malformation, and other underlying cardiovascular disease. This is relatively rare in clinical practice, as many studies suggest that respiratory infections and congenital cardiovascular malformations are important triggers and potential initiators in the development of AHF caused by EFE[10]. We had considered pediatric DCM before the available endomyocardial biopsy result was returned, yet the echocardiographic findings just showed a diffuse and uniform slight thickening of the left ventricular endocardium with echo dense and enhanced, and a clear demarcation between ventricular endocardium and myocardium, a slight thickening of the myocardium, only a small amount of mitral regurgitation, a left ventricular end-diastolic dimension of 42 mm (< 50 mm). In parallel, both bright-blood T_1-weighted image sequences and black-blood T_2-weighted image sequences of the CMR examination of the child demonstrated a general thickening of the endocardium. In fact, for DCM, the possible thickening of the ventricular wall will not appear on the endocardium, but rather more on the thickening of the myocardium, and there are no non-functional fibrotic changes similar to EFE with this thickening. In such cases, when DCM presents with AHF, it is possible that the indicators of left ventricular systolic function on the CDE may not be much decreased. Furthermore, though the ECG manifestations of both DCM and EFE in infants and toddlers are left ventricular high voltage, poor R-wave progression, ST-T segment changes, and various different arrhythmias, the primary characteristics of the former are typically atrial tachycardia and atrial fibrillation. These are all distinctly different from EFE. Of note, the bedside CDE on the 3rd day of admission suggested that the dilated left heart had begun to show retraction, but this is almost impossible in DCM. Because despite the fact that DCM can be relieved, it is difficult to reduce the size of the heart to normal. Combined with the child's age of onset, family history, and the findings of consultations with physicians from different departments, we unanimously agreed that EFE should be given a higher diagnostic priority. With more evidence pointing to EFE, we made a preliminary diagnosis of pediatric AHF caused by EFE prior to the result of the tissue biopsy was reported, which bought valuable time for early timely and correct intervention in the progression of the child's disease. More importantly, both the rapid improvement of the child's condition after treatment and the result of the endomyocardial biopsy report ultimately confirmed that our judgment was correct.

Unfortunately, no directed therapeutic approach for EFE is known since the rarity of the condition [18]. Yet, recovery of the enlarged heart and lost cardiac function in children with EFE is possible, and current clinically recommended treatment typically follows a standardized and vigorous decongestive therapy based on cardiac glycosides[19]. The child followed such a treatment principle from admission to the 9-mo follow-up cut-off point after discharge, and this hospital and domiciliary treatment has helped her well to maintain the sustainability of the decongestive therapy. In recent years, long-term follow-up studies have shown that bioimmunotherapy increases the clinical benefit of children with EFE and helps to improve endocardial hyperplasia and fibrosis[20]. Given the risk of future infection of the



DOI: 10.12998/wjcc.v11.i8.1771 **Copyright** ©The Author(s) 2023.

Figure 4 Timeline of the child's visit, hospitalization, and postdischarge follow-up. CDE: Color doppler echocardiography; CO_2CP: Carbon dioxide combining power; CRP: C-reactive protein; DCM: Dilated cardiomyopathy; HGB: Hemoglobin; i.m.: Intramuscular; i.v.: Intravenous; EFE: Endocardial fibroelastosis.

child's hepatic and renal cysts and the underlying physical conditions, there was no opportunity to apply steroid hormones or other biological immunomodulators to her. However, we still recommend the use of biological immunomodulators for those children with EFE who have indications, because they may improve the prognosis of heart failure. Compared with EFE, while DCM is also treated in the acute exacerbation phase using a heart failure management approach, it is generally managed with long-term diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and beta-blockers to control its progression of CHF and ventricular remodeling due to the irreversibility of cardiac enlargement and decline in cardiac function[21]. Additionally, though bioimmunotherapy for adult DCM seems to benefit a proportion of patients, to date such treatments have not raised sufficient promise for pediatric DCM, and there is no evidence that steroid hormones use reduce mortality and morbidity in children with DCM[22]. As a result, the treatment regimens for EFE and DCM in infants and toddlers are not always identical, and early misdiagnosis improper treatment may have potentially unintended consequences for the children's prognosis.

In infant and young childhood, EFE frequently presents with DCM and unfavorable progression, which makes it difficult for clinicians to distinguish these two diseases[6,23]. While the case we report is successful in differentiating EFE from DCM prior to the pathology report result, this is based more on extensive clinical work experience[24,25]. Limited by the objective one-sidedness of individual information, the early identification of such pediatric AHF caused by EFE masquerading as DCM still requires more clinical medical record information and data support.

CONCLUSION

Here, we report a case of pediatric AHF caused by EFE masquerading as DCM, which was accurately identified early in the course of the disease, for which we demonstrate that a primary diagnosis for EFE before the result of the endomyocardial biopsy is entirely possible. We hope that our report will give clinicians more decision support and attract sufficient attention when diagnosing similar diseases.

ACKNOWLEDGEMENTS

The information in this article does not necessarily reflect the government's position or government policy, and no official endorsement should be inferred. We thank Hulunbuir City People's Hospital for data and technical support. Also, a huge thanks to Miss. Li Qiu-Li for providing the audio, and I wish her all the best in her future wishes and happiness.

FOOTNOTES

Author contributions: Xie YY contributed to the conception of the report; Yang F contributed to the acquisition of the data and literature; Xie YY was responsible for analyzing and drafting the report; Li QL was responsible for editing the language; Li XL participated in manuscript's revision and created Figure 4; All authors reviewed and approved the final version of the manuscript.

Informed consent statement: Signed informed consent form was obtained from the patient for publication of this report. And all the real name information related to the patients had been de-identified.

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).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Yao-Ying Xie 0000-0001-9981-356X; Qiu-Li Li 0000-0003-1752-9552; Xin-Le Li 0000-0001-8833-853X; Fan Yang 0000-0002-4566-2353.

S-Editor: Liu XF
L-Editor: Filipodia

P-Editor: Liu XF

REFERENCES

1 **Ren MY**, Ren LH. Research progress of endocardial fibroelastosis[J]. *Xinxueguan Kangfu Yixue Zazhi* 2020; **29**: 723-726 [DOI: 10.3969/j.issn.1008-0074.2020.06.19]

2 **Xu X**, Friehs I, Zhong Hu T, Melnychenko I, Tampe B, Alnour F, Iascone M, Kalluri R, Zeisberg M, Del Nido PJ, Zeisberg EM. Endocardial fibroelastosis is caused by aberrant endothelial to mesenchymal transition. *Circ Res* 2015; **116**: 857-866 [PMID: 25587097 DOI: 10.1161/CIRCRESAHA.116.305629]

3 **Seki A**, Patel S, Ashraf S, Perens G, Fishbein MC. Primary endocardial fibroelastosis: an underappreciated cause of cardiomyopathy in children. *Cardiovasc Pathol* 2013; **22**: 345-350 [PMID: 23518027 DOI: 10.1016/j.carpath.2013.02.003]

4 **Zhang Yong**, Sun Lingli and Li Tao. Clinical features and outcomes of endocardial fibroelastosis in 60 children[J]. *Zhongguo Fuyou Jiankang Yanjiu* 2014; **5**: 790-792 [DOI: 10.3969/j.issn.1673-5293.2014.05.028]

5 **Pan Y**, Liu XY. Prevalence and predictors of left ventricular reverse remodeling after drug therapy in children with new-onset dilated cardiomyopathy[J]. *Journal of Clinical Pediatrics* 2020; **38**: 851-856 [DOI: 10.3969/j.issn.1000-3606.2020.11.012]

6 **Luca AC**, Lozneanu L, Miron IC, Trandafir LM, Cojocaru E, Pădureț IA, Mihăilă D, Leon-Constantin MM, Chiriac Ș, Iordache AC, Țarcă E. Endocardial fibroelastosis and dilated cardiomyopathy - the past and future of the interface between histology and genetics. *Rom J Morphol Embryol* 2020; **61**: 999-1005 [PMID: 34171049 DOI: 10.47162/RJME.61.4.02]

7 **Zhao Y**, Wang LK, Eskin A, Kang X, Fajardo VM, Mehta Z, Pineles S, Schmidt RJ, Nagiel A, Satou G, Garg M, Federman M, Reardon LC, Lee SL, Biniwale R, Grody WW, Halnon N, Khanlou N, Quintero-Rivera F, Alejos JC, Nakano A, Fishbein GA, Van Arsdell GS, Nelson SF, Touma M. Recessive ciliopathy mutations in primary endocardial fibroelastosis: a rare neonatal cardiomyopathy in a case of Alstrom syndrome. *J Mol Med (Berl)* 2021; **99**: 1623-1638 [PMID: 34387706 DOI: 10.1007/s00109-021-02112-z]

8 **Jiao M**, Han L, Wang HL, Jin M, Wang XF, Zheng K, Liang YM, Xiao YY. A long-term follow-up study on the clinical treatment of 75 cases with primary endocardial fibroelastosis [J]. *Zhonghua Erke Zazhi* 2010; **48**: 603-609 [DOI: 10.3760/cma.j.issn.0578-1310.2010.08.011]

9 **Ren SH**, Qu R, Xiao YJ. Progress of endocardial fibroelastosis[J]. *Zhongguo Xiaoer Jijiu Yixue* 2012; **19**: 437-439 [DOI: 10.3760/cma.j.issn.1673-4912.2012.04.035]

10 **Arya SO**, Karpawich PP, Gupta P, Buddhe S, Singh HR, Hussein Y, Gowda ST. Primary endocardial fibroelastosis presenting in a young child as incessant ventricular tachycardia and dilated cardiomyopathy. *Tex Heart Inst J* 2012; **39**: 714-718 [PMID: 23109776]

11 **Jarrar M**, Vaksmann G, Godart F, Rey C, Dupuis C. [Natural history and prognostic factors in primary endocardial fibroelastosis in infants]. *Arch Mal Coeur Vaiss* 1994; **87**: 653-656 [PMID: 7857189]

12 **Narayan R**, Menahem S, Chow CW, Dennett X. Endomyocardial biopsy in infants and children with cardiomyopathy. *Clin Cardiol* 1991; **14**: 903-907 [PMID: 1764827 DOI: 10.1002/clc.4960141109]

13 **Ponce CC**, Dinamarco PV. Primary endocardial fibroelastosis and nonimmune hydrops fetalis: case report with autopsy. *Fetal Pediatr Pathol* 2015; **34**: 136-139 [PMID: 25517884 DOI: 10.3109/15513815.2014.987936]

14 **Moons P**, Bratt EL, De Backer J, Goossens E, Hornung T, Tutarel O, Zühlke L, Araujo JJ, Callus E, Gabriel H, Shahid N, Sliwa K, Verstappen A, Yang HL, Thomet C. Transition to adulthood and transfer to adult care of adolescents with congenital heart disease: a global consensus statement of the ESC Association of Cardiovascular Nursing and Allied Professions (ACNAP), the ESC Working Group on Adult Congenital Heart Disease (WG ACHD), the Association for European Paediatric and Congenital Cardiology (AEPC), the Pan-African Society of Cardiology (PASCAR), the Asia-Pacific Pediatric Cardiac Society (APPCS), the Inter-American Society of Cardiology (IASC), the Cardiac Society of Australia and New Zealand (CSANZ), the International Society for Adult Congenital Heart Disease (ISACHD), the World Heart Federation (WHF), the European Congenital Heart Disease Organisation (ECHDO), and the Global Alliance for Rheumatic and Congenital Hearts (Global ARCH). *Eur Heart J* 2021; **42**: 4213-4223 [PMID: 34198319 DOI: 10.1093/eurheartj/ehab388]

15 **Liu Y**, Chen S, Zühlke L, Black GC, Choy MK, Li N, Keavney BD. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol* 2019; **48**: 455-463 [PMID: 30783674 DOI: 10.1093/ije/dyz009]

16 **Liu Y**, Chen S, Zühlke L, Babu-Narayan SV, Black GC, Choy MK, Li N, Keavney BD. Global prevalence of congenital heart disease in school-age children: a meta-analysis and systematic review. *BMC Cardiovasc Disord* 2020; **20**: 488 [PMID: 33213369 DOI: 10.1186/s12872-020-01781-x]

17 **Writing Group**, Sachdeva R, Valente AM, Armstrong AK, Cook SC, Han BK, Lopez L, Lui GK, Pickard SS, Powell AJ; Rating Panel, Bhave NM, Sachdeva R, Valente AM, Pickard SS, Baffa JM, Banka P, Cohen SB, Glickstein JS, Kanter JP, Kanter RJ, Kim YY, Kipps AK, Latson LA, Lin JP, Parra DA, Rodriguez FH 3rd, Saarel EV, Srivastava S, Stephenson EA, Stout KK, Zaidi AN; Solution Set Oversight Committee, Gluckman TJ, Aggarwal NR, Bhave NM, Dehmer GJ, Gilbert ON, Kumbhani DJ, Price AL, Winchester DE, Gulati M; Appropriate Use Criteria Task Force, Dehmer GJ, Doherty JU, Bhave NM, Daugherty SL, Dean LS, Desai MY, Gillam LD, Mehrotra P, Sachdeva R, Winchester DE. ACC/AHA/ASE/HRS/ISACHD/SCAI/SCCT/SCMR/SOPE 2020 Appropriate Use Criteria for Multimodality Imaging During the Follow-Up Care of Patients With Congenital Heart Disease: A Report of the American College of Cardiology Solution Set Oversight Committee and Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Pediatric Echocardiography. *J Am Soc Echocardiogr* 2020; **33**: e1-e48 [PMID: 33010859 DOI:

10.1016/j.echo.2020.04.026]
18 **Ozdemir D**, Cortopassi IO, McNamara RL. An illustrative case of endocardial fibroelastosis and recalcitrant intracardiac thrombosis: A case report. *Thromb J* 2019; **17**: 8 [PMID: 31182935 DOI: 10.1186/s12959-019-0199-3]
19 **Manning JA**, Sellers FJ, Bynum RS, Keith JD. The Medical Management of Clinical Endocardial Fibroelastosis. *Circulation* 1964; **29**: 60-65 [PMID: 14105031 DOI: 10.1161/01.cir.29.1.60]
20 **Jiao M**, Han L, Wang HL, Jin M, Wang XF, Zheng K, Liang YM, Xiao YY. [A long-term follow-up study on the clinical treatment of 75 cases with primary endocardial fibroelastosis]. *Zhonghua Er Ke Za Zhi* 2010; **48**: 603-609 [PMID: 21055306]
21 **Weintraub RG**, Semsarian C, Macdonald P. Dilated cardiomyopathy. *Lancet* 2017; **390**: 400-414 [PMID: 28190577 DOI: 10.1016/S0140-6736(16)31713-5]
22 **Soares P**, Rocha G, Pissarra S, Soares H, Flôr-de-Lima F, Costa S, Moura C, Dória S, Guimarães H. Neonatal dilated cardiomyopathy. *Rev Port Cardiol* 2017; **36**: 201-214 [PMID: 28256370 DOI: 10.1016/j.repc.2016.10.007]
23 **Shimada S**, Robles C, Illigens BM, Casar Berazaluce AM, del Nido PJ, Friehs I. Distention of the Immature Left Ventricle Triggers Development of Endocardial Fibroelastosis: An Animal Model of Endocardial Fibroelastosis Introducing Morphopathological Features of Evolving Fetal Hypoplastic Left Heart Syndrome. *Biomed Res Int* 2015; **2015**: 462469 [PMID: 26064914 DOI: 10.1155/2015/462469]
24 **Raboisson MJ**, Fouron JC, Sonesson SE, Nyman M, Proulx F, Gamache S. Fetal Doppler echocardiographic diagnosis and successful steroid therapy of Luciani-Wenckebach phenomenon and endocardial fibroelastosis related to maternal anti-Ro and anti-La antibodies. *J Am Soc Echocardiogr* 2005; **18**: 375-380 [PMID: 15846168 DOI: 10.1016/j.echo.2004.10.023]
25 **Weiner Z**, Shalev E. Doppler fetal echocardiography in endocardial fibroelastosis. *Obstet Gynecol* 2001; **98**: 933-935 [PMID: 11704210 DOI: 10.1016/s0029-7844(01)01505-8]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1782-1787

DOI: 10.12998/wjcc.v11.i8.1782

ISSN 2307-8960 (online)

CASE REPORT

Extensively infarcted giant solitary hamartomatous polyp treated with endoscopic full-thickness resection: A case report

Lu Ye, Ji-Hong Zhong, Yong-Pan Liu, Dan-Dan Chen, Si-Yi Ni, Fa-Quan Peng, Shuo Zhang

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

P-Reviewer: Meshikhes AW, Saudi Arabia; Oura S, Japan

Received: September 30, 2022
Peer-review started: September 30, 2022
First decision: January 3, 2023
Revised: January 17, 2023
Accepted: February 15, 2023
Article in press: February 15, 2023
Published online: March 16, 2023

Lu Ye, Dan-Dan Chen, The Second Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou 310053, Zhejiang Province, China

Ji-Hong Zhong, Yong-Pan Liu, Si-Yi Ni, Shuo Zhang, Department of Gastroenterology, The Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310005, Zhejiang Province, China

Fa-Quan Peng, Department of Pathology, The Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310005, Zhejiang Province, China

Corresponding author: Shuo Zhang, PhD, Chief Doctor, Professor, Department of Gastroenterology, The Second Affiliated Hospital of Zhejiang Chinese Medical University, No. 318 Chaowang Road, Gongshu District, Hangzhou 310005, Zhejiang Province, China. zhangshuotcm@163.com

Abstract

BACKGROUND

Solitary hamartomatous polyps (SHPs) are rare lesions. Endoscopic full-thickness resection (EFTR) is a highly efficient and minimally invasive endoscopic procedure that benefits from complete lesion removal and high safety.

CASE SUMMARY

A 47-year-old man was admitted to our hospital after experiencing hypogastric pain and constipation for over fifteen days. Computed tomography and endoscopy revealed a giant pedunculated polyp (approximately 18 cm long) in the descending and sigmoid colon. This is the largest SHP reported to date. Having considered the condition of the patient and mass growth, the polyp was removed using EFTR.

CONCLUSION

On the basis of clinical and pathological evaluations, the mass was considered an SHP.

Key Words: Solitary hamartomatous polyp; Endoscopic full-thickness resection; Diagnosis; Treatment; Descending colon; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Solitary hamartomatous polyps (SHPs) are rarely encountered and seldom reported in the literature. Most SHPs occur in the stomach and small intestine. An SHP in the descending colon has not been reported previously. In this report, we describe a giant pedunculated polyp, approximately 18 cm long, diagnosed as an extensively pedunculated giant SHP. We successfully resected this polyp using endoscopic full-thickness resection, which provides a viable option for the clinical resection of giant pedunculated polyps.

Citation: Ye L, Zhong JH, Liu YP, Chen DD, Ni SY, Peng FQ, Zhang S. Extensively infarcted giant solitary hamartomatous polyp treated with endoscopic full-thickness resection: A case report. *World J Clin Cases* 2023; 11(8): 1782-1787
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1782.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1782

INTRODUCTION

Solitary hamartomatous polyps (SHPs) are a rare type of gastrointestinal disorder that in 65% of cases occur in the stomach and small intestine. Previously, this type of polyp has been considered a variant of Peutz–Jeghers syndrome; however, it is now believed to be a distinct disease[1]. Notably, the disease has no typical clinical manifestations or signs, with most cases being discovered incidentally during physical examinations or visits for complications, such as intestinal bleeding, intussusception, and obstruction. The treatment of SHP involves endoscopic or surgical resection. In this report, we describe an extensively infarcted giant SHP, which was successfully resected using EFTR. We also describe the characteristics of colonic SHP and its treatment.

CASE PRESENTATION

Chief complaints

Abdominal pain with constipation of over fifteen days duration.

History of present illness

The patient reported to our hospital with a slight pain in the hypogastrium. The course of the disease was accompanied by the passage of pellet-like stools.

History of past illness

The patient had no history of past illness.

Personal and family history

There was no history of personal or family illness.

Physical examination

Physical examination revealed a soft, mobile, and ill-defined mass, with tenderness, in the hypogastrium. The skin of the patient was non-pigmented. There was no tension in his abdominal muscles, and he reported no experience rebound pain. However, his peristaltic bowel sounds were heightened.

Laboratory examinations

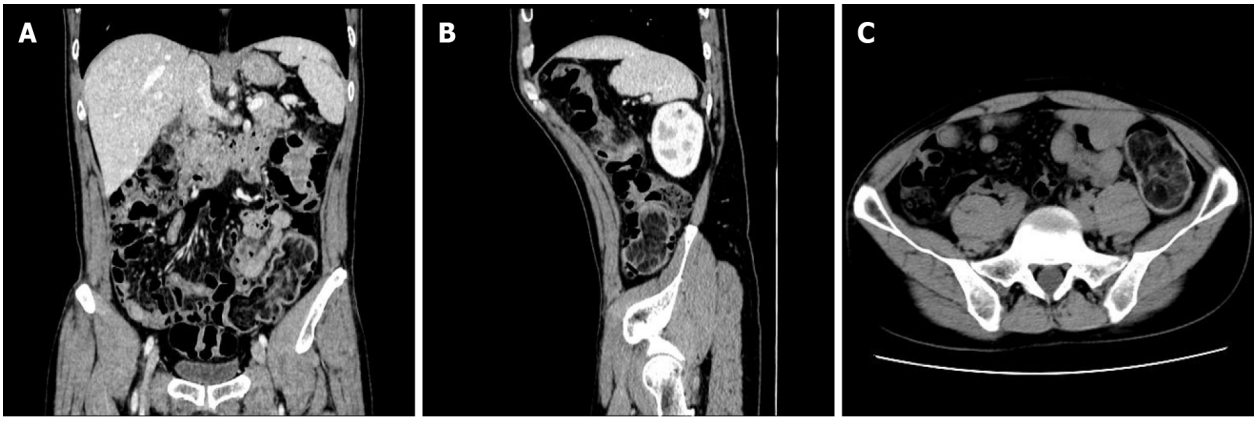
The results of all laboratory examinations were within normal limits.

Imaging examinations

Computerized tomography revealed a lipid-laden mass, leading to intussusception (Figure 1). Endoscopy revealed a giant mass in the descending and sigmoid colons. The stalk of the mass was attached to the colonic cavity 50 cm from the anus, and the surface of the surrounding colonic cavity was eroded (Figure 2).

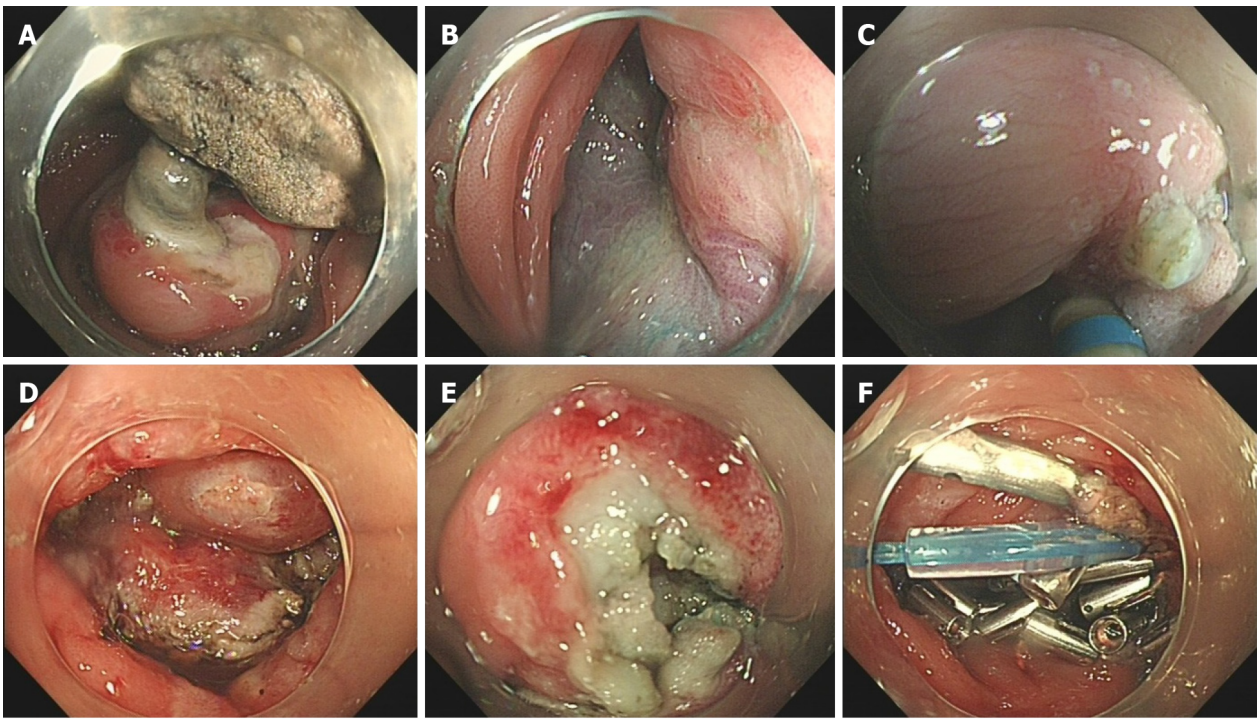
FINAL DIAGNOSIS

The resected specimen revealed an abnormally shaped polyp (Figure 3), and on the basis of clinical and pathological evaluations, the mass was diagnosed as an SHP.



DOI: 10.12998/wjcc.v11.i8.1782 **Copyright** ©The Author(s) 2023.

Figure 1 Abdominal computed tomography images. A: Coronal image; B: Sagittal image; C: Transverse image.

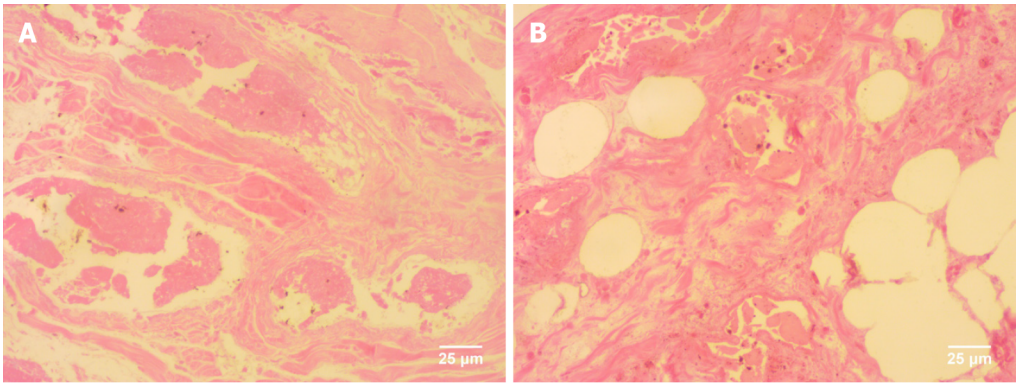


DOI: 10.12998/wjcc.v11.i8.1782 **Copyright** ©The Author(s) 2023.

Figure 2 Endoscopy images. A: The pedicle attached to the colon; B: Localized polyp patterns can be seen endoscopically; C: Circumferential pre-cutting around the lesion after submucosal injection; D: Endoscopic full-thickness resection of the polyp; E: Endoscopic transcanal incision; F: Closure of the wound using the purse-string closure method with nylon cord and multiple metallic clips.

TREATMENT

After a detailed discussion with the patient and his family, the decision was made to perform endoscopic full-thickness resection (EFTR) to clarify the diagnosis. Having defined the extent of the lesion, an endoscopist performed a submucosal injection, followed by circumferential dissection of the submucosa along the perimeter of the lesion, using a Dual Knife (KD-611L; Olympus, Tokyo, Japan). The mass associated with the lesion was then resected using an insulated-tip knife (KD-640L; Olympus, Tokyo, Japan). Nylon loops (L-L08-04; Leo Med, Changzhou, China) and resolution clips (M00522610; Boston Scientific, Marlborough, United States) were used to ligate the wounds (Figure 2). Following suturing, the distal end of the polyp was encircled with an endoscopic snare and slowly pulled toward the rectum. Although difficulty was experienced in passing the resected polyp through the anal canal, the polyp was pulled out of the intestine intact after the application of glycerin and manual dilatation of the anus (Figure 4). Subsequently, the entire gastric and colonic cavity were examined endoscopically, which revealed no other polyps. The patient experienced vague abdominal pain after EFTR. The findings of routine blood and C-reactive protein (CRP) tests revealed that the patient had a high white



DOI: 10.12998/wjcc.v11.i8.1782 **Copyright** ©The Author(s) 2023.

Figure 3 Pathological section of the specimen (hematoxylin and eosin staining, 400×). A: Histopathologic findings depicting widespread necrotic and liquified degenerated fibrous, smooth muscle and vascular adipose tissue; B: Lacunae of varying sizes intersperse with smooth muscle tissues. Necrotic degenerated epithelial lining is observed within the lumen.

blood cell count (average: 15.9 × 109/L, normal range: 3.9–9.5 × 109/L) and high levels of CRP (33.81 mg/L, normal range: 0–10 mg/L). Consequently, the administration of antibiotics (levofloxacin 0.5 g once daily) was continued to combat infection, and the patient was managed with fasting and parenteral nutrition. He was subsequently discharged from hospital after 10 d of monitoring.

OUTCOME AND FOLLOW-UP

At the time of discharge, the patient had no abdominal pain. Although he passed a flatus, the bowel was not voided. The final follow-up session took place nine months after the initial consultation, and he currently remains free of symptoms. Colonoscopy indicated a slight narrowing of the intestinal canal 50 cm from the anus, although no significant edema of the surrounding mucosa.

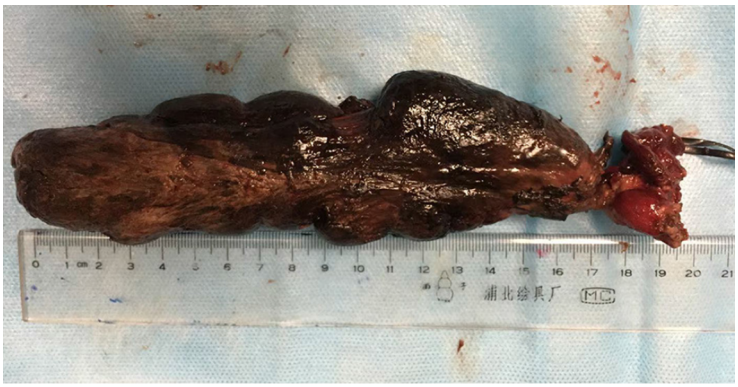
DISCUSSION

Colonic polyps, including adenomatous, inflammatory, hyperplastic, and hamartomatous polyps, and miscellaneous lesions, are among the most common diseases of the digestive tract. Hamartomatous polyps are particularly rare, with SHPs being the rarest type of gastrointestinal polyp. The SHP is a benign polyp with a considerably low incidence rate. Our review of reported cases of colonic SHP published in the EMBASE and PubMed databases revealed only five such cases[1-5]. Although patients with SHP lack specific clinical symptoms, they may have clinical manifestations, such as constipation, hematochezia, and changes in defecation habits associated with intestinal bleeding, intussusception, intestinal obstruction, and other complications. Among the cases we reviewed, one of the patients was diagnosed due to an intestinal obstruction, whereas in the other four cases, the patients were incidentally found to have a mass on physical examination. In general, colonic SHPs are less than 2 cm in size (Table 1). Endoscopically, colonic SHPs are lobulated and red, whereas microscopically, the polyp consists of glands, smooth muscle, and focal mature lymphoid tissue with a normal lamina propria structure[6]. On the basis of our analysis of the literature, we established that small hamartomatous polyps are commonly treated with endoscopic excision, whereas large polyps or polyps with other comorbidities are treated surgically. All but one of the aforementioned five patients did not have a follow-up visit, and the remainder of the patients experience no recurrence, regardless of surgical or endoscopic treatment. In the case reported herein, the polyp was endoscopically red in color and lobulated, and microscopically was characterized by widespread necrotic and liquified degenerated fibrous, smooth muscle and vascular adipose tissue. Lacunae of varying sizes were interspersed with smooth muscle tissues, and a necrotic epithelial lining was observed within the lumens. To the best of our knowledge, the extensive necrotic degeneration of the tissue owing to infarction was caused by interruption of the blood supply and obstruction of the venous return caused by twisting of the stalk of the mass.

Although gastrointestinal hamartomatous polyps are not classed as tumors, they are associated with the risk of cancer. In the case presented by Vanoli *et al*[3], the authors reported the occurrence of an intramucosal carcinoma arising within a solitary juvenile polyp of the transverse colon. Consequently, following a diagnosis of SHP, polyp removal and general examination are considered necessary. However, although there are no established guidelines; endoscopy and surgical resection are the main

Table 1 Reported cases of solitary hamartomatous polyps in the EMBASE and PubMed databases

No.	Ref.	Size (cm)	Location	Treatment	Complications	Follow-up
1	Oluyemi *et al*[1], 2021	Not mentioned	Sigmoid colon	Endoscopic	No complications	No recurrence
2	Papalampros *et al*[2], 2017	Not mentioned	Sigmoid colon	Surgery	Intestinal obstruction	No recurrence
3	Vanoli *et al*[3], 2015	0.18	Transverse colon	Endoscopic	Malignant transformation	No recurrence
4	Putra *et al*[4], 2019	2	Transverse colon	Not mentioned	No complications	Not mentioned
5	Itaba *et al*[5], 2009	1.8	Sigmoid colon	Endoscopic	No complications	No recurrence



DOI: 10.12998/wjcc.v11.i8.1782 **Copyright** ©The Author(s) 2023.

Figure 4 Macroscopic view of the specimen (hematoxylin and eosin staining, 400×). The specimen consists of a ham-hock-like mass with a stalk measuring 15.5 cm × 5.5 cm × 2.5 cm. The stalk was approximately 1.5 cm long and 0.7 cm in diameter. The parenchymatous mass was medium in texture, with a rough, dark red surface. The 3 cm × 2 cm × 2 cm mucosal tissue, which was dark red and smooth, was attached to the base of the stalk.

surgical methods. Compared with surgical procedures, endoscopy facilitates the examination of the entire intestine at a single time and can be used to directly remove polyps. In addition, EFTR leaves only small wounds and causes less blood loss. The procedure causes less disruption of the physiological structure, thereby ensuring maximal preservation of the normal physiological function of the digestive tract and minimizing complications caused by surgery. Moreover, EFTR is typically less expensive than other procedures and causes less operative morbidity and trauma, whilst facilitating a more rapid recovery and a better quality of life than surgery[7]. The EFTR procedure can, nevertheless, have certain complications, among which, infection and wound dehiscence are two most commonly reported[8]. Infections can, however, be successfully managed using antiseptics and wound dehiscence can be minimized under endoscopic treatment. Otherwise, additional surgery should be applied. Although the safety and efficacy of laparoscopic and endoscopic cooperative surgery (LECS) is similar to that of EFTR, the operator is required to master both endoscopic and laparoscopic techniques. Consequently, we believe that LECS could be used as a treatment option for patients with large SHPs that cannot be treated using the endoscopic procedure. In the case reported herein, the experienced endoscopist removed the 18-cm-long polyp *via* EFTR, having taken into consideration the patient's condition and the characteristics of the polyp. However, owing to the large nature of the resulting wound, prior to being discharged, the patient remained hospitalized for 10 d in order to prevent complications.

CONCLUSION

SHPs are a rare type of lesion that can lead to complications, including intussusception and bleeding. Consequently, SHPs should be excised at the earliest opportunity. Traditionally, surgery has been the standard approach for treating SHPs; however, with the development of endoscopic techniques, giant polyps can now be successfully removed using endoscopic surgery. EFTR thus provides a viable treatment option for the clinical removal of giant polyps.

FOOTNOTES

Author contributions: Ye L consulted the literature and drafted the manuscript; Zhong JH and Liu YP developed the patient's treatment plan and revised the manuscript; Chen DD and Ni SY contributed to the diagnosis and treatment

of the patient; Peng FQ made a pathological diagnosis; Zhang S completed colonoscopy surgery; All authors gave final approval for the version to be submitted.

Supported by the Natural Science Foundation of Zhejiang Province, China, No. LY21H290004.

Informed consent statement: Informed written consent was obtained from the patient regarding the publication of this report and accompanying images.

Conflict-of-interest statement: All the authors have no conflict of interest to declare.

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).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Lu Ye 0000-0003-0934-5788; Ji-Hong Zhong 0000-0002-6281-470X; Yong-Pan Liu 0000-0002-8172-9535; Dan-Dan Chen 0000-0002-9320-3522; Si-Yi Ni 0000-0002-2457-9630; Fa-Quan Peng 0000-0002-6710-0108; Shuo Zhang 0000-0003-1120-5872.

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

REFERENCES

1 **Oluyemi AO**, Odeghe EA, Awolola NA. Solitary peutz-jeghers type hamartoma in a Nigerian: A case report of a rare finding and review of literature. *Ann Afr Med* 2021; **20**: 307-309 [PMID: 34893571 DOI: 10.4103/aam.aam_37_20]
2 **Papalampros A**, Vailas MG, Sotiropoulou M, Baili E, Davakis S, Moris D, Felekouras E, Deladetsima I. Report of a case combining solitary Peutz-Jeghers polyp, colitis cystica profunda, and high-grade dysplasia of the epithelium of the colon. *World J Surg Oncol* 2017; **15**: 188 [PMID: 29047391 DOI: 10.1186/s12957-017-1253-x]
3 **Vanoli A**, Lucioni M, Biletta E, Chiaravalli AM, Alvisi C, Luinetti O. A Wolf in Sheep's Clothing: A Sporadic Juvenile Polyp of the Colon Harboring an Intramucosal Adenocarcinoma. *Int J Surg Pathol* 2015; **23**: 571-574 [PMID: 26215217 DOI: 10.1177/1066896915596809]
4 **Putra J**, Mulder DJ. Solitary Peutz-Jeghers type hamartomatous polyp in the transverse colon of an adolescent with ulcerative colitis. *Dig Liver Dis* 2019; **51**: 1738 [PMID: 31623956 DOI: 10.1016/j.dld.2019.09.005]
5 **Itaba S**, Iboshi Y, Nakamura K, Kanayama K, Akiho H, Goto A, Yao T, Takayanagi R. Education and imaging. Gastrointestinal: Solitary Peutz-Jeghers-type hamartoma of the colon. *J Gastroenterol Hepatol* 2009; **24**: 498 [PMID: 19335790 DOI: 10.1111/j.1440-1746.2009.05836.x]
6 **Cauchin E**, Touchefeu Y, Matysiak-Budnik T. Hamartomatous Tumors in the Gastrointestinal Tract. *Gastrointest Tumors* 2015; **2**: 65-74 [PMID: 26672891 DOI: 10.1159/000437175]
7 **Liu Q**, Ding L, Qiu X, Meng F. Updated evaluation of endoscopic submucosal dissection *vs* surgery for early gastric cancer: A systematic review and meta-analysis. *Int J Surg* 2020; **73**: 28-41 [PMID: 31783166 DOI: 10.1016/j.ijsu.2019.11.027]
8 **ASGE Technology Committee**, Aslanian HR, Sethi A, Bhutani MS, Goodman AJ, Krishnan K, Lichtenstein DR, Melson J, Navaneethan U, Pannala R, Parsi MA, Schulman AR, Sullivan SA, Thosani N, Trikudanathan G, Trindade AJ, Watson RR, Maple JT. ASGE guideline for endoscopic full-thickness resection and submucosal tunnel endoscopic resection. *VideoGIE* 2019; **4**: 343-350 [PMID: 31388606 DOI: 10.1016/j.vgie.2019.03.010]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1788-1793

DOI: 10.12998/wjcc.v11.i8.1788

ISSN 2307-8960 (online)

CASE REPORT

Combined hamartoma of the retina and retinal pigment epithelium: A case report

Qing Ren, Ning Han, Rui Zhang, Ruo-Fan Chen, Peng Yu

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Laddha UD, India; Lee WJA, Taiwan

Received: October 22, 2022
Peer-review started: October 22, 2022
First decision: January 3, 2023
Revised: January 19, 2023
Accepted: February 21, 2023
Article in press: February 21, 2023
Published online: March 16, 2023

Qing Ren, Ning Han, Rui Zhang, Ruo-Fan Chen, Peng Yu, Department of Ophthalmology, The Second Hospital of Jilin University, Changchun 130022, Jilin Province, China

Corresponding author: Peng Yu, Doctor, Deputy Director, Department of Ophthalmology, The Second Hospital of Jilin University, No. 4026 Yatai Street, Nanguan District, Changchun 130022, Jilin Province, China. ypeng@jlu.edu.cn

Abstract

BACKGROUND

Combined hamartoma of the retina and retinal pigment epithelium (CHRRPE) is a rare congenital benign tumor which is commonly monocular. Typical CHRRPE comprises slightly raised lesions at the posterior pole, with proliferation membrane often leading to vascular distortion. In severe cases, macular edema, macular hole, retinal detachment or vitreous hemorrhage may occur. Patients with atypical clinical manifestations are prone to misdiagnosis by inexperienced ophthalmologists.

CASE SUMMARY

A 33-year-old man reported onset of right eye blurred vision for one week prior. Anterior segment and intraocular pressure were normal in both eyes. Left eye fundus photography was normal. Right eye ophthalmoscopy showed vitreous hemorrhage and off-white raised retinal lesions below the optic disc. Proliferative membranes on the lesion surfaces resulted in superficial retinal detachment and tortuosity and occlusion of peripheral blood vessels. A horseshoe-like tear in the temporal periphery was surrounded by retinal detachment. Optical coherence tomography revealed retinal thickening at the focal site with structural disturbance indicated by high reflectance. Right eye ultrasound showed retinal thickening at the lesion, stretching and uplifting of the proliferative membrane, with moderately patchy echo at the optic disc edge. Cytokines and antibodies were detected in vitreous fluids during the operation to rule out other diseases. Fundus fluorescein angiography (FFA) at postoperative follow-up led to final diagnosis of CHRRPE.

CONCLUSION

FFA is helpful in diagnosing retinal and retinal pigment epithelial combined hamartoma. In addition, other cytokine and etiological tests facilitate further differential diagnosis to rule out other suspected diseases.

Key Words: Combined hamartoma of the retina and retinal pigment epithelium; Ocular toxoplasmosis; Fundus fluorescein angiography; Vitreous hemorrhage; Retinal tears; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Combined hamartoma of the retina and retinal pigment epithelium(CHRRPE) is a rare benign retinal tumor, especially in atypical cases with vitreous hemorrhage and retinal hole, and is likely to be misdiagnosed by inexperienced young doctors. Fundus fluorescein angiography is instructive when diagnosis is difficult, and some etiological tests can also help to identify other inflammatory diseases. This article provides an example of diagnosis to aid young doctors' reflection and learning.

Citation: Ren Q, Han N, Zhang R, Chen RF, Yu P. Combined hamartoma of the retina and retinal pigment epithelium: A case report. *World J Clin Cases* 2023; 11(8): 1788-1793
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1788.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1788

INTRODUCTION

Combined hamartoma of the retina and retinal pigment epithelium (CHRRPE) typically occurs in retinopathy with a very mild elevation of the optic disc or with a tightly attached hyperplastic membrane. Retinal blood vessels are often distorted or even occluded by traction of fibrous membrane, and the macula may be displaced through a macular hole[1]. In the present case, an off-white lesion was found below the optic disc during specialist physical examination, and vitreous hemorrhage. Temporal retinal tear exist independently. We report a rare case of CHRRPE with independent retinal breaks.

CASE PRESENTATION

Chief complaints

A 33-year-old male presented to our hospital reporting impaired vision in his right eye.

History of present illness

The patient reported no accompanying symptoms such as headache or eye pain and had no known disease. He denied rheumatic immune disease; infectious diseases such as tuberculosis and acquired immunodeficiency syndrome were excluded by routine examination after admission.

History of past illness

Unremarkable.

Personal and family history

The patient denied a family history of genetic disease, had no history of pet feeding, eating raw meat, working in a farm or slaughterhouse, and no family history of Toxoplasma infection. His parents were not consanguineous.

Physical examination

No anterior segment abnormalities were found on slit lamp examination. Under the ophthalmoscope, vitreous hemorrhage and off-white raised retinal lesions were observed below the right optic disc. Proliferative membranes on the lesion surfaces resulted in superficial retinal detachment and tortuosity and occlusion of peripheral blood vessels. A horseshoe-like tear in the temporal periphery was surrounded by retinal detachment.

Laboratory examinations

On ophthalmic examination, the patient's best corrected visual acuity was 20/40 in the right eye and 20/20 in the left eye, and intraocular pressure was 14 mmHg in the right eye and 15 mmHg in the left eye (1 mmHg = 0.133 kpa). The patient underwent vitrectomy on his right eye on January 5, 2022. During the procedure, vitreous fluid was collected to test for the following pathogenic microorganisms: Bacteria, viruses, fungi, parasites and other pathogens (including mycobacterium and mycoplasma/chlamydia). Test results were negative. Other cytokines and antibodies were detected in vitreous fluids

(Table 1). Interleukin (IL)-10 and IL-6 were in the normal range, with only a slight increase in IL-8, excluding uveitis. Basic fibroblast growth factor (which can stimulate cell mitosis and promote collagen production in fibrocytes) and its receptors are present in proliferative vitreoretinopathy, proliferative membranes and vascular endothelial cells. In this case, increased BEGF content in vitreous fluid corresponds to the formation of proliferative film on the lesion surface. Vascular endothelial cell adhesion molecules are associated with blood-eye barrier breakdown, and moderately elevated titers indicate moderate intraocular tissue edema.

Imaging examinations

Fundus photography of the right eye showed vitreous hemorrhage and off-white elevated retinal lesions just below the optic disc, with irregular edges protruding into the vitreous cavity. Proliferative membranes observed on the surface of the lesions had resulted in superficial retinal detachment and tortuosity and occlusion of peripheral blood vessels. A horseshoe-like tear about 1 disc diameter in size was seen in the temporal peripheral retina, surrounded by a small area of retinal detachment (Figure 1A). Optical coherence tomography revealed retinal thickening at the focal site with retinal structural disturbances indicated by areas of high and low reflectance (Figure 1B). Color ultrasound of the right eye showed retinal thickening at the lesion, stretching and uplifting of the proliferative membrane, moderate strength patchy echo at the edge of the optic disc, and sound shadow behind the echo (Figure 1C). Twelve days after the surgery, fundus fluorescein angiography (FFA) was performed and revealed vascular lesions of about 1.5 disc diameters below the optic disc of the right eye, with surrounding pigment disorder and atrophy, twisted blood vessels below the optic disc and fluorescence leakage. Indocyanine green angiography (ICGA) showed persistently low fluorescence below the optic disc (Figures 1D and E). These features led to the diagnosis of CHRRPE.

FINAL DIAGNOSIS

CHRRPE.

TREATMENT

CHRRPE is a congenital benign retinal tumor which grows slowly and generally does not require treatment in the absence of ocular symptoms. In the present case, due to the superficial retinal detachment caused by the formation of anterior retinal membrane, accompanied by vitreous hemorrhage and retinal tears, right eye vitrectomy combined with silicon oil tamponade was performed on January 5, 2022. Intraoperatively, the proliferative membrane on the surface of the lesion was removed and the final stage of the procedure was to fill with silicone oil, which is essential to allow time for chorioretinal adhesions to form after laser treatment. There were no adverse events during or after surgery.

OUTCOME AND FOLLOW-UP

The patient was reexamined two weeks after surgery and examination showed good retinal reduction and sealing of the original retinal tears. Regular reexamination was arranged and silicone oil was removed from the eye as appropriate.

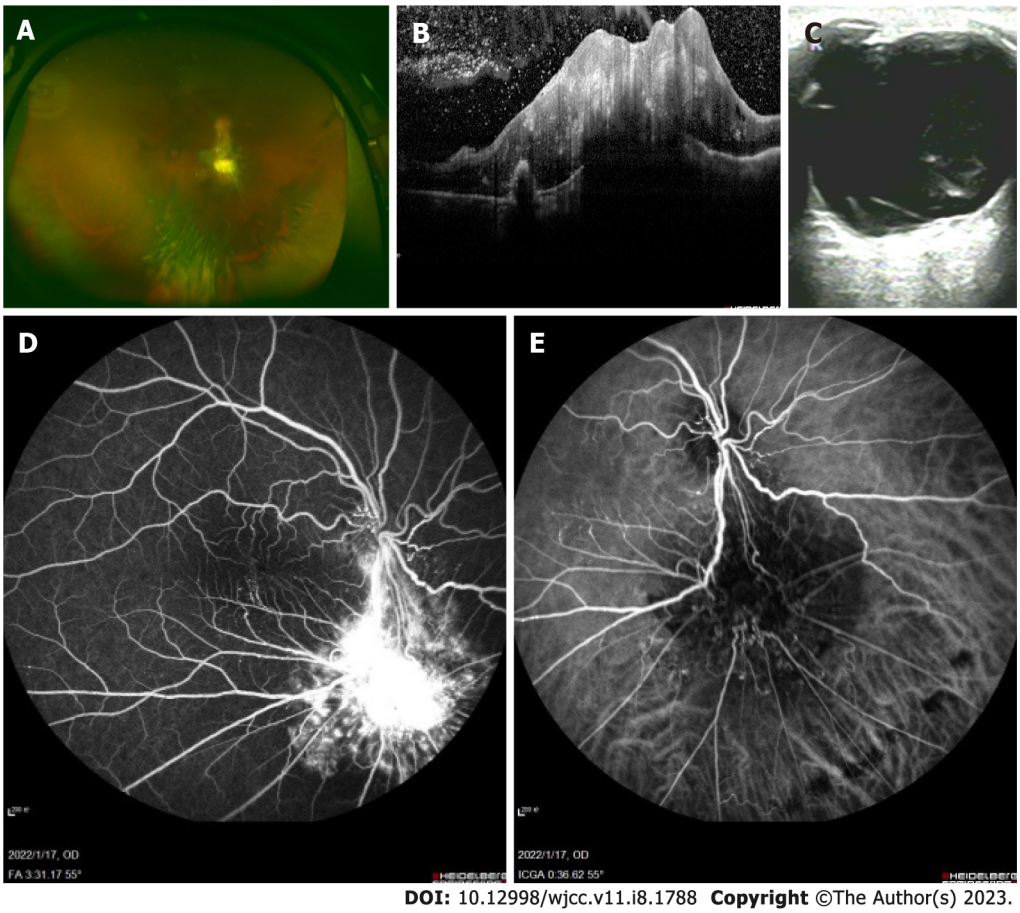
DISCUSSION

CHRRPE was first reported by Gass[2] in 1973 and tends to occur in children, but has also been reported in young people or the elderly[3,4]. It usually occurs in one eye and is rarely associated with systemic disease, but a few cases may be associated with type II or type I neurofibromatosis[5]. The common symptoms of CHRRPE are painless vision loss and strabismus, but it may be symptomless and detected only on fundus examination, depending on the lesion location[6,7]. In the present case, the patient was hospitalized due to painless vision loss caused by vitreous hemorrhage, and an off-white lesion was found below the optic disc during specialist physical examination. Typical CHRRPE commonly manifests as mild elevation of the retina at the optic disc or posterior pole, with a layer of proliferative membranes tightly attached to the surface. Retinal blood vessels are often distorted by traction of the fibrous membrane, and the macula may be displaced through macular holes. Vascular leakage, also caused by traction of the fibrous membrane, is a rare occurrence which results in macular edema, retinal detachment, and even vitreous hemorrhage[8]. Retinal tears are an important cause of vitreous

Table 1 Results of cytokine test in vitreous fluid

No.	Test item	Result	U	Reference range	T
1	TB-IgG	0.24	S/CO	< 1	-
2	Toxoplasma IgG	1.01	IU/mL	< 4	-
3	IL-10/IL-6	0.05	-	< 1	Cytometric bead array
4	VEGF	1.0	pg/mL	0-40.0	Cytometric bead array
5	BFGF	13.4	pg/mL	< 1.0	Cytometric bead array
6	IL-6	26.7	pg/mL	0-50.0	Cytometric bead array
7	IL-10	1.3	pg/mL	0-5.0	Cytometric bead array
8	VCAM	3034.1	pg/mL	200-1000	Cytometric bead array
9	IL-8	63.6	pg/mL	0-20.0	Cytometric bead array

TB-IgG: Tuberculosis-immunoglobulin G; IL: Interleukin; VEGF: Vascular endothelial growth factor; BFGF: Basic fibroblast growth factor; VCAM: Vascular cell adhesion molecule.



DOI: 10.12998/wjcc.v11.i8.1788 **Copyright** ©The Author(s) 2023.

Figure 1 Imaging photos. A: Fundus photography findings. Off-white swelling lesions below the optic disc; horseshoe-like tear in the temporal peripheral retina; B: Optical coherence tomography findings. Retinal thickening at the focal site with structural disturbances in the retina featuring areas of high and low reflectance; C: Color ultrasound. Thickening of the retina at the lesion, stretching and uplifting of the proliferative membrane, and sound shadow behind the moderate strength patchy echo; D: Fluorescein angiography. Twisted blood vessels below the optic disc and fluorescein leakage; E: Indocyanine green choroidal angiography. Persistent low fluorescence below the optic disc.

hemorrhage and are mainly horseshoe shaped and located in the superior temporal quadrant[9,10], consistent with the present case findings. During surgery in this case, we observed that vascular occlusion was caused by traction of the proliferative membrane on the surface of the lesion, no bleeding was observed during the removal of the membrane, and there was no significant correlation between the temporal retinal tear and the lesion below the optic disc. The patient was considered to have

spontaneous retinal tears complicated by CHRRPE, and vitreous hemorrhage originated from the former. The FFA manifestations were typical of CHRRPE. In the early stage of angiography, the choroidal background fluorescence was weak and obscured, particularly in highly pigmented areas. The retinal vessels in the lesion area were clearly tortuous and deformed, while other vessels appeared normal. Due to telangiectasia, microhemangioma and vascular permeability changes in the lesion area, fluorescein leakage may occur in the late stage of angiography. As a result, the lesion area shows high fluorescence, while the pulled vessels around the lesion show no apparent fluorescein leakage[6]. In the present case, FFA after surgery showed vascular lesions with a diameter of about 1.5 disc below the right optic disc, peripheral retinal pigment disorder and atrophy, twisted blood vessels under the optic disc, with obvious fluorescence leakage in the late stage. ICGA showed persistently low fluorescence below the optic disc. Cytokines and antibodies in the vitreous were detected during the operation to exclude inflammatory diseases.

CONCLUSION

For CHRRPE with atypical clinical manifestations. In addition to the examination of vitreous fluid, aqueous humor antibodies, detailed inquiry about the past living and working environment, FFA and ICGA are also important auxiliary means. In this case, the vascular occlusion around the lesion was determined to be related to anterior retinal membrane traction, the retinal hiatus in the temporal side was considered to be spontaneous, and the vitreous hemophore was also caused by the hole.

FOOTNOTES

Author contributions: Han N provided patient information and operated on him; Yu P designed the study; Zhang R and Chen RF collected the examination information; Ren Q wrote the manuscript and revised it as required.

Informed consent statement: Written informed consent was obtained from the patient's for publication of this case report.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Qing Ren 0000-0002-5212-0085; Ning Han 0000-0002-6702-3069; Rui Zhang 0000-0003-2561-7050; Ruo-Fan Chen 0000-0001-8388-7476; Peng Yu 0000-0002-0846-418X.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

REFERENCES

1 **Stavrakas P**, Vachtsevanos A, Karakosta E, Kozeis N, Triantafylla M, Tranos P. Full-thickness macular hole associated with congenital simple hamartoma of retinal pigment epithelium (CSHRPE). *Int Ophthalmol* 2018; **38**: 2179-2182 [PMID: 28828540 DOI: 10.1007/s10792-017-0676-2]

2 **Gass JD**. An unusual hamartoma of the pigment epithelium and retina simulating choroidal melanoma and retinoblastoma. *Trans Am Ophthalmol Soc* 1973; **71**: 171-83; discussions 184 [PMID: 10949597]

3 **Kaprinis K**, Bobat H, De Salvo G. MultiColor(TM) imaging in combined hamartoma of the retina and retinal pigment epithelium. *Eye (Lond)* 2018; **32**: 1478-1482 [PMID: 29789660 DOI: 10.1038/s41433-018-0123-2]

4 **Ledesma-Gil G**, Essilfie J, Gupta R, Fung AT, Lupidi M, Pappuru RR, Nayak S, Sahoo NK, Kaliki S, Yannuzzi LA, Reid K, Lim L, Sacconi R, Dave V, Singh SR, Ayachit A, Gabrielle PH, Cai S, Lima LH, Querques G, Arevalo JF, Freund KB, Shields CL, Chhablani J. Presumed Natural History of Combined Hamartoma of the Retina and Retinal Pigment Epithelium. *Ophthalmol Retina* 2021; **5**: 1156-1163 [PMID: 33516918 DOI: 10.1016/j.oret.2021.01.011]

5 **Chawla R**, Kumar V, Tripathy K, Kumar A, Venkatesh P, Shaikh F, Vohra R, Molla K, Verma S. Combined Hamartoma of the Retina and Retinal Pigment Epithelium: An Optical Coherence Tomography-Based Reappraisal. *Am J Ophthalmol* 2017; **181**: 88-96 [PMID: 28669779 DOI: 10.1016/j.ajo.2017.06.020]

6 **Waelti S**, Fischer T, Sturm V, Heckmann J. Combined hamartoma of the retina and retinal pigment epithelium - MRI features of a rare paediatric intraocular tumour. *BJR Case Rep* 2021; **7**: 20200077 [PMID: 33841897 DOI: 10.1259/bjrcr.20200077]

7 **Mirzayev I**, Gündüz AK. Hamartomas of the Retina and Optic Disc. *Turk J Ophthalmol* 2022; **52**: 421-431 [PMID: 36578224 DOI: 10.4274/tjo.galenos.2022.25979]

8 **Diana C**. Complications of combined retinal and retinal pigment epithelium hamartoma involving the optic disc in a child, treated with Avastin - a review of the literature and case presentation. *Rom J Ophthalmol* 2015; **59**: 255-262 [PMID: 29450317]

9 **Shunmugam M**, Shah AN, Hysi PG, Williamson TH. The pattern and distribution of retinal breaks in eyes with rhegmatogenous retinal detachment. *Am J Ophthalmol* 2014; **157**: 221-226.e1 [PMID: 24200230 DOI: 10.1016/j.ajo.2013.09.011]

10 **Mitry D**, Singh J, Yorston D, Siddiqui MA, Wright A, Fleck BW, Campbell H, Charteris DG. The predisposing pathology and clinical characteristics in the Scottish retinal detachment study. *Ophthalmology* 2011; **118**: 1429-1434 [PMID: 21561662 DOI: 10.1016/j.ophtha.2010.11.031]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1794-1798

DOI: 10.12998/wjcc.v11.i8.1794

ISSN 2307-8960 (online)

CASE REPORT

Testicular pain originating from lumbar disc degeneration: A case report

Xiu-Jie Yan, Bing Wu, Xin He, Zi-Kai Tian, Bao-Gan Peng

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Rakhshan V, Iran; Zhou T, China

Received: November 1, 2022
Peer-review started: November 1, 2022
First decision: December 19, 2022
Revised: January 7, 2023
Accepted: February 15, 2023
Article in press: February 15, 2023
Published online: March 16, 2023

Xiu-Jie Yan, Bing Wu, Xin He, Zi-Kai Tian, Bao-Gan Peng, Department of Spine Surgery, The Third Medical Center, PLA (People's Liberation Army) General Hospital, Beijing 100039, China

Corresponding author: Bao-Gan Peng, MD, PhD, Professor, Surgeon, Department of Spine Surgery, The Third Medical Center, PLA (People's Liberation Army) General Hospital, No. 69 Yongding Road, Beijing 100039, China. pengbaogan76611@163.com

Abstract

BACKGROUND

Testicular pain caused by lumbar disease is uncommon in the clinic. Here we reported a case of discogenic low back pain with testicular pain that was successfully cured.

CASE SUMMARY

A 23-year-old male patient presented to our department with chronic low back pain. Based on his clinical symptoms, signs and imaging, he was diagnosed with discogenic low back pain. Since conservative treatment for more than half a year did not significantly improve his low back pain, we decided to treat it with intradiscal methylene blue injection. During the course of surgery, we again identified the low back pain as originating from the degenerated lumbar disc by analgesic discography. Interestingly, the patient's low back pain disappeared along with the testicular pain that had been present for more than 3 mo. After the operation, the patient's low back pain improved, and the testicular pain did not reappear.

CONCLUSION

Intradiscal methylene blue injection is a convenient and effective surgical intervention for the treatment of discogenic low back pain. Lumbar disc degeneration may also be a possible clinical cause of testicular pain. Methylene blue injection in the diseased disc improved the low back pain, and the accompanying testicular pain was successfully managed.

Key Words: Disc degeneration; Testicular pain; Low back pain; Case report; Intradiscal methylene blue injection

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Herein, we present a case of a patient who was cured of testicular pain after treatment of discogenic low back pain. Lumbar disc degeneration may be a possible etiology of testicular pain.

Citation: Yan XJ, Wu B, He X, Tian ZK, Peng BG. Testicular pain originating from lumbar disc degeneration: A case report. *World J Clin Cases* 2023; 11(8): 1794-1798
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1794.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1794

INTRODUCTION

Chronic testicular pain is a common symptom in urology[1]. Clinicians have found numerous causes that can evoke testicular pain, including infections, tumors, varicocele and referred pain. However, many patients still suffer from testicular pain of unknown pathogenesis that cannot be effectively treated[2]. Lumbar disc degeneration has been proven to be a major source of low back pain, and some researchers have proposed that lumbar disc herniation could also lead to testicular pain[3]. Nevertheless, there has been no high-quality study on testicular pain caused by lumbar disc degeneration. The relationship between lumbar disc degeneration and testicular pain or the pathogenesis of discogenic testicular pain remains elusive. In this paper, we reported a young male whose testicular pain was cured after treating discogenic low back pain and analyzed the possible pathogenesis of testicular pain induced by lumbar disc degeneration.

CASE PRESENTATION

Chief complaints

A 23-year-old man had a 1-year history of severe low back pain, which seriously affected his quality of life.

History of present illness

Prior to presenting at our department, the patient had been on nonsteroidal anti-inflammatory drugs and physical therapy for more than 8 mo. However, the low back pain did not improve and instead continued to worsen.

History of past illness

The patient had also suffered from bilateral testicular pain for more than 3 mo. After detailed physical examination and related ultrasonography, the urologists hypothesized that the testicular pain was not caused by a urinary system disease. No other illnesses were documented, and the patient had no relevant traumatic history.

Personal and family history

It was unremarkable.

Physical examination

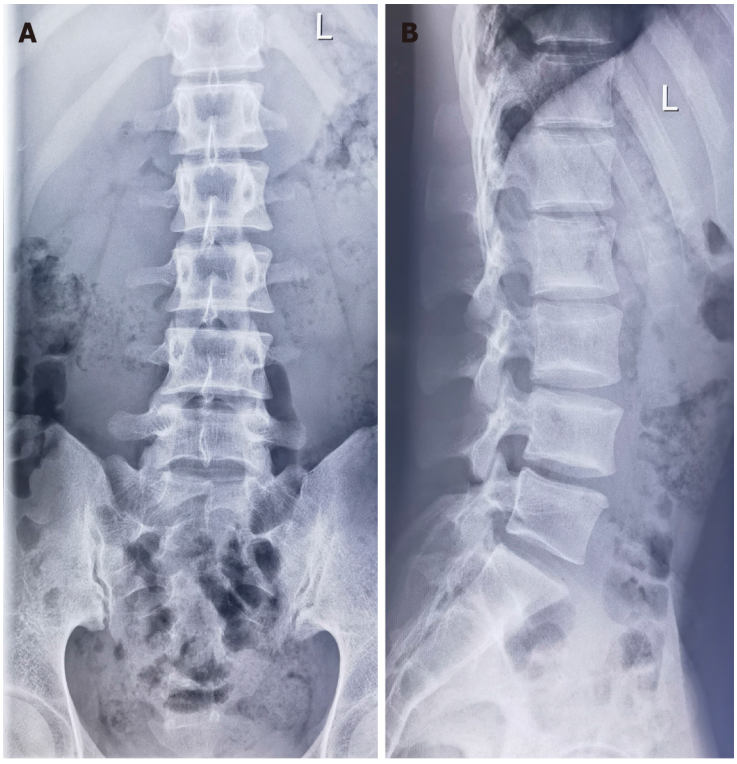
The pressure pain of $L_{4/5}$ intervertebral space was positive. No abnormal sensory or motor function of either lower extremity. The scrotum was normal, and the testicles were in the scrotum without enlargement. The right testis was slightly tender. Visual analogue scale (VAS) score of low back pain was 8 and the testicular pain was 7.

Laboratory examinations

It was unremarkable.

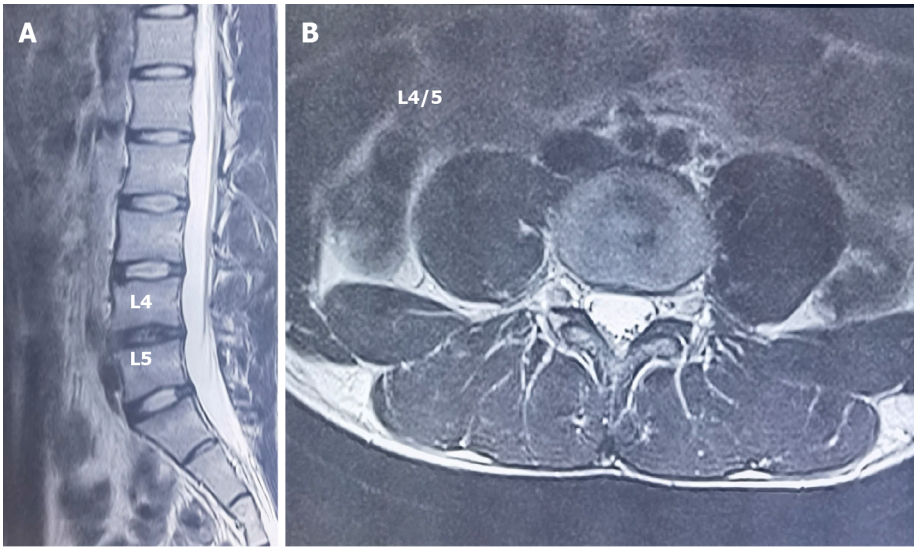
Imaging examinations

The height of $L_{4/5}$ intervertebral space was lower in the radiographs of lumbar spine (Figure 1); Sagittal (left) and axial (right) T2-weighted magnetic resonance imaging of the lumbar spine images showed obvious degeneration of the $L_{4/5}$ disc (Figure 2).



DOI: 10.12998/wjcc.v11.i8.1794 **Copyright** ©The Author(s) 2023.

Figure 1 Normal lumbar spine radiography in the anterior-posterior and lateral positions. A: Mild lumbar scoliosis, spina bifida occulta of S_1; B: Lower height of $L_{4/5}$ intervertebral space.



DOI: 10.12998/wjcc.v11.i8.1794 **Copyright** ©The Author(s) 2023.

Figure 2 Sagittal and axial T2-weighted magnetic resonance imaging. A: Obvious $L_{4/5}$-disc degeneration in the sagittal view; B: No disc protrusion or compression of bilateral nerve roots in the axial view.

FINAL DIAGNOSIS

Discogenic low back pain with testicular pain.

TREATMENT

The procedure was performed under fluoroscopy, and we used a standard posterolateral approach and

a double needle technique[4]. We conducted the discography for the $L_{3/4}$ disc and the $L_{4/5}$ disc. About 0.2 mL of 2% lidocaine hydrochloride was slowly injected into the nucleus pulposus after the needle was accurately inserted into the center of the disc. When performing discography on the $L_{3/4}$ disc, there was no change in low back pain or testicular pain. In contrast, when discography on the $L_{4/5}$ disc was performed, the patient clearly demonstrated a significant improvement in low back pain. At almost the same time, testicular pain disappeared. Subsequently, about 0.3 mL of 1% methylene blue was injected into the diseased disc. The patient required bedrest for the 24 h after surgery.

OUTCOME AND FOLLOW-UP

The patient's bilateral testicular pain quickly disappeared after the analgesic discography. The testicular pain VAS score was 0, and the low back pain VAS score was 2.

At the 1-year follow-up, the patient's testicular pain did not recur, and the patient's low back pain improved significantly.

DISCUSSION

Chronic testicular pain originating from lumbar disc degeneration is very rare clinically. This may be due to the insufficient awareness of this disease or the lack of a clear diagnostic method. In 2003, Doubleday *et al*[5] reported a case who had central low back symptoms and right testicular pain with a small central disc protrusion between the T12 and L1 vertebrae. They successfully eased the symptoms with 12 sessions of physical therapy during a 3-mo period. Peng *et al*[6] has also reported that degenerative lumbar spondylolisthesis can cause testicular pain and suggested that this type of testicular pain is an involvement pain arising from lumbar spine disease.

Bogduk *et al*[7] showed the innervation of cervical and lumbar intervertebral discs, which receive innervation posteriorly from the sinuvertebral nerves, laterally from the vertebral nerve and anteriorly from the sympathetic trunks. Furthermore, the innervation of cervical and lumbar discs is multi-segmental[8,9]. For example, low back pain caused by $L_{4/5}$ or L_5/S_1 disc degeneration is not transmitted upward *via* the L_5 or S_1 spinal nerves as traditionally believed but is transmitted through the paravertebral sympathetic chain to the dorsal root ganglia of L_1 and L_2 and then to the center[6]. In addition, the distribution of nerves in the lumbar disc is consistent with the distribution of nerves in the testis (genitofemoral nerve and genital branch of the ilioinguinal nerve), mainly originating from the L_1 and L_2 nerve roots[9]. Such neural pathways provide the basis for testicular pain induced by intervertebral disc degeneration.

Lumbar discography and methylene blue injection are common clinical methods for the diagnosis and treatment of discogenic lower back pain. The vascularized granulation tissue and the tissue repair process of injurious nerve fibers growing into the degenerated disc are important pathophysiological mechanisms of discogenic lower back pain[10]. Methylene blue as a nerve inactivator can inhibit the nociceptive nerves growing into the lumbar disc, eventually making the pain disappear[10]. For the patient in this case, the imaging manifestations and positive signs were typical signs of discogenic low back pain, and the analgesic discography improved both low back pain and testicular pain. After intradiscal methylene blue injection, the low back pain and testicular pain improved, suggesting that the testicular pain possibly originated from lumbar disc degeneration rather than the testis itself.

The mechanism of discogenic testicular pain may therefore originate from the pain induced by the degenerated $L_{4/5}$ disc non-segmentally transmitted through the paravertebral sympathetic chain to the L_1 and L_2 spinal nerve roots and then upward in conjunction with visceral sympathetic afferent nerves transmitted in the L_1 and L_2 spinal nerve roots[11]. In the present case, the patient's diagnosis and treatment were based on discogenic low back pain rather than specifically on testicular pain. Although lumbar analgesic discography suppressed both low back pain and testicular pain, this does not mean that lumbar analgesic discography is an effective method for diagnosed testicular pain. However, the disappearance of testicular pain in the patient after the procedure may further support that lumbar disc degeneration is a significant clinical resource for testicular pain.

CONCLUSION

In this case, we found that disc degeneration, as the etiology of low back pain, can also evoke concomitant testicular pain. Analgesic discography can be chosen as an effective diagnostic method, and intradiscal methylene blue injection can significantly improve low back pain and testicular pain.

FOOTNOTES

Author contributions: Yan XJ, Wu B, He X and Tian ZK contributed equally to this work; Wu B wrote the manuscript; He X and Yan XJ collected data for review; Peng BG reviewed the manuscript; Wu B, and Tian ZK treated the patient; All authors read and approved the final version of the manuscript.

Informed consent statement: The patient provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: The authors report having no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Bing Wu 0000-0001-5629-0287; Xiu-Jie Yan 0000-0003-2055-2526; Xin He 0000-0002-1689-0189; Zi-Kai Tian 0000-0003-2398-4033; Bao-Gan Peng 0000-0003-1667-4125.

S-Editor: Liu GL
L-Editor: Filipodia
P-Editor: Liu GL

REFERENCES

1 **Calixte N**, Brahmbhatt J, Parekattil S. Chronic Testicular and Groin Pain: Pathway to Relief. *Curr Urol Rep* 2017; **18**: 83 [PMID: 28866773 DOI: 10.1007/s11934-017-0722-7]
2 **Vanoli S**, Vouga L, Iselin C. [Chronic testicular pain: A multidisciplinary challenge]. *Rev Med Suisse* 2021; **17**: 2086-2089 [PMID: 34851056]
3 **Chu ECP**. Taming of the Testicular Pain Complicating Lumbar Disc Herniation With Spinal Manipulation. *Am J Mens Health* 2020; **14**: 1557988320949358 [PMID: 32772625 DOI: 10.1177/1557988320949358]
4 **Schwarzer AC**, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. *Spine (Phila Pa 1976)* 1995; **20**: 1878-1883 [PMID: 8560335 DOI: 10.1097/00007632-199509000-00007]
5 **Doubleday KL**, Kulig K, Landel R. Treatment of testicular pain using conservative management of the thoracolumbar spine: a case report. *Arch Phys Med Rehabil* 2003; **84**: 1903-1905 [PMID: 14669201 DOI: 10.1016/s0003-9993(03)00283-1]
6 **Peng B**, Li D, Pang X. Degenerative lumbar spondylolisthesis with testicular pain. *Pain Med* 2014; **15**: 169-170 [PMID: 24118937 DOI: 10.1111/pme.12246]
7 **Bogduk N**, Windsor M, Inglis A. The innervation of the cervical intervertebral discs. *Spine (Phila Pa 1976)* 1988; **13**: 2-8 [PMID: 3381132 DOI: 10.1097/00007632-198801000-00002]
8 **Wu B**, Yang L, Peng B. Ingrowth of Nociceptive Receptors into Diseased Cervical Intervertebral Disc Is Associated with Discogenic Neck Pain. *Pain Med* 2019; **20**: 1072-1077 [PMID: 30848823 DOI: 10.1093/pm/pnz013]
9 **Masarani M**, Cox R. The aetiology, pathophysiology and management of chronic orchialgia. *BJU Int* 2003; **91**: 435-437 [PMID: 12603394 DOI: 10.1046/j.1464-410x.2003.04094.x]
10 **Peng B**, Pang X, Wu Y, Zhao C, Song X. A randomized placebo-controlled trial of intradiscal methylene blue injection for the treatment of chronic discogenic low back pain. *Pain* 2010; **149**: 124-129 [PMID: 20167430 DOI: 10.1016/j.pain.2010.01.021]
11 **Murata Y**, Kato Y, Miyamoto K, Takahashi K. Clinical study of low back pain and radicular pain pathways by using l2 spinal nerve root infiltration: a randomized, controlled, clinical trial. *Spine (Phila Pa 1976)* 2009; **34**: 2008-2013 [PMID: 19730208 DOI: 10.1097/BRS.0b013e3181b1fb96]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1799-1807

DOI: 10.12998/wjcc.v11.i8.1799

ISSN 2307-8960 (online)

CASE REPORT

Glucocorticoid-induced thrombotic microangiopathy in paroxysmal nocturnal hemoglobinuria: A case report and review of literature

Xiao-Dong Yang, Bo Ju, Jia Xu, Nuan-Nuan Xiu, Xiao-Yun Sun, Xi-Chen Zhao

Specialty type: Hematology

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: Barik R, India; Tajiri K, Japan

Received: November 7, 2022
Peer-review started: November 7, 2022
First decision: November 25, 2022
Revised: December 2, 2022
Accepted: February 8, 2023
Article in press: February 8, 2023
Published online: March 16, 2023

Xiao-Dong Yang, Bo Ju, Jia Xu, Nuan-Nuan Xiu, Xiao-Yun Sun, Xi-Chen Zhao, Department of Hematology, The Central Hospital of Qingdao West Coast New Area, Qingdao 266555, Shandong Province, China

Corresponding author: Xi-Chen Zhao, MD, Chief Physician, Department of Hematology, The Central Hospital of Qingdao West Coast New Area, No. 9 Huangpujiang Road, Qingdao 266555, Shandong Province, China. zhaoxichen2003@163.com

Abstract

BACKGROUND

Thrombotic microangiopathy (TMA) is a group of disorders that converge on excessive platelet aggregation in the microvasculature, leading to consumptive thrombocytopenia, microangiopathic hemolysis and ischemic end-organ dysfunction. In predisposed patients, TMA can be triggered by many environmental factors. Glucocorticoids (GCs) can compromise the vascular endothelium. However, GC-associated TMA has rarely been reported, which may be due to the lack of awareness of clinicians. Given the high frequency of thrombocytopenia during GC treatment, particular attention should be given to this potentially fatal complication.

CASE SUMMARY

An elderly Chinese man had a 12-year history of aplastic anemia (AA) and a 3-year history of paroxysmal nocturnal hemoglobinuria (PNH). Three months earlier, methylprednisolone treatment was initiated at 8 mg/d and increased to 20 mg/d to alleviate complement-mediated hemolysis. Following GC treatment, his platelet counts and hemoglobin levels rapidly decreased. After admission to our hospital, the dose of methylprednisolone was increased to 60 mg/d in an attempt to enhance the suppressive effect. However, increasing the GC dose did not alleviate hemolysis, and his cytopenia worsened. Morphological evaluation of the marrow smears revealed increased cellularity with an increased percentage of erythroid progenitors without evident dysplasia. Cluster of differentiation (CD)55 and CD59 expression was significantly decreased on erythrocytes and granulocytes. In the following days, platelet transfusion was required due to severe thrombocytopenia. Observation of platelet transfusion refractoriness indicated that the exacerbated cytopenia may have been caused by the development of TMA due to GC treatment because the transfused platelet concentrates had no defects in glycosylphosphatidylinositol-anchored proteins. We examined blood smears and found a small number of schistocytes, dacryocytes, acan-

thocytes and target cells. Discontinuation of GC treatment resulted in rapidly increased platelet counts and steady increases in hemoglobin levels. The patient's platelet counts and hemoglobin levels returned to the levels prior to GC treatment 4 weeks after GC discontinuation.

CONCLUSION

GCs can drive TMA episodes. When thrombocytopenia occurs during GC treatment, TMA should be considered, and GCs should be discontinued.

Key Words: Aplastic anemia; Paroxysmal nocturnal hemoglobinuria; Glucocorticoid; Methylprednisolone; Thrombotic microangiopathy; Platelet transfusion refractoriness; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Glucocorticoid-associated thrombotic microangiopathy has rarely been reported. Here, we report a patient with paroxysmal nocturnal hemoglobinuria whose hematological parameters worsened during methylprednisolone treatment, and increasing methylprednisolone doses further exacerbated the cytopenia. Observation of platelet transfusion refractoriness suggested the possibility of thrombotic microangiopathy development. Significant hematological improvement was achieved after discontinuation of methylprednisolone treatment, confirming that methylprednisolone treatment acted as the triggering factor to promote platelet aggregation within the microcirculation. Given the wide use of glucocorticoids in clinical practice and the high incidence of thrombocytopenia during glucocorticoid treatment, particular attention should be given to this potentially fatal complication.

Citation: Yang XD, Ju B, Xu J, Xiu NN, Sun XY, Zhao XC. Glucocorticoid-induced thrombotic microangiopathy in paroxysmal nocturnal hemoglobinuria: A case report and review of literature. *World J Clin Cases* 2023; 11(8): 1799-1807

URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1799.htm

DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1799

INTRODUCTION

Thrombotic microangiopathy (TMA) is caused by uncontrolled adhesion, activation and aggregation of platelets within the microvasculature, leading to consumptive thrombocytopenia, microangiopathic hemolysis and ischemic end-organ dysfunction. Mutations and polymorphisms in genes of the complement and coagulation systems predispose patients to TMA development[1,2]. The delayed onset and diverse penetrance indicate that the development of symptomatic TMA requires an engagement of environmental factors to trigger acute episodes. A variety of precipitating factors compromise the vascular endothelium, increase the shear stress of blood flow, stimulate ultralarge von Willebrand factor (UL-vWF) secretion, activate innate immune cells, exacerbate complement dysregulation, accelerate coagulation cascade, promote platelet activation and drive platelet aggregation, thereby triggering TMA episodes in genetically susceptible individuals or initiating TMA occurrence by the combined effects of acquired susceptibilities and precipitating factors[1-3]. In TMA development, interactions among the vascular endothelium, vasomotoricity, vWF, platelets, coagulation factors, complement components and immune cells synergistically facilitate platelet aggregation and microthrombogenesis[4-8]. Endothelial injury and subsequent UL-vWF secretion play a pivotal role in this process[8,9], and complement activation, particularly the generation of anaphylotoxins, provokes and exacerbates endothelial injury[5,7,10,11]. Previously reported environmental factors that can trigger TMA episodes include various infections, malignant hypertension, autoimmune disorders, neoplasms, pregnancy, organ transplantation, critical illness, severe trauma, vitamin B_{12} deficiency and drugs[1-3].

Drug-induced TMA has been reported to involve immune- and nonimmune-mediated mechanisms. Immune-mediated TMA is caused by the generation of autoantibodies that activate endothelial cells and platelets in a dose-independent manner, whereas nonimmune-mediated TMA is caused by drugs that directly compromise the vascular endothelium, activate platelets or disrupt the immune system in a dose-dependent manner. Drug-induced TMA is frequently associated with chemotherapeutic agents, anti-vascular endothelial growth factor (VEGF) antibodies, VEGF receptor inhibitors, heparin, platelet inhibitors, thrombopoietin receptor agonists, immune suppressants, recombinant cytokines and immune checkpoint inhibitors[12-15]. Glucocorticoids (GCs) are widely used drugs, and the occurrence of thrombocytopenia during GC treatment is a common event in clinical practice. GC treatment can trigger TMA episodes[16-20] and exacerbate preexisting TMA[21,22]. However, GC-associated TMA has rarely been reported, which may be due to the lack of awareness of clinicians, the complexity of the

underlying conditions and the lack of sufficient evidence for the diagnosis of microangiopathic hemolysis in most circumstances[2,23,24]. In this case report, we present a patient with paroxysmal nocturnal hemoglobinuria (PNH) who developed TMA following GC treatment.

CASE PRESENTATION

Chief complaints

The patient experienced rapid decreases in hemoglobin and platelet levels for 3 months.

History of present illness

Past treatment for blood diseases: Twelve years earlier, a 51-year-old Chinese man was diagnosed with acquired aplastic anemia (AA) in several blood disease centers due to gradually aggravated fatigue. He was prescribed cyclosporine and stanozolol, achieving significant hematological improvement.

Three years ago, the patient developed evident hemoglobinuria and was diagnosed with PNH based on increased marrow cellularity and a significant decrease in cluster of differentiation (CD)55 and CD59 expression on erythrocytes and granulocytes. Cyclosporine and stanozolol were tapered off, and antiplatelet drugs became his main treatment. During the three years of PNH history, his complete blood count (CBC) results fluctuated within the following range: White blood cell (WBC) count, 5.50–7.50 × 10^9/L; red blood cell (RBC) count, 2.90-3.30 × 10^{12}/L; hemoglobin (Hb) level, 80-100 g/L; and platelet (Plt) count, 170-230 × 10^9/L.

Three months earlier, the patient's hemoglobinuria worsened, and he initiated oral administration of methylprednisolone at a dose of 8 mg/d and sodium bicarbonate at a dose of 1.0 g three times per day at another hospital to alleviate complement-mediated hemolysis.

Rapid decreases in hemoglobin and platelet levels following GC treatment: Before methylprednisolone treatment, the patient's CBC showed the following results: WBC count, 6.73 × 10^9/L; RBC count, 3.15 × 10^{12}/L; Hb level, 85 g/L; Plt count, 195 × 10^9/L; and absolute reticulocyte (Ret) count, 290.2 × 10^9/L. Following GC treatment, the patient's fatigue worsened, and headache, palpitation and dyspnea symptoms emerged and worsened. Seven days after initiating methylprednisolone treatment, his CBC showed the following results: WBC count, 5.28 × 10^9/L; RBC count, 2.73 × 10^{12}/L; Hb level, 70 g/L; Plt count, 106 ×10^9/L; and Ret count, 283.3 × 10^9/L. From that time, intermittent transfusion of packed RBCs was initiated, and the dose of methylprednisolone was increased to 20 mg/d. Along with the increase in methylprednisolone dose, his Hb level and Plt count further decreased, and the frequency of blood transfusion increased. Four days before presenting at our center, the patient's fatigue was severe with intolerable palpitations and dyspnea.

History of past illness

The patient had no history of diseases in hematological, immunological or other systems before the diagnosis of AA.

Personal and family history

The patient had no family history of inherited, hematological, autoimmune or malignant diseases.

Physical examination

The physical examination results of the patient were as follows: height of 171 cm; body weight of 70 kg; body temperature of 36.1 °C; breathing rate of 19 breaths per minute; heart rate of 90 beats per minute; and blood pressure of 130/90 mmHg. Physical examination revealed the presence of a pale face and conjunctiva in the absence of conspicuous mucocutaneous hemorrhage, jaundice and exanthemata. No significant signs of nervous system, respiratory system, cardiovascular system, gastrointestinal system, urogenital system or skeletal musculature system abnormalities were found.

Laboratory examinations

Routine laboratory examinations: On admission, the patient's CBC showed the following results: WBC count, 4.75 × 10^9/L; RBC count, 1.72 × 10^{12}/L; Hb level, 65 g/L; Plt count, 98 × 10^9/L; and Ret count, 274.90 × 10^9/L. The coagulation profile was within the normal limits with a D-dimer level of 0.77 mg/L. Urine examination revealed occult blood of 3+ and protein of 1+. Biochemical analysis revealed elevated serum levels of conjugated bilirubin (10.4 μmol/L), unconjugated bilirubin (24.4 μmol/L), lactate dehydrogenase (LDH, 3349 U/L) and hydroxybutyric dehydrogenase (HBDH, 2695 U/L) in the absence of abnormalities in hepatic and renal functions. The results for hepatitis A, B, and C viruses as well as human immunodeficiency virus were negative. Various antinuclear antibodies and biomarkers of neoplasms were also negative.

Specific laboratory examinations for blood diseases: Morphological examination of the marrow smears revealed increased cellularity with a significantly increased percentage of erythroid precursors

in the absence of evident dysplastic features (Figure 1A). Bone marrow biopsy confirmed the increased cellularity and increased erythropoiesis. Coomb's test was negative. Significantly decreased CD55 and CD59 expression on erythrocytes (11.24% and 7.80%) and granulocytes (40.26% and 37.35%) was identified by flow cytometric analysis. Decreased serum levels of complement C3 but not C4 were detected. Serum levels of ferritin were slightly decreased, and serum levels of folic acid and vitamin B_{12} were within the normal limits. Anti-erythrocyte and anti-platelet antibodies were undetectable. Myeloid neoplasm-associated gene mutations were also undetectable.

Imaging examinations

No evident abnormalities were found in the patient's chest and abdominal computed tomography scans.

FINAL DIAGNOSIS

These laboratory data fulfilled the diagnostic criteria for PNH.

TREATMENT

After hospitalization, the patient was prescribed intravenous administration of methylprednisolone at a dose of 60 mg/d and 5% sodium bicarbonate (100 mL) two times per day. After transfusion of 800 mL of packed RBCs, his Hb level increased to 88 g/L. In the following days, however, his Hb and Plt levels rapidly declined, and the speed of decline in the Hb levels was disproportionate to the expected life of normal blood cells, indicating that hemolysis occurred not only in the PNH clones but also in normal RBCs. On the 16th day of hospitalization, his Hb level decreased to 61 g/L, and his Plt level decreased to 7×10^9/L. The patient was transfused with 10 U of platelet concentrate and demonstrated platelet transfusion refractoriness. Observation of platelet transfusion refractoriness suggested that the patient was probably complicated with the development of TMA due to GC treatment because the transfused platelet concentrates did not have defects in GPI-anchored proteins. We then examined the blood smears (Figure 1B) and found the presence of a small number of schistocytes, dacryocytes, acanthocytes and target cells, confirming the existence of microangiopathic hemolysis[2,24]. Thereafter, GC treatment was discontinued.

OUTCOME AND FOLLOW-UP

Rapid increase in Hb levels and Plt counts occurred after discontinuation of glucocorticoid treatment

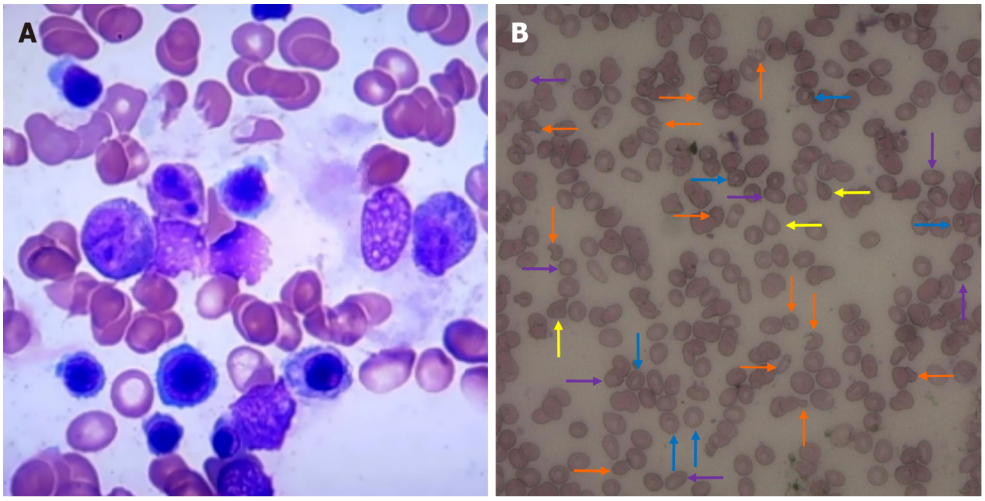
After discontinuation of GC treatment, the patient's platelet counts and Hb levels increased without the need for blood transfusions. Eleven days after the discontinuation of GC treatment, CBC monitoring showed an Hb level of 69 g/L and platelet counts of 28×10^9/L. The patient was then discharged from our center.

Hematological changes following initiation and discontinuation of glucocorticoid treatment

After the patient was discharged from our center, repeated CBC monitoring revealed that his platelet counts rapidly increased and his Hb levels steadily increased. The patient's WBC counts, Hb levels, Plt counts and Ret counts in the following CBC monitoring are shown in Figure 2.

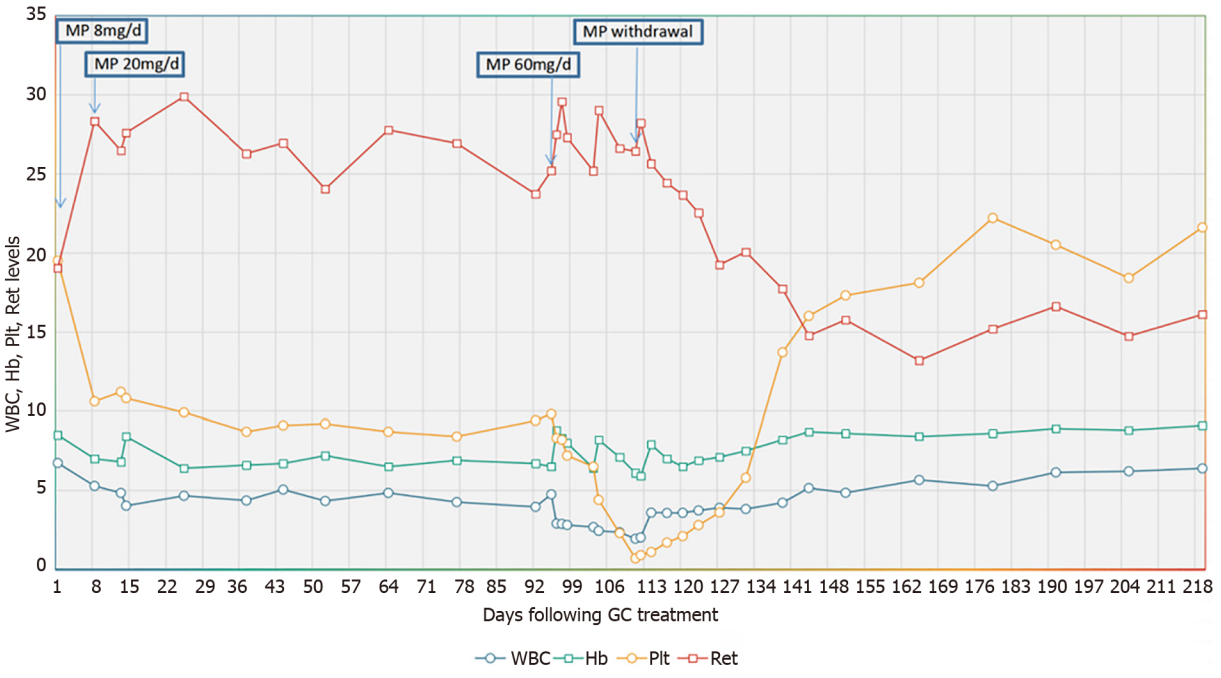
DISCUSSION

The patient was treated with methylprednisolone to reduce complement-mediated hemolysis. Initially, he was prescribed methylprednisolone at 8 mg/d, which failed to ameliorate hemoglobinuria and worsened the hematological profile. In the following months, the dose was increased to 20 mg/d. After hospitalization, the morphological, immunological, cytogenetic and molecular biological examinations of the marrow and blood samples met the diagnostic criteria for PNH. The dose was increased to 60 mg/d, and the hematological profile was rapidly exacerbated. The longevity of transfused RBCs was greatly reduced with further increases in the HBDH and LDH levels, and the Plt counts in CBC monitoring severely decreased, resulting in the requirement for platelet transfusion. Observation of platelet transfusion refractoriness and mental symptoms suggested the development of TMA. Therefore, we examined the blood smears and found a small number of schistocytes, dacryocytes, acanthocytes and target cells. Although the number of schistocytes was no more than 10%, their appearance was



DOI: 10.12998/wjcc.v11.i8.1799 **Copyright** ©The Author(s) 2023.

Figure 1 Morphological examination of marrow and blood smears. A: Morphological examination of the marrow smears showed significantly increased cellularity with an increased percentage of erythroid progenitors in the absence of evident dysplasia. The number of megakaryocytes was within the normal level without immature and dysplastic features; B: Morphological examination of the blood smears revealed the presence of a small number of schistocytes (orange arrows), dacryocytes (yellow arrows), acanthocytes (purple arrows) and target cells (blue arrows), confirming the existence of microangiopathic hemolysis. Platelets were rarely visualized.



DOI: 10.12998/wjcc.v11.i8.1799 **Copyright** ©The Author(s) 2023.

Figure 2 Sequential hematological changes following initiation and discontinuation of glucocorticoid treatment. Following initiation of methylprednisolone treatment, the hemoglobin levels (Hb ×10 g/L) and platelet counts (Plt × 10 × 10^9/L) rapidly decreased, together with a decrease in white blood cells (WBC ×10^9/L) and an increase in absolute reticulocyte count (Ret × 10 × 10^9/L). Increasing the methylprednisolone dose after hospitalization resulted in the worsening of platelet consumption and intravenous hemolysis. Discontinuation of methylprednisolone treatment showed significant hematological improvement with restoration of hemoglobin levels and platelet counts similar to those prior to methylprednisolone treatment.

sufficient to confirm the existence of microangiopathic hemolysis[2,24]. GC treatment was discontinued. As expected, the platelets rapidly increased and the LDH and BHDH levels rapidly decreased. The hematological improvement after discontinuation of GC treatment suggested that the exacerbated cytopenia was caused by TMA development due to GC treatment[12].

GCs are widely used drugs for treating a variety of conditions, and the development of thrombocytopenia during GC treatment is a common complication in clinical practice. However, GC-induced TMA has rarely been reported[18-23]. The major reason for the rarity of GC-induced TMA reports may be due to the lack of awareness of clinicians, the dilemma for clinicians to make a definitive diagnosis by

examining blood smears on which the percentage of fragmented erythrocytes is not enough to meet the diagnostic criteria[2,23,24] and the complexity of underlying conditions for GC treatment. In the present case, TMA development was not considered during the 3 months of GC treatment due to the intravenous hemolysis of PNH itself and the lack of awareness of GC-induced TMA.

The promotion of TMA onset by GCs may be due to their physiological functions and pharmacologic effects. GCs and catecholamines are the main components of acute and chronic stress responses[25,26]. GCs increase the sensitivity of precapillary arterioles to catecholamine-induced contraction, thus increasing the shear stress of the microcirculation[25-27]. High-dose GCs can induce vasospasm and aggravate preexisting vasoconstriction[28,29]. GCs inhibit VEGF, inflammation, hypoxemia-induced angiogenesis and vascular repair, which damages vascular endothelial integrity[30-32]. GCs inhibit the biosynthesis of prostacyclin[33,34], nitric oxide[35] and hydrogen sulfide[36], which increases the shear stress of the microcirculation[37,38], promotes the adherent activity of vWF[39] and activates platelet aggregation[40,41]. All of these effects of GCs are precipitating factors for TMA development[1-3].

In PNH pathogenesis, deranged activation of the alternative complement pathway is caused by extremely low levels of the CD55 (decay accelerating factor, ADF) and CD59 (membrane inhibitor of reactive lysis, MIRL) complement regulatory proteins on blood cells. Thrombotic propensity due to complement-mediated platelet activation and intravenous hemolysis is an intrinsic property of PNH[42, 43]. In the present case, GC treatment likely acted as a precipitating factor, breaking down the vulnerable balance between prothrombotic and antithrombotic factors in the context of defects in the complement regulatory components, thereby provoking vascular endothelial injury and promoting C3 deposition to the vascular endothelium.

When thrombocytopenia develops during GC treatment, GC-induced TMA should be considered because the predisposing factors are unknown in most cases[44,45]. Reduced serum levels of complement C3, increased serum levels of LHD and increased Ret counts in CBC monitoring were useful parameters to suggest the occurrence of TMA. The presence of schistocytes on blood smears, although no more than 10%, facilitated the diagnosis of TMA[2,24]. However, the absence of schistocytes cannot exclude the diagnosis of TMA[23]. If TMA is suspected, GC treatment should be discontinued, and drugs that inhibit platelet aggregation and complement activation should be considered[1,2]. Drugs that increase the biosynthesis of endogenous prostacyclin are beneficial for the reduction of GC-mediated vascular injury[40,46,47].

The present study had limitations. The diagnosis of GC-induced TMA was mainly based on exacerbated cytopenia after GC treatment and hematological improvement after discontinuation of GC treatment. The fragmented erythrocytes on blood smears were no more than 10% of the total RBCs. Although the presence of hyaline thrombi in biopsied tissue is direct evidence of platelet aggregation in the microvasculature, a biopsy was not performed in the present case.

CONCLUSION

GC treatment can cause TMA in predisposed patients, and GC-induced TMA has been underestimated. Because GCs are widely used in treating various diseases and TMA is a potentially fatal condition, GC-induced TMA should be promptly diagnosed. In the case of a significant decrease in platelet counts during GC treatment, GC-induced TMA should be taken into consideration. In this situation, blood smears should be carefully examined, and GC treatment should be discontinued. If an increase in platelets occurs promptly after GC discontinuation, the diagnosis of GC-induced TMA can be established.

FOOTNOTES

Author contributions: Zhao XC developed the idea; Yang XD, Ju B and Xu J analyzed the data and drafted the manuscript; Yang XD, Ju B, Xu J and Xiu NN participated in the treatment; Sun XY supervised the treatment; and Zhao XC revised and approved the final manuscript; all authors have read and approved the final version of the manuscript.

Supported by Specialized Scientific Research Fund Projects of The Medical Group of Qingdao University, No. YLJT20201002.

Informed consent statement: Informed written consent was obtained from the patient for publishing this case report and any accompanying laboratory data.

Conflict-of-interest statement: The authors have no conflicts of interest to declare that are relevant to the content of 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).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial license (CC BY-NC 4.0), which permits others to distribute, remix, adapt, build upon this work noncommercially and license their derivative works on different terms, provided the original work is properly cited and the use is noncommercial. Please see https://creativecommons.org/Licenses/bync/4.0/

Country/Territory of origin: China

ORCID number: Xiao-Dong Yang 0000-0001-6754-9004; Bo Ju 0000-0003-1610-8481; Jia Xu 0000-0002-2444-8980; Nuan-Nuan Xiu 0000-0003-4369-0147; Xiao-Yun Sun 0000-0002-4667-9974; Xi-Chen Zhao 0000-0002-3304-2851.

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

REFERENCES

1 **Hanna RM**, Henriksen K, Kalantar-Zadeh K, Ferrey A, Burwick R, Jhaveri KD. Thrombotic Microangiopathy Syndromes-Common Ground and Distinct Frontiers. *Adv Chronic Kidney Dis* 2022; **29**: 149-160.e1 [PMID: 35817522 DOI: 10.1053/j.ackd.2021.11.006]
2 **Thompson GL**, Kavanagh D. Diagnosis and treatment of thrombotic microangiopathy. *Int J Lab Hematol* 2022; **44** Suppl 1: 101-113 [PMID: 36074708 DOI: 10.1111/ijlh.13954]
3 **Bayer G**, von Tokarski F, Thoreau B, Bauvois A, Barbet C, Cloarec S, Mérieau E, Lachot S, Garot D, Bernard L, Gyan E, Perrotin F, Pouplard C, Maillot F, Gatault P, Sautenet B, Rusch E, Buchler M, Vigneau C, Fakhouri F, Halimi JM. Etiology and Outcomes of Thrombotic Microangiopathies. *Clin J Am Soc Nephrol* 2019; **14**: 557-566 [PMID: 30862697 DOI: 10.2215/CJN.11470918]
4 **Mandel J**, Casari M, Stepanyan M, Martyanov A, Deppermann C. Beyond Hemostasis: Platelet Innate Immune Interactions and Thromboinflammation. *Int J Mol Sci* 2022; **23** [PMID: 35409226 DOI: 10.3390/ijms23073868]
5 **Rawish E**, Sauter M, Sauter R, Nording H, Langer HF. Complement, inflammation and thrombosis. *Br J Pharmacol* 2021; **178**: 2892-2904 [PMID: 33817781 DOI: 10.1111/bph.15476]
6 **Noone DG**, Riedl M, Pluthero FG, Bowman ML, Liszewski MK, Lu L, Quan Y, Balgobin S, Schneppenheim R, Schneppenheim S, Budde U, James P, Atkinson JP, Palaniyar N, Kahr WH, Licht C. Von Willebrand factor regulates complement on endothelial cells. *Kidney Int* 2016; **90**: 123-134 [PMID: 27236750 DOI: 10.1016/j.kint.2016.03.023]
7 **Theofilis P**, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis C, Tousoulis D. Inflammatory Mechanisms Contributing to Endothelial Dysfunction. *Biomedicines* 2021; **9** [PMID: 34356845 DOI: 10.3390/biomedicines9070781]
8 **Chang JC**. Molecular Pathogenesis of Endotheliopathy and Endotheliopathic Syndromes, Leading to Inflammation and Microthrombosis, and Various Hemostatic Clinical Phenotypes Based on "Two-Activation Theory of the Endothelium" and "Two-Path Unifying Theory" of Hemostasis. *Medicina (Kaunas)* 2022; **58** [PMID: 36143988 DOI: 10.3390/medicina58091311]
9 **Mathew RO**, Nayer A, Asif A. The endothelium as the common denominator in malignant hypertension and thrombotic microangiopathy. *J Am Soc Hypertens* 2016; **10**: 352-359 [PMID: 26778772 DOI: 10.1016/j.jash.2015.12.007]
10 **Gianni P**, Goldin M, Ngu S, Zafeiropoulos S, Geropoulos G, Giannis D. Complement-mediated microvascular injury and thrombosis in the pathogenesis of severe COVID-19: A review. *World J Exp Med* 2022; **12**: 53-67 [PMID: 36157337 DOI: 10.5493/wjem.v12.i4.53]
11 **Aiello S**, Gastoldi S, Galbusera M, Ruggenenti P, Portalupi V, Rota S, Rubis N, Liguori L, Conti S, Tironi M, Gamba S, Santarsiero D, Benigni A, Remuzzi G, Noris M. C5a and C5aR1 are key drivers of microvascular platelet aggregation in clinical entities spanning from aHUS to COVID-19. *Blood Adv* 2022; **6**: 866-881 [PMID: 34852172 DOI: 10.1182/bloodadvances.2021005246]
12 **Al-Nouri ZL**, Reese JA, Terrell DR, Vesely SK, George JN. Drug-induced thrombotic microangiopathy: a systematic review of published reports. *Blood* 2015; **125**: 616-618 [PMID: 25414441 DOI: 10.1182/blood-2014-11-611335]
13 **Font C**, de Herreros MG, Tsoukalas N, Brito-Dellan N, Espósito F, Escalante C, Oo TH; MASCC Hemostasis Study Group. Thrombotic microangiopathy (TMA) in adult patients with solid tumors: a challenging complication in the era of emerging anticancer therapies. *Support Care Cancer* 2022; **30**: 8599-8609 [PMID: 35545722 DOI: 10.1007/s00520-022-06935-5]
14 **Tjepkema M**, Amini S, Schipperus M. Risk of thrombosis with thrombopoietin receptor agonists for ITP patients: A systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2022; **171**: 103581 [PMID: 35007700 DOI: 10.1016/j.critrevonc.2022.103581]
15 **Hvas AM**, Favaloro EJ, Hellfritzsch M. Heparin-induced thrombocytopenia: pathophysiology, diagnosis and treatment. *Expert Rev Hematol* 2021; **14**: 335-346 [PMID: 33736552 DOI: 10.1080/17474086.2021.1905512]
16 **Nishi K**, Sato M, Ogura M, Okutsu M, Ishikura K, Kamei K. Two cases of idiopathic steroid-resistant nephrotic syndrome complicated with thrombotic microangiopathy. *BMC Nephrol* 2020; **21**: 323 [PMID: 32746791 DOI: 10.1186/s12882-020-01985-5]
17 **Miyamoto T**, Ishikawa Y, Yamamoto J, Yamamura T, Kawata T. Thrombotic microangiopathy secondary to steroid pulse therapy administered for refractory nephrotic syndrome. *Intern Med* 2013; **52**: 2099-2103 [PMID: 24042520 DOI:

10.2169/internalmedicine.52.0470]
18 **Fukuda M**, Mizuno H, Hiramatsu R, Sekine A, Kawada M, Hasegawa E, Yamanouchi M, Suwabe T, Hoshino J, Sawa N, Takaichi K, Kinowaki K, Ohashi K, Fujii T, Miyazono M, Ubara Y. A case of thrombotic microangiopathy associated with polymyositis. *Clin Nephrol* 2021; **95**: 339-344 [PMID: 33769275 DOI: 10.5414/CN109989]
19 **Yoshioka K**, Hattori T, Isaka Y, Yamaguchi T, Yamagami K, Morikawa T, Konishi Y, Sato T, Imanishi M. Thrombotic microangiopathy due to malignant hypertension following corticosteroid therapy for microscopic polyangitis. *Intern Med* 2007; **46**: 785-788 [PMID: 17541236 DOI: 10.2169/internalmedicine.46.6291]
20 **Maruyama A**, Nagashima T, Ikenoya K, Aoki Y, Matsuyama Y, Iwamoto M, Minota S. Glucocorticoid-induced normotensive scleroderma renal crisis: a report on two cases and a review of the literature in Japan. *Intern Med* 2013; **52**: 1833-1837 [PMID: 23955620 DOI: 10.2169/internalmedicine.52.0400]
21 **Ito M**, Katsuno T, Kachi A, Ito Y. Hypertensive emergency presenting with diffuse alveolar hemorrhaging and thrombotic microangiopathy: A case report and review of the literature. *Clin Nephrol Case Stud* 2020; **8**: 53-61 [PMID: 32728521 DOI: 10.5414/CNCS109939]
22 **Xie X**, Wang G, Cheng H, Sun L, Dong H. Scleroderma-associated thrombotic microangiopathy in overlap syndrome of systemic sclerosis and systemic lupus erythematosus: A case report and literature review. *Medicine (Baltimore)* 2020; **99**: e22582 [PMID: 33031308 DOI: 10.1097/MD.0000000000022582]
23 **Saha BK**, Saha A, Chong W, Beegle S. A Fatal Case of Thrombotic Microangiopathy Without Schistocytosis and Absent Biochemical Markers of Hemolysis. *Am J Med Sci* 2020; **359**: 296-302 [PMID: 32265009 DOI: 10.1016/j.amjms.2020.01.019]
24 **Chang JC**. Sepsis and septic shock: endothelial molecular pathogenesis associated with vascular microthrombotic disease. *Thromb J* 2019; **17**: 10 [PMID: 31160889 DOI: 10.1186/s12959-019-0198-4]
25 **Schaeuble D**, Myers B. Cortical-Hypothalamic Integration of Autonomic and Endocrine Stress Responses. *Front Physiol* 2022; **13**: 820398 [PMID: 35222086 DOI: 10.3389/fphys.2022.820398]
26 **Suzuki T**, Nakamura Y, Moriya T, Sasano H. Effects of steroid hormones on vascular functions. *Microsc Res Tech* 2003; **60**: 76-84 [PMID: 12500264 DOI: 10.1002/jemt.10246]
27 **Yang S**, Zhang L. Glucocorticoids and vascular reactivity. *Curr Vasc Pharmacol* 2004; **2**: 1-12 [PMID: 15320828 DOI: 10.2174/1570161043476483]
28 **Tulipan J**, Lutsky K, Beredjiklian P. Transient Vasospastic Response Following the Injection of Corticosteroid into the Hand. *Bull Hosp Jt Dis (2013)* 2017; **75**: 217-219 [PMID: 28902610]
29 **Singhal AB**, Topcuoglu MA. Glucocorticoid-associated worsening in reversible cerebral vasoconstriction syndrome. *Neurology* 2017; **88**: 228-236 [PMID: 27940651 DOI: 10.1212/WNL.0000000000003510]
30 **Arias A**, Schander JA, Bariani MV, Correa F, Domínguez Rubio AP, Cella M, Cymeryng CB, Wolfson ML, Franchi AM, Aisemberg J. Dexamethasone-induced intrauterine growth restriction modulates expression of placental vascular growth factors and fetal and placental growth. *Mol Hum Reprod* 2021; **27** [PMID: 33528567 DOI: 10.1093/molehr/gaab006]
31 **Soleimani AA**, Mohammadi A, Ghasempour G, Abkenar BR, Shokri N, Najafi M. Dexamethasone suppresses the proliferation and migration of VSMCs by FAK in high glucose conditions. *BMC Pharmacol Toxicol* 2022; **23**: 63 [PMID: 35978346 DOI: 10.1186/s40360-022-00604-3]
32 **Yu H**, Liu P, Zuo W, Sun X, Liu H, Lu F, Guo W, Zhang Q. Decreased angiogenic and increased apoptotic activities of bone microvascular endothelial cells in patients with glucocorticoid-induced osteonecrosis of the femoral head. *BMC Musculoskelet Disord* 2020; **21**: 277 [PMID: 32349721 DOI: 10.1186/s12891-020-03225-1]
33 **Rosenstock M**, Katz S, Danon A. Glucocorticoids regulate both phorbol ester and calcium ionophore-induced endothelial prostacyclin synthesis. *Prostaglandins Leukot Essent Fatty Acids* 1997; **56**: 1-8 [PMID: 9044429 DOI: 10.1016/s0952-3278(97)90517-2]
34 **Jun SS**, Chen Z, Pace MC, Shaul PW. Glucocorticoids downregulate cyclooxygenase-1 gene expression and prostacyclin synthesis in fetal pulmonary artery endothelium. *Circ Res* 1999; **84**: 193-200 [PMID: 9933251 DOI: 10.1161/01.res.84.2.193]
35 **Liu Y**, Mladinov D, Pietrusz JL, Usa K, Liang M. Glucocorticoid response elements and 11 beta-hydroxysteroid dehydrogenases in the regulation of endothelial nitric oxide synthase expression. *Cardiovasc Res* 2009; **81**: 140-147 [PMID: 18716005 DOI: 10.1093/cvr/cvn231]
36 **d'Emmanuele di Villa Bianca R**, Mitidieri E, Donnarumma E, Tramontano T, Brancaleone V, Cirino G, Bucci M, Sorrentino R. Hydrogen sulfide is involved in dexamethasone-induced hypertension in rat. *Nitric Oxide* 2015; **46**: 80-86 [PMID: 25461303 DOI: 10.1016/j.niox.2014.11.013]
37 **Hunter RW**, Bailey MA. Glucocorticoids and 11β-hydroxysteroid dehydrogenases: mechanisms for hypertension. *Curr Opin Pharmacol* 2015; **21**: 105-114 [PMID: 25666420 DOI: 10.1016/j.coph.2015.01.005]
38 **Frey FJ**, Odermatt A, Frey BM. Glucocorticoid-mediated mineralocorticoid receptor activation and hypertension. *Curr Opin Nephrol Hypertens* 2004; **13**: 451-458 [PMID: 15199296 DOI: 10.1097/01.mnh.0000133976.32559.b0]
39 **Roberts W**, Michno A, Aburima A, Naseem KM. Nitric oxide inhibits von Willebrand factor-mediated platelet adhesion and spreading through regulation of integrin alpha(IIb)beta(3) and myosin light chain. *J Thromb Haemost* 2009; **7**: 2106-2115 [PMID: 19765213 DOI: 10.1111/j.1538-7836.2009.03619.x]
40 **Braune S**, Küpper JH, Jung F. Effect of Prostanoids on Human Platelet Function: An Overview. *Int J Mol Sci* 2020; **21** [PMID: 33260972 DOI: 10.3390/ijms21239020]
41 **Jones CI**, Barrett NE, Moraes LA, Gibbins JM, Jackson DE. Endogenous inhibitory mechanisms and the regulation of platelet function. *Methods Mol Biol* 2012; **788**: 341-366 [PMID: 22130718 DOI: 10.1007/978-1-61779-307-3_23]
42 **Szlendak U**, Budziszewska B, Spychalska J, Drozd-Sokołowska J, Patkowska E, Nowak J. Paroxysmal nocturnal hemoglobinuria: advances in the understanding of pathophysiology, diagnosis, and treatment. *Pol Arch Intern Med* 2022; **132** [PMID: 35699625 DOI: 10.20452/pamw.16271]
43 **Lee JW**, Brodsky RA, Nishimura JI, Kulasekararaj AG. The role of the alternative pathway in paroxysmal nocturnal hemoglobinuria and emerging treatments. *Expert Rev Clin Pharmacol* 2022; **15**: 851-861 [PMID: 35980222 DOI: 10.1080/17512433.2022.2109462]

44 **Roldão M**, Valério Alves R, Escoli R, Gonçalves H, Lopes K. Hypertension-associated thrombotic microangiopathy in an adult patient with complement factor H autoantibodies and a rare heterozygous variant in the CFH gene. *Clin Nephrol* 2021; **96**: 124-128 [PMID: 34032207 DOI: 10.5414/CN110416]

45 **Pinte L**, Sorohan BM, Prohászka Z, Gherghiceanu M, Băicuş C. COVID-19: a trigger for severe thrombotic microangiopathy in a patient with complement gene variant. *Rom J Intern Med* 2022; **60**: 138-142 [PMID: 34997957 DOI: 10.2478/rjim-2021-0040]

46 **Morrow JD**, Parsons WG 3rd, Roberts LJ 2nd. Release of markedly increased quantities of prostaglandin D2 *in vivo* in humans following the administration of nicotinic acid. *Prostaglandins* 1989; **38**: 263-274 [PMID: 2475889 DOI: 10.1016/0090-6980(89)90088-9]

47 **van Wyk V**, Luus HG, Heyns AD. The *in vivo* effect in humans of pyridoxal-5'-phosphate on platelet function and blood coagulation. *Thromb Res* 1992; **66**: 657-668 [PMID: 1519226 DOI: 10.1016/0049-3848(92)90042-9]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1808-1813

DOI: 10.12998/wjcc.v11.i8.1808

ISSN 2307-8960 (online)

CASE REPORT

Giant juvenile fibroadenoma in a 14-year old Chinese female: A case report

Jing Wang, Dai-Di Zhang, Jia-Mao Cheng, Hai-Yan Chen, Rong-Jiao 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): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Corvino A, Italy; Jamali R, Iran

Received: November 18, 2022
Peer-review started: November 18, 2022
First decision: December 26, 2022
Revised: January 4, 2023
Accepted: February 16, 2023
Article in press: February 16, 2023
Published online: March 16, 2023

Jing Wang, Dai-Di Zhang, Hai-Yan Chen, Rong-Jiao Yang, Department of Ultrasound, First Affiliated Hospital of Dali University (The People's Fourth Hospital of Yunnan Province), Dali 671000, Yunnan Province, China

Dai-Di Zhang, Hai-Yan Chen, Rong-Jiao Yang, Department of Ultrasound, School of Clinical Medicine, Dali University, Dali 671000, Yunnan Province, China

Jia-Mao Cheng, Department of Anatomy, College of Basic Medicine, Dali University, Dali 671000, Yunnan Province, China

Corresponding author: Jia-Mao Cheng, MM, Assistant Professor, Department of Anatomy, College of Basic Medicine, Dali University, No. 2 Hongsheng Road, Dali 671000, Yunnan Province, China. chjmao@163.com

Abstract

BACKGROUND

A giant juvenile fibroadenoma (GJF) is a rare, benign breast tumor that affects females < 18 years of age. GJFs are generally suspected based on a palpable mass. GJFs influence breast shape and mammary gland development *via* the pressure effect from their enormous size.

CASE SUMMARY

Herein we report a case involving a 14-year-old Chinese female with a GJF in the left breast. GJF is a rare, benign breast tumor that usually occurs between 9 and 18 years of age and accounts for 0.5%-4.0% of all fibroadenomas. In severe cases, breast deformation may occur. This disease is rarely reported in Chinese people and has a high clinical misdiagnosis rate due to the absence of specific imaging features. On July 25, 2022, a patient with a GJF was admitted to the First Affiliated Hospital of Dali University. The preoperative clinical examination and conventional ultrasound diagnosis needed further clarification. The mass was shown to be an atypical lobulated mass during the operation and confirmed to be a GJF based on pathologic examination.

CONCLUSION

GJF is also a rare, benign breast tumor in Chinese women. Evaluation of such masses consists of a physical examination, radiography, ultrasonography, computer tomography, and magnetic resonance imaging. GJFs are confirmed by histopathologic examination. Mastectomy is not selected when the patient benefits from a complete resection of the mass with breast reconstruction and an

uneventful recovery.

Key Words: Giant juvenile fibroadenoma; Fibroadenoma; Breast tumor; Ultrasonography; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Giant juvenile fibroadenoma (GJF) is a rare benign breast tumor below 18 years of age and can be suspected mainly through palpable masses in clinical practice. Breast ultrasonography shows left masses > 5 cm with benign features (Breast Imaging Reporting and Data System score 3) through the preferred examination for breast imaging in this GJF case. The breast mass of GJF patients in this report showed a lobulated shape and many lobular ducts. Therefore, it is necessary to differentiate GJF from phosphotyrosine binding by histopathology. Clinicians should be aware of this diagnosis for a better approach and early conservative treatment instead of blindly performing mastectomy.

Citation: Wang J, Zhang DD, Cheng JM, Chen HY, Yang RJ. Giant juvenile fibroadenoma in a 14-year old Chinese female: A case report. *World J Clin Cases* 2023; 11(8): 1808-1813
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1808.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1808

INTRODUCTION

A fibroadenoma (FA) is characterized by aberrant proliferation of epithelial and mesenchymal elements, and is the most common benign lesion of the breast in females < 30 years of age[1]. FAs are mostly solitary and can be unilateral or bilateral, with 10%-20% occurring in multiple fashions[1] and divided into adult- and juvenile-types[1,2]. A giant fibroadenoma (GFA) is a specific type of FA that weighs > 500 g, measures > 50 mm in diameter, or is disproportionally large compared with the rest of the breast [2]. The exact etiology of GFA is unknown[2]; however, unopposed estrogen stimulation, increased estrogen receptor sensitivity, or diminished estrogen antagonist sensitivity are thought to be the chief causative factors[1]. FAs are commonly detected incidentally during routine physical examination, ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT), and are diagnosed based on pathologic evaluation. Gene detection and artificial intelligence have been shown to have high prediction accuracy, sensitivity, and specificity in the differential diagnosis of large breast masses[3,4].

CASE PRESENTATION

Chief complaints

On July 25, 2022, a 14-year-old girl was hospitalized in the Department of Thyroid and Breast Surgery of the First Affiliated Hospital of Dali University (China), for evaluation of a giant left breast mass, which had been developing for nearly 6 mo without an apparent cause. Indeed, the mass had enlarged from the initial size of a mung bean to the current size of a hen's egg.

History of present illness

The patient had normal menstruation in the past. She denied any family history of breast masses.

History of past illness

The patient had no history of any other illness.

Personal and family history

The patient denied any history of chest disease, irradiation or estrogen supplementation. There was no family history of breast or ovarian cancer.

Physical examination

The physical examination revealed a 100.0 mm × 40.0 mm mass on the left breast with an unclear border, tough texture, poor mobility, and tenderness. There was no skin erythema, surgical scars, or nipple depression involving the affected breast. The right breast and both axillae were normal. In addition, there were no abnormalities on the biological examination.

Laboratory examinations

There were no abnormalities on routine blood testing, blood biochemistry, blood coagulation function, or routine stool and urine testing.

Imaging examinations

Breast ultrasonography (BUSG) (Toshiba Aplio 500© with a 7.5-MHz probe) of the patient's left breast showed a large hypoechoic solid lesion (110.4 mm × 41.6 mm in size), which had an oval shape, clear boundaries, horizontal growth, and even distribution. A few irregular liquid dark areas were noted in the breast mass without obvious calcifications and no enlarged lymph nodes in the bilateral axillae (Figure 1A). A color Doppler examination revealed few punctate flow signals at the edge of the breast mass (Figure 1B). The lesion was classified as Breast Imaging Reporting and Data System (BI-RADS) category 3.

FINAL DIAGNOSIS

A tru-cut biopsy of frozen sections was reported as a juvenile fibroadenoma (JFA), which was characterized by small oval gland ducts and interstitial collagen fibers (Figure 2).

Differential diagnosis

A GJF is mainly differentiated from phyllodes tumor of the breast (PTB). A PTB is considered a rare fibroepithelial neoplasm of the breast that can be detected in all ages; however, the median age of presentation is 45 years[5]. PTB constitutes around 1% of all FAs and 2.5% of fibroepithelial breast lumps[6]. The World Health Organization (WHO) has classified PTBs histologically as benign, borderline, and malignant[5,6]. The benign variant of a PTB is the most common and close resembles an FA, but is usually larger and recurs more frequently; the rare malignant type is aggressive[6]. The clinical symptoms of a PTB include rapidly growing breast masses; imaging features resemble GFAs or JFAs with benign features[7]. Therefore, a histopathologic examination is the best way to distinguish a GJF from a PTB.

TREATMENT

On July 27, 2022, the patient successfully underwent a simple surgical excision under general anesthesia. The excised lump was smooth, mobile, lobulated, and 100 mm × 90 mm × 50 mm in size (Figure 3). Because she benefited from a complete resection of the mass with breast reconstruction and recovered uneventfully, a mastectomy was not indicated.

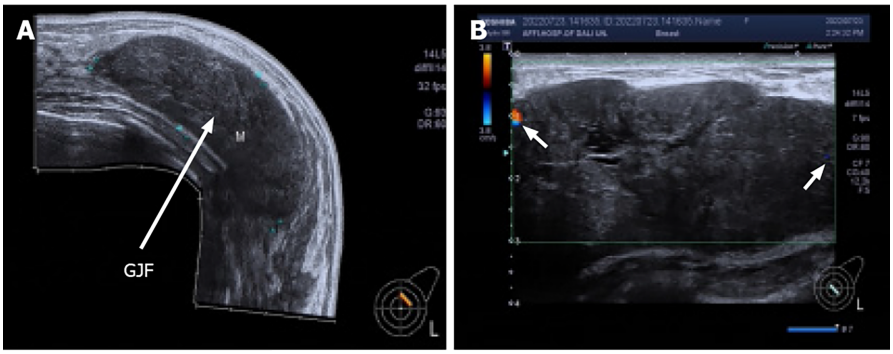
OUTCOME AND FOLLOW-UP

The breast development of the patient was restored to normal. Three months after surgery, her routine outpatient follow-up BUSG evaluation was normal.

DISCUSSION

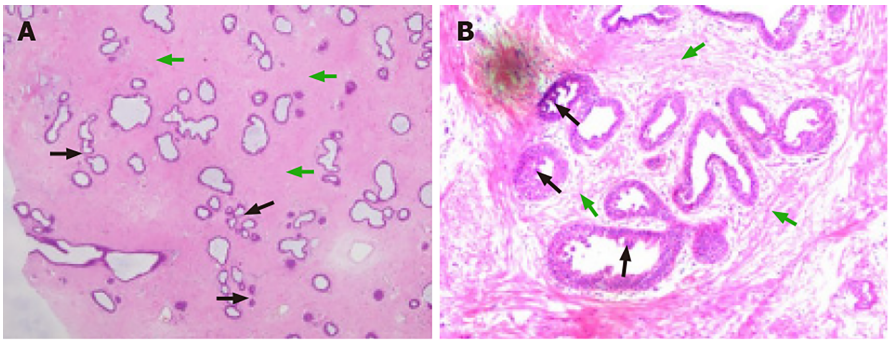
FAs are the most common benign tumors in adolescent women. FAs commonly present in late adolescence and comprise 91% of all histologically-evaluated solid breast masses among patients < 19 years of age based on a radiologic study[8]. Among women with FAs, only 15% have 2-4 masses in one breast, and only 11% have bilateral masses[9]. According to the size and histologic features, adolescent breast masses usually include six types: Simple, complex, multiple, giant, juvenile FAs, and phosphotyrosine binding[7,10,11]. While simple FAs of the breast are the most common lesion, giant juvenile fibroadenomas (GJFs) are a very rare variant with an incidence of 0.5%-2.0%, representing 7%-8% of all FA subtypes, and the most common cause of unilateral gigantomastia in young female patients[7]. In fact, GFAs in patients between 10 and 18 years of age are defined as JFAs, eventually becoming GFAs due to rapid growth[12].

Fibroepithelial breast tumors are biphasic neoplasms formed by an organoid pattern of ductal structures with a striking stromal appearance composed of extensive vascular proliferation, including common FAs and rare phyllodes tumors[13,14]. The FA stroma is usually of low cellularity, with myxoid, fibroblastic, or hyalinized appearances, displaying an interlacing fascicular arrangement of fibroblasts and myofibroblasts with a peri-canalicular pattern[8]. The epithelial proliferation may disclose gynecomastia features with fine filigree-like narrow micropapillary epithelial protrusions[8].



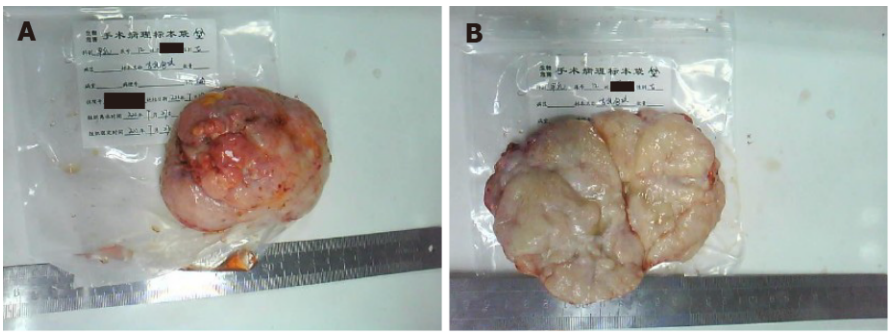
DOI: 10.12998/wjcc.v11.i8.1808 **Copyright** ©The Author(s) 2023.

Figure 1 Breast ultrasonography. A: Panoramic ultrasound imaging reveals the left breast with a large benign mass (long arrow); B: Punctate Doppler flow signals (short arrow) at the edge of the breast mass.



DOI: 10.12998/wjcc.v11.i8.1808 **Copyright** ©The Author(s) 2023.

Figure 2 Pathological examination. A: Low magnification (10 × 10 times) shows a massive ductal epithelial hyperplasia (black arrow) surrounded by a comparatively homogeneous stromal component (green arrow). The interstitial cells in the local lesions are dense, and there is no mitotic phase or cell abnormality; B: Low magnification (10 × 20 times) shows the columnar cells with punctate protrusion in the mammary ducts (black arrow). The density of stromal cells increased without obvious heteromorphism, which was mainly manifested by the interlaced cluster arrangement of fibroblasts and myofibroblasts (green arrow), showing the peritubular type.



DOI: 10.12998/wjcc.v11.i8.1808 **Copyright** ©The Author(s) 2023.

Figure 3 Macroscopic view of the removed lump. A: Excised specimen of a well-defined giant juvenile fibroadenoma with a well-circumscribed, smooth, and bosselated outer surface; B: The mucilaginous section is grayish yellow, lobulated, and medium hardness.

Phyllodes tumors, neoplasms with the potential for recurrence, show an exaggerated intracanalicular growth pattern with broad stromal fronded architecture and stromal hypercellularity[13]. Although the breast mass of the patient in this report had a lobulated shape and a large number of lobular ducts, the histopathologic report was not a phyllodes tumor, thus more longitudinal follow-up is required.

Imaging plays an important role in diagnosing and differentiating GJFs, and a histopathologic exam is used to define the diagnosis further. In a retrospective analysis of 52 articles (n = 153 patients), most patients (86%) presented with a single breast mass[15]. Imaging modalities included BUSG in 72.5% of the patients and mammography (MMG) in 26.1% of the patients[15]. A tissue diagnosis was obtained using a core-needle biopsy in 18.3% of the patients, fine-needle aspiration (FNA) in 25.5% of the patients, and excisional biopsy in 11.1% of the patients[15]. BUSG and MMG are two basic techniques

for routine imaging in diagnosing breast diseases, such as FAs, phyllodes tumors, hamartomas, cysts, hematomas, abscesses, and carcinomas, which are difficult to distinguish clinically based on interview, clinical manifestations, and physical examination. The accuracy of MMG is reduced because of the high density of glandular tissue in adolescent breasts[16], thus MMG is not recommended[7]. If it is not feasible to establish the diagnosis of a JFA clinically, further studies are necessary (BUSG and FNA)[16]. BUSG is the main diagnostic examination in children and adolescents associated with a breast MRI[7]. The 7.5-MHz probe used in this study is commonly recommended in classic textbooks. Sonographic imaging of the breasts with a 7.5-MHz probe achieved a sensitivity of 83% and an net present value of 84%. The same concept applies to Doppler scanning[17]. A high-frequency (20-30 MHz) probe was used in a targeted manner to image breasts in prospective studies. High-quality scans were obtained with optimal spatial resolution and anatomic detail[17]. The typical appearance of a GJF on BUSG is the presence of well-circumscribed round or oval-shaped masses, sometimes lobulated, with a parallel orientation, fairly uniform hypoechoic or anechoic areas with low-level internal echoes, and sometimes with a posterior acoustic enhancement[7]. A GJF on Doppler evaluation can be avascular or show some central vascularity[7]. The diagnosis and treatment of GJFs are heterogeneous. The most common diagnostic modalities include a core needle or excisional biopsy, and the mainstay of treatment is complete excision with an emphasis on preserving the developing breast parenchyma and nipple-areolar complex[15]. Women with BI-RADS category 3 or less breast lesions have a low risk of malignancy, in which case an FNA would reduce the excisional biopsy rate[18]. In the treatment of our patient, although the mass was removed directly without an FNA, it was confirmed by BUSG and verified by pathologic evaluation.

CONCLUSION

GJFs are benign tumors that can influence breast shape and mammary gland development through a pressure effect due to the enormous size of the mass. GJFs usually require surgical resection of the mass to offer a complete cure and acceptable cosmetic results. In this case report, the breast ultrasound provided a preoperative diagnostic basis for surgical treatment, while the postoperative histopathologic diagnosis avoided an unnecessary mastectomy.

ACKNOWLEDGEMENTS

We thank all clinicians who provided pictures and laboratory results.

FOOTNOTES

Author contributions: Wang J performed the ultrasonic examination; Zhang DD contributed to the data curation and writing-original draft preparation; Cheng JM wrote the manuscript and reviewed and edited the manuscript; Chen HY involved in the visualization and validation; Yang RJ participated to the investigation of the manuscript.

Informed consent statement: Written informed consent was obtained from the patient for publication of this report and any accompanying images. We guarantee patient anonymity.

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).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Jing Wang 0000-0001-7540-3005; Jia-Mao Cheng 0000-0003-3464-3920; Hai-Yan Chen 0000-0002-4592-8932.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

REFERENCES

1 **Zeeshan S**, Shaikh K, Tariq MU, Vohra LM. Giant Juvenile Fibroadenoma of the breast in a 13-year-old Pakistani girl with excellent cosmetic outcome after subareolar enucleation - A case report. *Int J Surg Case Rep* 2021; **79**: 450-454 [PMID: 33757260 DOI: 10.1016/j.ijscr.2021.01.094]

2 **Islam S**, Saroop S, Bheem V, Naraynsingh V. Largest giant juvenile fibroadenoma of the breast. *BMJ Case Rep* 2019; **12** [PMID: 30696639 DOI: 10.1136/bcr-2018-227277]

3 **Yin Lee JP**, Thomas AJ, Lum SK, Shamsudin NH, Hii LW, Mai CW, Wong SF, Leong CO. Gene expression profiling of giant fibroadenomas of the breast. *Surg Oncol* 2021; **37**: 101536 [PMID: 33677364 DOI: 10.1016/j.suronc.2021.101536]

4 **Niu S**, Huang J, Li J, Liu X, Wang D, Wang Y, Shen H, Qi M, Xiao Y, Guan M, Li D, Liu F, Wang X, Xiong Y, Gao S, Yu P, Zhu J. Differential diagnosis between small breast phyllodes tumors and fibroadenomas using artificial intelligence and ultrasound data. *Quant Imaging Med Surg* 2021; **11**: 2052-2061 [PMID: 33936986 DOI: 10.21037/qims-20-919]

5 **Rayzah M**. Phyllodes Tumors of the Breast: A Literature Review. *Cureus* 2020; **12**: e10288 [PMID: 32923300 DOI: 10.7759/cureus.10288]

6 **Alipour S**, Eskandari A. Phyllodes Tumor of the Breast in Pregnancy and Lactation. *Adv Exp Med Biol* 2020; **1252**: 137-142 [PMID: 32816274 DOI: 10.1007/978-3-030-41596-9_19]

7 **Belkouchi L**, El Haddad S, Mrani Alaoui N, Allali N, Chat L. Child gigantomastia revealing juvenile giant fibroadenomas. *BJR Case Rep* 2022; **8**: 20210181 [PMID: 36177259 DOI: 10.1259/bjrcr.20210181]

8 **Tan PH**. Fibroepithelial lesions revisited: implications for diagnosis and management. *Mod Pathol* 2021; **34**: 15-37 [PMID: 32461622 DOI: 10.1038/s41379-020-0583-3]

9 **Im CJ**, Miller A, Balassanian R, Mukhtar RA. Early onset, multiple, bilateral fibroadenomas of the breast: a case report. *BMC Womens Health* 2021; **21**: 170 [PMID: 33882939 DOI: 10.1186/s12905-021-01311-7]

10 **Jayasinghe Y**, Simmons PS. Fibroadenomas in adolescence. *Curr Opin Obstet Gynecol* 2009; **21**: 402-406 [PMID: 19606032 DOI: 10.1097/GCO.0b013e32832fa06b]

11 **Panda SK**, Patro B, Mishra J, Dora RK, Subudhi BS. Multiple fibroadenomas in bilateral breasts of a 46-year-old Indian woman - A case report. *Int J Surg Case Rep* 2014; **5**: 262-264 [PMID: 24709623 DOI: 10.1016/j.ijscr.2013.12.013]

12 **Basara Akin I**, Balci P. Fibroadenomas: a multidisciplinary review of the variants. *Clin Imaging* 2021; **71**: 83-100 [PMID: 33186871 DOI: 10.1016/j.clinimag.2020.10.058]

13 **Lerwill MF**, Lee AHS, Tan PH. Fibroepithelial tumours of the breast-a review. *Virchows Arch* 2022; **480**: 45-63 [PMID: 34505197 DOI: 10.1007/s00428-021-03175-6]

14 **Hanna W**, AL-Maghrabi J, Malik A. Aggressive giant fibroepithelial lesion with unusual vascular stroma--a case report. *Mod Pathol* 2003; **16**: 823-827 [PMID: 12920228 DOI: 10.1097/01.MP.0000075644.61258.85]

15 **Sosin M**, Pulcrano M, Feldman ED, Patel KM, Nahabedian MY, Weissler JM, Rodriguez ED. Giant juvenile fibroadenoma: a systematic review with diagnostic and treatment recommendations. *Gland Surg* 2015; **4**: 312-321 [PMID: 26312217 DOI: 10.3978/j.issn.2227-684X.2015.06.04]

16 **Mareti E**, Vatopoulou A, Spyropoulou GA, Papanastasiou A, Pratilas GC, Liberis A, Hatzipantelis E, Dinas K. Breast Disorders in Adolescence: A Review of the Literature. *Breast Care (Basel)* 2021; **16**: 149-155 [PMID: 34012369 DOI: 10.1159/000511924]

17 **Corvino A**, Varelli C, Catalano F, Cocco G, Delli Pizzi A, Boccatonda A, Corvino F, Basile L, Catalano O. Use of High-Frequency Transducers in Breast Sonography. *J Pers Med* 2022; **12** [PMID: 36556182 DOI: 10.3390/jpm12121960]

18 **Chen Z**, Salibay C, Elatre W, Naritoku WY, Ma Y, Martin SE, Wang T. Performance of breast fine needle aspiration as an initial diagnostic tool: A large academic hospital experience. *Cytopathology* 2022; **33**: 707-715 [PMID: 35869577 DOI: 10.1111/cyt.13171]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1814-1822

DOI: 10.12998/wjcc.v11.i8.1814

ISSN 2307-8960 (online)

CASE REPORT

A complementary comment on primary hepatic angiosarcoma: A case report

Ali Osman Gulmez, Sonay Aydin, Mecit Kantarci

Specialty type: Radiology, nuclear medicine and medical imaging

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Moshref RH, Saudi Arabia; Reis F, Brazil

Received: November 17, 2022
Peer-review started: November 17, 2022
First decision: November 25, 2022
Revised: December 1, 2022
Accepted: January 20, 2023
Article in press: January 20, 2023
Published online: March 16, 2023

Ali Osman Gulmez, Sonay Aydin, Mecit Kantarci, Department of Radiology, Erzincan University, Erzincan 24100, Turkey

Corresponding author: Ali Osman Gulmez, MD, Doctor, Department of Radiology, Erzincan University, Mengucek Gazi Education and Research Hospital, BaşbağlarMahallesiHacı Ali Akın Caddesi No. 32 Erzincan/Merkez, Erzincan 24100, Erzincan 24100, Turkey.
aliosmangulmez.2@gmail.com

Abstract

BACKGROUND

This article examines primary hepatic angiosarcoma (PHA) and fat-poor angiomyolipoma (AML), two uncommon vascular cancers. Clinical decisions in these situations are frequently aided by pathology reports and imaging techniques. Uncommon malignant tumors of the vascular endothelium include PHA. Another diagnosis that should not be overlooked when employing contrast-enhanced MR and contrast-enhanced computed tomography (CT) imaging techniques is fat-poor AML, one of the uncommon vascular tumors of the liver. In both conditions, biopsy is the primary means of diagnosis.

CASE SUMMARY

In our article, besides the diagnosis of PHA, fat-poor AML, one of the other rare vascular tumors of the liver, is mentioned. In the case, a 50-year-old female patient with VHL Syndrome was admitted to our hospital with nonspecific lesions such as right upper quadrant pain, weight loss, and nausea. Abdominal ultrasonography (US) revealed a hypoechoic heterogeneous lesion with occasional faint contours. In computed tomography, it was observed as a hyperdense nodular lesion in segment 4. Magnetic resonance imaging (MRI) revealed that the lesion did not contain fat. In connection with the known history of VHL Syndrome, we first evaluated the possibility of AML. Thereupon, a histopathological sample was taken and the diagnosis was made as fat-poor AML with 5% fat content.

CONCLUSION

In conclusion, PHA in our case report and fat-poor AML in our clinic are two uncommon liver vascular malignancies with comparable incidences. Important imaging techniques like contrast-enhanced US (CEUS), CECT, and CEMRI give us substantial advantages in both cases. However, a biopsy is used to provide the final diagnosis.

Key Words: Primary hepatic angiosarcoma; Hepatic angiomyolipoma; Ultrasonic diagnosis; Imaging; Pathology; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In this review, two rare vascular tumors, namely primary hepatic angiosarcoma (PHA) and fat-poor angiomyolipoma (AML), were mentioned. Special mention is made of the diagnosis of PHA by contrast-enhanced ultrasound (CEUS) in these case reports. Meanwhile we introduced a new ultrasound technology and CEUS has many specific manifestations in the diagnosis and differential diagnosis of PHA and has great clinical value in diagnosing PHA. Although imaging methods have an important place in the diagnosis of fat-poor AML, one of the points especially mentioned in the study is that the definitive diagnosis of both tumors will be made with a pathology report after biopsy.

Citation: Gulmez AO, Aydin S, Kantarci M. A complementary comment on primary hepatic angiosarcoma: A case report. *World J Clin Cases* 2023; 11(8): 1814-1822
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1814.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1814

INTRODUCTION

This article reviews two uncommon vascular cancers, primary hepatic angiosarcoma (PHA) and fat-poor angiomyolipoma (AML). However, in this study, besides the diagnosis of PHA, fat-poor AML, one of the other rare vascular tumors of the liver, is mentioned. In these cases, pathology reports and imaging techniques often assist clinical decisions. Another diagnosis that should not be overlooked when using contrast-enhanced MR and contrast-enhanced computed tomography (CT) imaging techniques is fat-poor AML, one of the rare vascular tumors of the liver. In both cases, biopsy is the primary diagnostic tool. We will mention two rare diagnoses that doctors and healthcare professionals involved in the diagnosis should be careful about.

CASE PRESENTATION

Chief complaints

We would like to talk about the case report of our patient who was diagnosed with fat-poor AML, which is one of the rare liver tumors like PHA. Our patient is a 50-year-old female patient who was previously diagnosed with VHL syndrome. Nonspecific symptoms such as right upper quadrant pain, weight loss, and nausea are the primary complaints at admission to our clinic.

History of present illness

If we look at the patient's current disease, nonspecific symptoms such as right upper quadrant pain, weight loss and nausea make us think that he already has a disease related to the gastroenterological system.

History of past illness

When we look at the patient's past disease history, VHL syndrome was diagnosed and it is known that he has AMLs in both kidneys.

Personal and family history

When the family history was taken apart from the patient's history, no condition that could be associated with the current disease status was found in the family members.

Physical examination

If we look at the physical examination findings, no significant finding was observed except for the right upper quadrant tenderness.

Laboratory examinations

Laboratory examinations, especially liver function tests, were within normal limits.

Imaging examinations

At the beginning of the introduction, we would like to talk about the case presentation of our patient, who was diagnosed with fat-poor AML, which is one of the rare liver tumors such as PHA. Our patient is a 50-year-old female patient who was previously diagnosed with VHL syndrome. The main complaints of admission to our clinic are nonspecific symptoms such as right upper quadrant pain, weight loss and nausea. When evaluated together with the patient's current disease and past disease history, he was diagnosed with VHL syndrome and had AMLs in both kidneys. Apart from the patient's personal health history, when the family history was taken, no related condition was found in the family members to be associated with the current disease state. When evaluated by physical examination, no significant finding was observed except right upper quadrant tenderness. In laboratory examinations, other tests, especially liver function tests, were within normal ranges.

If we look at the imaging methods, a hypoechoic heterogeneous lesion with faint contours was detected in the abdominal ultrasonography (US). The mass lesion was 15 mm × 16 mm in size and was located in segment 4. On computed tomography (CT), it was observed as a hyperdense nodular (approximately 16 mm in diameter) lesion in the venous phase. In magnetic resonance imaging (MRI), in-phase and out-of-phase images obtained with the 'Dual echo' method; When both sequences were compared, it was understood that the lesion did not contain fat. Iohexol (Opaxol 350 mg/100 mL) was used in CT and gadoxic acid disodium (Primovist 0.25 mmol/mL) was used as hepatospecific agent in MR. In addition, the lesion showed slight diffusion restriction on diffusion-weighted images. It was hypointense compared to normal liver parenchyma on pre-contrast T1-weighted images. It showed strong peripheral enhancement in the arterial phase. Hepatobiliary phase images showed hypointense associated with normal parenchyma.

FINAL DIAGNOSIS

Radiographic findings showed a benign, highly vascular tumor devoid of hepatocytes. In connection with the known history of VHL Syndrome, we first evaluated the possibility of AML; however, the lack of lesion fat made it difficult to establish the diagnosis. Thereupon, histopathological sampling was taken for diagnosis and the final diagnosis came as fat-poor AML with 5% fat content.

TREATMENT

If we look at the treatment point, medical, surgical or embolic ablative treatment methods were not required at this stage because of the fact that the patient did not grow more than 0.5 cm per year in the follow-ups and the dimensions did not exceed 3 cm at the initial diagnosis stage. It was decided that the patient should come to the controls at regular intervals.

OUTCOME AND FOLLOW-UP

As a result, histopathological sampling is required for definitive diagnosis together with physical examination, laboratory and imaging methods. The patient was followed up with laboratory and imaging methods at regular intervals.

DISCUSSION

Although more detailed information is given in the continuation of the article about hepatic AMLs, which we mentioned over the case, it is important to remember that it should be kept in mind as it is a rare tumor.

PHA in our case report and fat-poor AML in our clinic are two rare vascular tumors of the liver with a similar incidence. In both, important imaging modalities such as CEUS, CECT and CEMRI provide us with significant gains. However, the definitive diagnosis is made by biopsy.

We read with great interest the case report of Wang *et al*[1] on the diagnosis and treatment of PHA in the November 2022 issue of the World Journal of Clinical Cases. They described a situation when the patient complained of abdominal soreness. After a comprehensive investigation, including contrast-enhanced ultrasound (CEUS), CECT, and CEMRI, the findings were combined with the biopsy result and the diagnosis of PHA was made. We appreciate the dedication of the authors to raise awareness of the diagnosis and treatment of PHA.

PHA is a rare malignant tumor. It arises from spindle pleomorphic cells that line or grow within the lumen of sinusoids and pre-existing vascular spaces such as terminal hepatic venules in the liver.

Worldwide, only about 200 cases are detected annually. However, it is the most common primary malignant mesenchymal tumor of the liver in adults, accounting for 2% of all primary hepatic malignancies. It accounts for less than 5% of all angiosarcoma[2,3]. A quarter of PHA is thought to be bound to various substances such as vinyl chloride[1]. The cause of the remaining three quarters is unknown. Patients most commonly present with vague symptoms such as right upper quadrant pain, weight loss, fatigue, and abdominal mass[4].

If we look at the differential diagnosis point, as stated in many studies, it is difficult to distinguish PHA from hemangioma, hepatocellular carcinoma (HCC), cholangiocarcinoma, metastases and hepatic abscess[1,5]. Although CECT and CEMRI guide us, CEUS, which was especially emphasized in the study, has started to take its place in daily practice as an important and simultaneous imaging method [1]. In the arterial and portal phases of the CEUS, nodular peripheral enhancement is seen, and in the late phase nodules, low contrast enhancement is shown together with non-contrast areas[1,6,7].

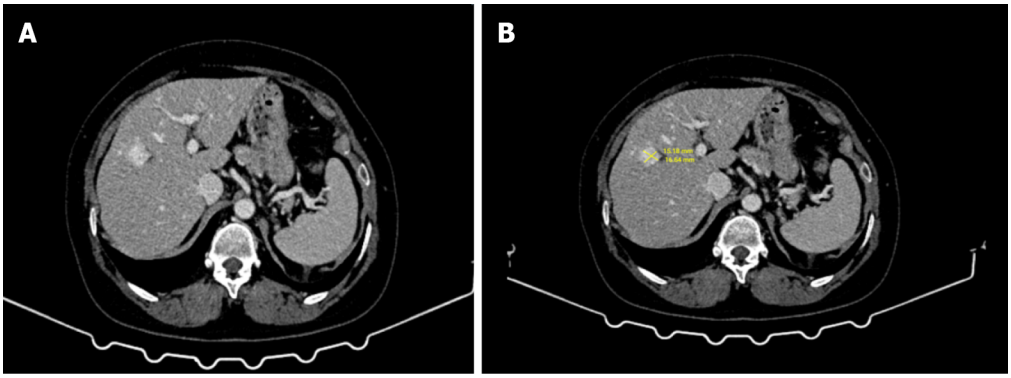
Although radiological imaging has an important place in the diagnosis of PHA, the actual diagnosis is finalized with the result of pathological biopsy[8]. In immunohistochemical stains, CD31, CD34, and factor VIII-associated antigen are often used in combination for the diagnosis of angiosarcomas, as 40% of tumors lose expression of one or more markers. The combination of CD31 and factor VIII-related antigen is defined as the most sensitive one by expressing one of the two markers in 90% of cases[8,9]. Although the treatment point was also mentioned in our study, when combined with some other studies, surgical resection seems to be the key to improving the prognosis in the best way[10,11].

In addition to the article, we would like to talk about fat-poor AML, which is one of the rare vascular tumors of the liver like PHA. AMLs are benign mesenchymal tumors that usually involve the kidneys and rarely the liver[12]. Renal AMLs are also seen as a subcomponent of some syndromes. Von Hippel-Lindau syndrome (VHL syndrome) is one of these syndromes. VHL syndrome is caused by germline mutations of the VHL tumor suppressor gene located on chromosome 3p25. VHL syndrome is an inherited cancer syndrome characterized by the development of vascular tumors of the nervous system and retina, pheochromocytomas, pancreatic islet cell tumors, endolymphatic sac tumors, AMLs, especially cysts in the kidney, as well as the development of benign cysts affecting various organs[13].

Before proceeding to the case report of our patient with a prediagnosis of VHL, we would like to give some more general information about VHL syndrome. VHL syndrome, as we mentioned in the above paragraph, is an autosomal dominant inherited tumor disease that occurs due to germline mutations in the VHL gene located on the short arm of chromosome 3. Patients with VHL can develop multiple benign and malignant tumor structures that can affect various organ systems at various levels. To give examples, retinal hemangioblastomas (HBs), central nervous system (CNS) HBs, endolymphatic sac tumors, pancreatic neuroendocrine tumors, pancreatic cystadenomas, pancreatic cysts, clear cell renal cell carcinomas, renal cysts, pheochromocytomas, paragangliomas, and epididia and large ligament cystadenomas can be given as examples of many findings. One of the most important points in making a clinically meaningful diagnosis and initiating treatment is to know that VHL syndrome can be divided into groups according to the forms that we may encounter in daily practice. Each phenotype is associated with a particular genotype. It is basically divided into 2 types, type 1 and type 2. Type 2 is divided into 3 types as type 2A, type 2B and type 2C. In Type 1, there is a minimal likelihood of developing a medullary adrenal gland tumor, but a high likelihood of developing clear cell kidney cancer, hemangioblastomas, and different pancreatic diseasesAlthough there is a high risk of pheochromocytoma in all kinds 2A, 2b, and 2C, the fact that type 2C alone has a very high risk is significant. Additionally crucial to the distinction of 2A and 2B types is clear cell renal cancer. Type 2B is more likely to experience it than type 2A, where its occurrence is lower. We have summarized the types of VHL syndrome in general[14].

VHL syndrome is a syndrome that requires lifelong prophylactic surveillance. The surveillance data we have are based on best medical judgment. However, there is no evidence of any effect[15]. VHL syndrome is a multisystem-related familial cancer syndrome with a prevalence ranging from 1 in 31000 to 1 in 85000[16,17]. It is autosomal dominant in inheritance type and the estimated incidence of its newly developed mutation is 1%-23%[18,19]. After the diagnosis of VHL syndrome, various surveillance begins in patients; because this syndrome affects many organs at the same time. We will now touch on these through examples. Imaging of the central nervous system begins at age 15; but if the diagnosis is made earlier, a basic examination can be done once in the age range of 5-14 years. Eye examination starts directly upon diagnosis and is repeated every 12 mo. Imaging of the abdominal region begins at age 15; but if the diagnosis is made earlier, a basic examination can be done once in the age range of 5-14 years. Neurological examination starts directly upon diagnosis and is repeated every 12 mo. A 24-h urine test for catecholamine levels basically begins at age 15; but if the diagnosis is made earlier, a basic examination can be done once in the age range of 5-14 years. Audiometric examination begins at age 15. Since the risk of ocular and neurological findings and poor prognosis is higher, examinations are performed at more frequent intervals as the diagnosis is made[14].

We want to get started with the imaging features. Here we will relate it to the finding that it is associated with organs. Starting with the kidney first, it is seen in more than two-thirds of patients with histological subtype VHL syndrome with multicentric renal cysts and clear cell RCCs in the kidney[14]. Although there is a high risk of pheochromocytoma in all kinds 2A, 2B, and 2C, the fact that type 2C alone has a very high risk is significant. Additionally crucial to the distinction of 2A and 2B types is

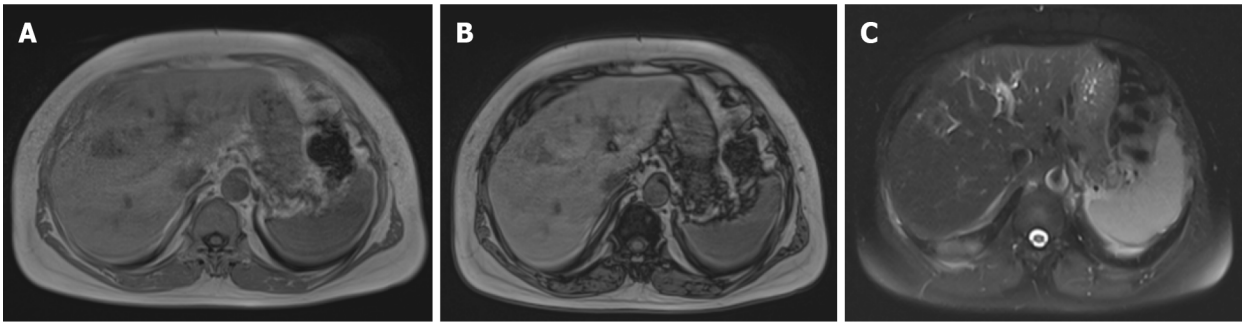


DOI: 10.12998/wjcc.v11.i8.1814 **Copyright** ©The Author(s) 2023.

Figure 1 Computed tomography. A and B: Contrast-enhanced computed tomography, in the venous phase, a 15 mm × 16 mm hyperdense tumor was observed in liver segment 4 with blurred contours in places.

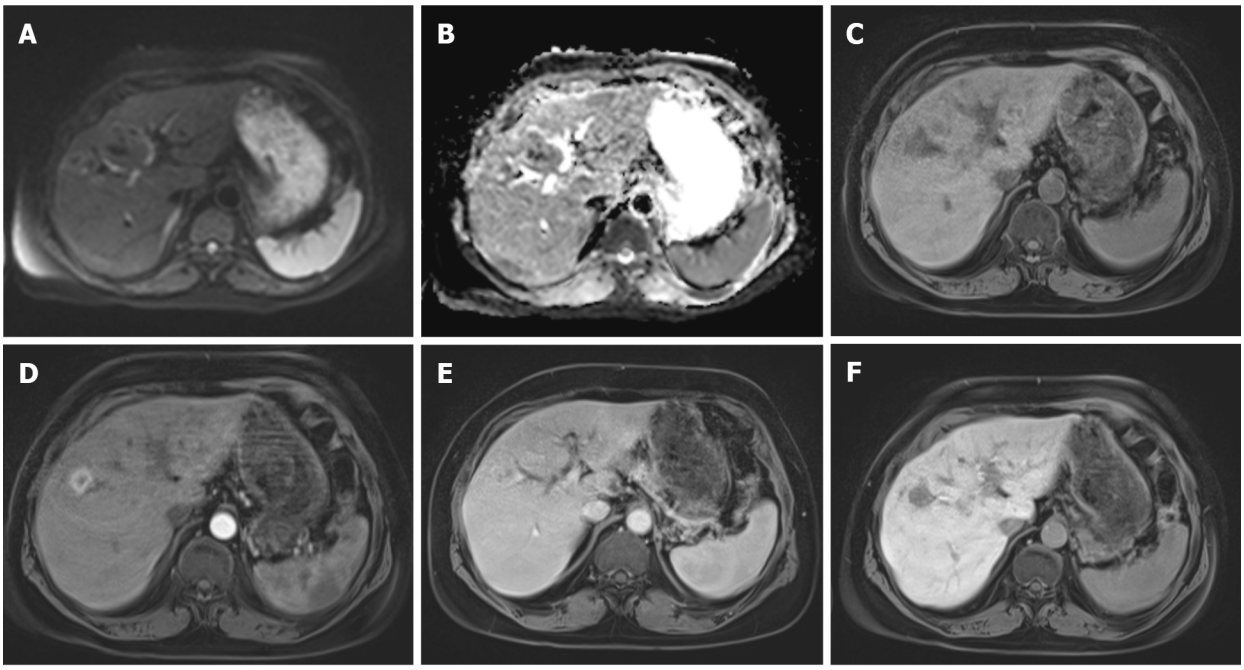
clear cell renal cancer. Type 2B is more likely to experience it than type 2A, where its occurrence is lower [14,20,21]. Especially CT and MRI are two important imaging modalities that are frequently used in the evaluation of kidney lesions suspected to be BCC and in the staging of such lesions. In CT, increases below 10 HU are considered within the normal range and are not classified as increases[22]. Another crucial fact to keep in mind is that even straightforward cystic lesions may become more prevalent in more than one in twenty MRI findings[23]. The main purpose of imaging and the treatment applied with it is to detect lesions before new lesions appear. If we look at the imaging features of the pancreas, pancreatic cyst may develop in 42% of patients with VHL syndrome, while serous cystadenoma and neuroendocrine tumor influencing the pancreas can be observed in approximately one in 10 patients, respectively[24]. Such pancreatic cysts are usually multicenter and can be seen as hypotenuated lesions without contrast enhancement. On MRI, serous cystadenomas are typically hyperintense on T2-weighted images and hypointense on T1-weighted images; however, if there is intracystic hemorrhage, an increase in signal is observed that can be hyperintense in both. When a fibrotic central scar is present, a hypointense signal is produced with delayed contrast enhancement on T1- and T2-weighted images. Although pathognomonic, a central scar is seen only in 20%-30% of cases. In the absence of scar, the combination of microcystic appearance and vascular contrast enhancement may support the diagnosis. Serous cystadenomas are not associated with the pancreatic duct. Pancreatic neuroendocrine tumors can be seen in 9%-17% of patients with VHL syndrome. Compared with sporadic pancreatic neuroendocrine tumors, those associated with VHL syndrome appear earlier (mean, 35 years *vs* 58 years). The neuroendocrine tumors seen in VHL are typically multifocal and most commonly located in the pancreatic head section and the uncinate process. On non-contrast CT imaging, they often appear hypotenuated. On imaging, it usually exhibits the same contrast enhancement as the rest of the body. Pancreatic neuroendocrine tumors in people with VHL syndrome are typically identified solely by imaging[14,24]. These individuals frequently experience the triad of headache, perspiration, and tachycardia linked to arterial hypertension. In cases of VHL disease, approximately one in every 4 patients has an adrenal medullary tumor, while paragangliomas are seen in about one in every 6 patients[24,25]. Like its clinical presentations, imaging findings are diverse. These individuals frequently experience the triad of headache, perspiration, and tachycardia linked to arterial hypertension. Despite the fact that there is a strong augmentation visible after contrast application, this shows that they are hypervascular, especially in their solid components[14,21]. It's crucial to keep in mind that absolute or relative resolution may be seen on CT in benign lesions like adenoma or malignant tumors[26,27]. The bulb sign, or high signal intensity on T2-weighted MRI scans of a pheochromocytoma, is a crucial component for diagnosis and is present in 11%-65% of patients[28]. Usually isointense; but if there is bleeding it may also present with a hyperintense appearance. As a result of different degrees of pathological degeneration, pheochromocytomas may present in many different forms as imaging. Radiologists refer to them as "chameleon tumors" because of this. Functional investigations are frequently necessary to be included in the diagnosis for pheochromocytomas and paragangliomas, as well as to detect non-adrenal or metastatic illness, due to the wide range of imaging symptoms[29]. In conclusion, it is crucial for the initial diagnosis as well as the detection and monitoring of lesions in accordance with the advised abdominal imaging follow-up protocols[15,30,31]. Radiologists, with multidisciplinary approaches and medical equipment more treatment modalities for patients with VHL syndrome They seek to improve their quality of life and aim to reduce the mortality and morbidity caused by the disease.

A 50-year-old female patient with VHL Syndrome was admitted to our hospital with nonspecific lesions such as right upper quadrant pain, weight loss and nausea. In laboratory tests, liver function test results were measured in normal values. Abdominal ultrasonography (US) revealed a hypoechoic heterogeneous lesion with faint contours in places; The tumor was 15 mm × 16 mm in size and was located in the 4th (Figure 1B) segment of the liver. On computed tomography (CT), it was observed as a



DOI: 10.12998/wjcc.v11.i8.1814 **Copyright** ©The Author(s) 2023.

Figure 2 Magnetic resonance imaging. A-C: In magnetic resonance imaging (MRI), the in-phase (A) and out-phase (B) images of the liver segment 4 obtained by the "Dual echo" method of the tumor with faint contours; no significant signal loss was observed when both sequences were compared. In the fat-suppressed T2-weighted MRI image (C), no significant signal loss was also present (findings to indicate absence of fatty content).



DOI: 10.12998/wjcc.v11.i8.1814 **Copyright** ©The Author(s) 2023.

Figure 3 A 16 mm diameter lesion located at the segment 4. A and B: The lesion has mild diffusion restriction on diffusion-weighted images and apparent diffusion coefficient maps; C: It is hypointense in the precontrast phase; D: It showes strongperipheral enhancement in the arterial phase; E: Continues toenhance in venous phase; F: The lesion is seen relatively hypointense in the hepatobiliary phase images (20th min). The diagnosis was confirmed by pathology as fat-poor angiomyolipoma.

nodular (diameter 16 mm) lesion with hyperdense appearance in the venous phase (Figure 1). In MRI, in phase and out phase images obtained by "Dual echo" method; When both sequences are compared, it is understood that the lesion does not contain any fat (Figure 2).

In this case from our hospital, iohexol (Opaxol 350 mg/100 mL) was used in CT and gadoxtic acid disodium (Primovist 0.25 mmol/mL) was used as hepatospecific agent in MR. In addition, the lesion revealed mild diffusion restriction on diffusion-weighted images, it was hypointense in comparison with normal liver parenchyma on T1 weighted image precontrast phase, it showed strong peripheral enhancement in the arterial phase, and continued to enhance in the venous and late venous phases. In the hepatobiliary phase images it was seen hypointense related to the normal parenchyma (Figure 3). The radiographic findings indicated a benign, highly vascular tumour devoid of hepatocytes. In conjunction with the known history of VHL Syndrome, we primarily considered the possibility of AML; nevertheless, the lesion's lack of fat made it difficult to determine the diagnosis. Thereupon, histopathological sampling was taken and the diagnosis came as fat-poor AML with 5% fat content.

We would like to give some more general information about the hepatic AMLs we have mentioned over the case. Ishak[32] first described hepatic AMLs in 1976; they are tumors made up of altered fat, epithelioid and spindle smooth muscle cells, and thick-walled blood vessels. There is a clear female predominance in hepatic AMLs, which can affect patients of all ages. Patients with hepatic AML are

typically asymptomatic; the tumor is frequently discovered by chance during physicals or tests for other illnesses. Patients with big AMLs experience symptoms brought on by the tumor's compression[33,34].

The prevalence of this condition has increased as a result of recent developments in imaging techniques and a deeper comprehension of hepatic AMLs. Approximately 200 cases of hepatic AML have so far been recorded[16]. Additionally, it has been discovered that the relative proportions of the tumor components affect the imaging characteristics of hepatic AMLs[14-34]. Due to their rarity and varying imaging characteristics, hepatic AMLs are challenging to correctly diagnose preoperatively. In regions where HCC is prevalent, it is crucial to differentiate between hepatic AMLs and HCCs. Hepatic AMLs typically have a characteristic appearance on imaging tests due to their fat content, allowing for the preoperative separation of hepatic AMLs from HCCs[17-35].

CONCLUSION

In conclusion, the PHA in our case report and the fat-poor AML we presented from our clinic are two rare vascular tumors of the liver with similar incidences. In both, important imaging methods such as CEUS, CECT, and CEMRI provide us with significant gains. However, the definitive diagnosis is found by biopsy.

FOOTNOTES

Author contributions: Gulmez AO and Aydin S contributed equally to this work; Gulmez AO, Aydin S, and Kantarci M designed the research study; Gulmez AO carried out the research; Aydin S contributed new reagents and analytical tools; Kantarci M analyzed the data and wrote the draft; all authors have read and approved the final draft.

Informed consent statement: Informed written consent was obtained from the patients for the publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no 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).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Turkey

ORCID number: Ali Osman Gulmez 0000-0001-7050-1765; Sonay Aydin 0000-0002-3812-6333; Mecit Kantarci 0000-0002-1043-6719.

S-Editor: Chen YL
L-Editor: A
P-Editor: Chen YL

REFERENCES

1 **Wang J**, Sun LT. Primary hepatic angiosarcoma: A case report. *World J Clin Cases* 2022; **10**: 11590-11596 [PMID: 36387808 DOI: 10.12998/wjcc.v10.i31.11590]
2 **Lahat G**, Dhuka AR, Hallevi H, Xiao L, Zou C, Smith KD, Phung TL, Pollock RE, Benjamin R, Hunt KK, Lazar AJ, Lev D. Angiosarcoma: clinical and molecular insights. *Ann Surg* 2010; **251**: 1098-1106 [PMID: 20485141 DOI: 10.1097/SLA.0b013e3181dbb75a]
3 **Fayette J**, Martin E, Piperno-Neumann S, Le Cesne A, Robert C, Bonvalot S, Ranchère D, Pouillart P, Coindre JM, Blay JY. Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. *Ann Oncol* 2007; **18**: 2030-2036 [PMID: 17974557 DOI: 10.1093/annonc/mdm381]
4 **Chaudhary P**, Bhadana U, Singh RA, Ahuja A. Primary hepatic angiosarcoma. *Eur J Surg Oncol* 2015; **41**: 1137-1143 [PMID: 26008857 DOI: 10.1016/j.ejso.2015.04.022]
5 **Zhu YP**, Chen YM, Matro E, Chen RB, Jiang ZN, Mou YP, Hu HJ, Huang CJ, Wang GY. Primary hepatic angiosarcoma: A report of two cases and literature review. *World J Gastroenterol* 2015; **21**: 6088-6096 [PMID: 26019478 DOI: 10.3748/wjg.v21.i19.6088]

6 **Zhou Y**, Hou P, Wang F, Li B, Gao J. Primary hepatic malignant vascular tumors: a follow-up study of imaging characteristics and clinicopathological features. *Cancer Imaging* 2020; **20**: 59 [PMID: 32795351 DOI: 10.1186/s40644-020-00336-9]

7 **Trojan J**, Hammerstingl R, Engels K, Schneider AR, Zeuzem S, Dietrich CF. Contrast-enhanced ultrasound in the diagnosis of malignant mesenchymal liver tumors. *J Clin Ultrasound* 2010; **38**: 227-231 [PMID: 20336772 DOI: 10.1002/jcu.20690]

8 **Zheng YW**, Zhang XW, Zhang JL, Hui ZZ, Du WJ, Li RM, Ren XB. Primary hepatic angiosarcoma and potential treatment options. *J Gastroenterol Hepatol* 2014; **29**: 906-911 [PMID: 24372769 DOI: 10.1111/jgh.12506]

9 **Rao P**, Lahat G, Arnold C, Gavino AC, Lahat S, Hornick JL, Lev D, Lazar AJ. Angiosarcoma: a tissue microarray study with diagnostic implications. *Am J Dermatopathol* 2013; **35**: 432-437 [PMID: 23689692 DOI: 10.1097/DAD.0b013e318271295a]

10 **Duan XF**, Li Q. Primary hepatic angiosarcoma: a retrospective analysis of 6 cases. *J Dig Dis* 2012; **13**: 381-385 [PMID: 22713088 DOI: 10.1111/j.1751-2980.2012.00600.x]

11 **Weitz J**, Klimstra DS, Cymes K, Jarnagin WR, D'Angelica M, La Quaglia MP, Fong Y, Brennan MF, Blumgart LH, Dematteo RP. Management of primary liver sarcomas. *Cancer* 2007; **109**: 1391-1396 [PMID: 17315167 DOI: 10.1002/cncr.22530]

12 **Banshodani M**, Ishiyama K, Amano H, Tashiro H, Arihiro K, Itamoto T, Ohdan H. Hepatic Angiomyolipoma with Minimal Intratumoral Fat Content. *Case Rep Gastroenterol* 2009; **3**: 324-331 [PMID: 21103249 DOI: 10.1159/000255355]

13 **Maher ER**, Kaelin WG. Von Hippel-Lindau disease. *Medicine* 1997; **76**: 381-391 [DOI: 10.1097/00005792-199711000-00001]

14 **Ganeshan D**, Menias CO, Pickhardt PJ, Sandrasegaran K, Lubner MG, Ramalingam P, Bhalla S. Tumors in von Hippel-Lindau Syndrome: From Head to Toe-Comprehensive State-of-the-Art Review. *Radiographics* 2018; **38**: 849-866 [PMID: 29601266 DOI: 10.1148/rg.2018170156]

15 **Poulsen ML**, Budtz-Jørgensen E, Bisgaard ML. Surveillance in von Hippel-Lindau disease (vHL). *Clin Genet* 2010; **77**: 49-59 [PMID: 19863552 DOI: 10.1111/j.1399-0004.2009.01281.x]

16 **Maher ER**, Iselius L, Yates JR, Littler M, Benjamin C, Harris R, Sampson J, Williams A, Ferguson-Smith MA, Morton N. Von Hippel-Lindau disease: a genetic study. *J Med Genet* 1991; **28**: 443-447 [PMID: 1895313 DOI: 10.1136/jmg.28.7.443]

17 **Neumann HP**, Berger DP, Sigmund G, Blum U, Schmidt D, Parmer RJ, Volk B, Kirste G. Pheochromocytomas, multiple endocrine neoplasia type 2, and von Hippel-Lindau disease. *N Engl J Med* 1993; **329**: 1531-1538 [PMID: 8105382 DOI: 10.1056/NEJM199311183292103]

18 **Choyke PL**, Glenn GM, Walther MM, Patronas NJ, Linehan WM, Zbar B. von Hippel-Lindau disease: genetic, clinical, and imaging features. *Radiology* 1995; **194**: 629-642 [PMID: 7862955 DOI: 10.1148/radiology.194.3.7862955]

19 **Sgambati MT**, Stolle C, Choyke PL, Walther MM, Zbar B, Linehan WM, Glenn GM. Mosaicism in von Hippel-Lindau disease: lessons from kindreds with germline mutations identified in offspring with mosaic parents. *Am J Hum Genet* 2000; **66**: 84-91 [PMID: 10631138 DOI: 10.1086/302726]

20 **Fernandes DA**, Mourão JLV, Duarte JÁ, Dalaqua M, Reis F, Caserta NMG. Imaging manifestations of von Hippel-Lindau disease: an illustrated guide focusing on abdominal manifestations. *Radiol Bras* 2022; **55**: 317-323 [PMID: 36320367 DOI: 10.1590/0100-3984.2021.0121-en]

21 **Schwingel R**, Duarte SB, Oshima MM, Mesquita JV, Reis F. Which is your diagnosis? *Radiol Bras* 2015; **48**: XI-XIII [PMID: 25987761 DOI: 10.1590/0100-3984.2015.48.2qd]

22 **Tappouni R**, Kissane J, Sarwani N, Lehman EB. Pseudoenhancement of renal cysts: influence of lesion size, lesion location, slice thickness, and number of MDCT detectors. *AJR Am J Roentgenol* 2012; **198**: 133-137 [PMID: 22194488 DOI: 10.2214/AJR.10.6057]

23 **Gläsker S**, Vergauwen E, Koch CA, Kutikov A, Vortmeyer AO. Von Hippel-Lindau Disease: Current Challenges and Future Prospects. *Onco Targets Ther* 2020; **13**: 5669-5690 [PMID: 32606780 DOI: 10.2147/OTT.S190753]

24 **Choi YA**, Kim CK, Park BK, Kim B. Evaluation of adrenal metastases from renal cell carcinoma and hepatocellular carcinoma: use of delayed contrast-enhanced CT. *Radiology* 2013; **266**: 514-520 [PMID: 23151828 DOI: 10.1148/radiol.12120110]

25 **Aufforth RD**, Ramakant P, Sadowski SM, Mehta A, Trebska-McGowan K, Nilubol N, Pacak K, Kebebew E. Pheochromocytoma Screening Initiation and Frequency in von Hippel-Lindau Syndrome. *J Clin Endocrinol Metab* 2015; **100**: 4498-4504 [PMID: 26451910 DOI: 10.1210/jc.2015-3045]

26 **Blake MA**, Kalra MK, Maher MM, Sahani DV, Sweeney AT, Mueller PR, Hahn PF, Boland GW. Pheochromocytoma: an imaging chameleon. *Radiographics* 2004; **24** Suppl 1: S87-S99 [PMID: 15486252 DOI: 10.1148/rg.24si045506]

27 **Schieda N**, Alrashed A, Flood TA, Samji K, Shabana W, McInnes MD. Comparison of Quantitative MRI and CT Washout Analysis for Differentiation of Adrenal Pheochromocytoma From Adrenal Adenoma. *AJR Am J Roentgenol* 2016; **206**: 1141-1148 [PMID: 27011100 DOI: 10.2214/AJR.15.15318]

28 **Jacques AE**, Sahdev A, Sandrasagara M, Goldstein R, Berney D, Rockall AG, Chew S, Reznek RH. Adrenal phaeochromocytoma: correlation of MRI appearances with histology and function. *Eur Radiol* 2008; **18**: 2885-2892 [PMID: 18641999 DOI: 10.1007/s00330-008-1073-z]

29 **Prasad V**, Tiling N, Denecke T, Brenner W, Plöckinger U. Potential role of (68)Ga-DOTATOC PET/CT in screening for pancreatic neuroendocrine tumour in patients with von Hippel-Lindau disease. *Eur J Nucl Med Mol Imaging* 2016; **43**: 2014-2020 [PMID: 27293206 DOI: 10.1007/s00259-016-3421-6]

30 **Mourão JLV**, Borella LFM, Duarte JÁ, Dalaqua M, Fernandes DA, Reis F. Imaging manifestations of von Hippel-Lindau disease: an illustrated guide focusing on the central nervous system. *Radiol Bras* 2022; **55**: 188-192 [PMID: 35795602 DOI: 10.1590/0100-3984.2021.0080-en]

31 **VHL Alliance**. The VHL handbook: What you need to know about VHL. Boston, MA: VHL Alliance. Independently published, 2020 [DOI: 10.7554/elife.14319.020]

32 **Ishak KG**. Mesenchymal Tumors of the Liver. New York: John Wiley Medical, 1976: 247-307

33 **Ren N**, Qin LX, Tang ZY, Wu ZQ, Fan J. Diagnosis and treatment of hepatic angiomyolipoma in 26 cases. *World J*

Gastroenterol 2003; **9**: 1856-1858 [PMID: 12918138 DOI: 10.3748/wjg.v9.i8.1856]

34 **Jiang TA**, Zhao QY, Chen MY, Wang LJ, Ao JY. Diagnostic analysis of hepatic angiomyolipoma. *Hepatobiliary Pancreat Dis Int* 2005; **4**: 152-155 [PMID: 15730942]

35 **Högemann D**, Flemming P, Kreipe H, Galanski M. Correlation of MRI and CT findings with histopathology in hepatic angiomyolipoma. *Eur Radiol* 2001; **11**: 1389-1395 [PMID: 11519547 DOI: 10.1007/s003300000750]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1823-1829

DOI: 10.12998/wjcc.v11.i8.1823

ISSN 2307-8960 (online)

CASE REPORT

Primary membranous nephrotic syndrome with chylothorax as first presentation: A case report and literature review

Le-Le Feng, Jie Du, Chen Wang, Shui-Li Wang

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Arunachalam J, India; Ullah K, Pakistan

Received: December 13, 2022
Peer-review started: December 13, 2022
First decision: January 17, 2023
Revised: February 1, 2023
Accepted: February 21, 2023
Article in press: February 21, 2023
Published online: March 16, 2023

Le-Le Feng, Jie Du, Chen Wang, Shui-Li Wang, Department of Respiratory and Critical Care Medicine I, Shaanxi Provincial People's Hospital, Xi'an 710068, Shaanxi Province, China

Le-Le Feng, Department of Respiratory and Critical Care Medicine I, Xi'an Medical University, Xi'an 710068, Shaanxi Province, China

Corresponding author: Shui-Li Wang, Doctor, Chief Physician, Department of Respiratory and Critical Care Medicine I, Shaanxi Provincial People's Hospital, No. 256 Youyi West Road, Beilin District, Xi'an 710068, Shaanxi Province, China. fw0604@163.com

Abstract

BACKGROUND

Primary membranous nephrotic syndrome with chylothorax as the first manifestation is an unusual condition. To date, only a few cases have been reported in clinical practice.

CASE SUMMARY

The clinical data of a 48-year-old man with primary nephrotic syndrome combined with chylothorax admitted to the Department of Respiratory and Critical Care Medicine of Shaanxi Provincial People's Hospital were retrospectively analysed. The patient was admitted to the hospital for 12 d due to shortness of breath. Imaging showed pleural effusion, laboratory tests confirmed true chylothorax, and renal biopsy revealed membranous nephropathy. After primary disease treatment and early active symptom treatment, the prognosis of the patient was good. This case suggests that chylothorax is a rare complication of primary membranous nephrotic syndrome in adults, and early lymphangiography and renal biopsy can assist in the diagnosis when there are no contraindications.

CONCLUSION

Primary membranous nephrotic syndrome combined with chylothorax is rare in clinical practice. We report a relevant case to provide case information for clinicians and to improve diagnosis and treatment.

Key Words: Adult; Chylothorax; Primary nephrotic syndrome; Membranous nephropathy; Pleural effusion; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Chylothorax is a white or milky pleural effusion, and primary membranous nephrotic syndrome is a rare cause of chylothorax. This article reports a case of primary membranous nephrotic syndrome combined with chylothorax and summarizes the relevant cases to raise awareness of chylothorax among clinicians.

Citation: Feng LL, Du J, Wang C, Wang SL. Primary membranous nephrotic syndrome with chylothorax as first presentation: A case report and literature review. *World J Clin Cases* 2023; 11(8): 1823-1829
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1823.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1823

INTRODUCTION

Chylothorax is a white, milky or muddy fluid containing a high level of triglycerides and chylomicron emulsion that is present in the pleural cavity and is rarely seen clinically. It is mainly caused by trauma, malignant tumours, and autoimmune diseases. Adult primary membranous nephrotic syndrome, which is a rare cause of chylothorax, has been poorly reported in the national and international literature, with only isolated cases and no relevant epidemiological reports. Moreover, the related mechanism and clinical characteristics of primary membranous nephrotic syndrome combined with chylothorax are still unclear.

Here, we report a case of primary membranous nephrotic syndrome with chylothorax in an adult and review and summarize the related mechanisms, clinical characteristics, and treatment of primary membranous nephrotic syndrome with chylothorax to help clinicians improve the diagnosis, treatment, and prognosis of this disease.

CASE PRESENTATION

Chief complaints

A 48-year-old Chinese man presented to the hospital with a complaint of dyspnoea for 12 d.

History of present illness

The patient presented 12 d earlier with dyspnoea after activity, facial oedema, which was prominent in the morning, pitting oedema of both lower limbs that resolved after rest, occasional dry coughing, and no low-grade fever, chills, or night sweats.

History of past illness

The patient was previously healthy and free from any disease. And he denied hospitalizations. There was no history of recent surgery, catheter insertion, trauma, drug or food allergies, or chemical or toxic material exposure.

Personal and family history

The patient denied any family history of the condition.

Physical examination

The vital signs were as follows: Body temperature, 36.3 ℃; blood pressure, 140/76 mmHg; heart rate, 70 beats per min; and respiratory rate, 30 breaths per min. The patient was tachypneic. Physical examination showed slightly weakened breath movements on the right side of the chest, with decreased breath sounds on both sides of the chest, but especially on the right side, and no rales or pleural friction sounds were heard. Cardiac and abdominal examinations were unremarkable.

Laboratory examinations

Related pleural effusion tests showed a chyle-like fluid, total pleural effusion cholesterol of 1.0 mmol/L, pleural effusion triglycerides of 2.68 mmol/L, and a positive chyle test. Routine urinalysis showed leukocyturia and tubular proteinuria; liver function showed hypoproteinaemia; blood lipid profile showed total cholesterol of 11.68 mmol/L and triglycerides of 2.22 mmol/L; urine protein quantification showed a urine protein concentration of 8160 mg/L, urine volume of 2.65 L, and total urine protein of 21624 mg/24 h; urinary chyle qualitative testing was positive; erythrocyte sedimentation rate was 68 mm/h; and some of the tumour indicators, namely, glycoantigens CA-125 and CA19-9, were elevated. Autoimmune series, routine haematology, coagulation function, viral hepatitis, rheumatic series,

thyroid function, T-cell test for tuberculosis infection, and renal function were normal. Repeated pleural effusion and bronchoalveolar lavage smears did not reveal tuberculosis, or bacterial or fungal infections.

Imaging examinations

A computed tomography (CT) scan of the chest showed bilateral pleural effusion (moderate on the right and small on the left) (Figure 1A). Bronchoscopy, cardiac ultrasound, CT of the abdomen and pelvis, and whole-body positron emission tomography/CT were normal.

Further diagnostic work-up

The patient underwent closed thoracic drainage after admission (Figure 2). In combination with the history, symptoms, signs and relevant laboratory tests, the patient was determined to be suffering from nephrotic syndrome after a consultation with nephrologists. To further clarify the diagnosis, a positive anti-phospholipase A2 receptor antibody (PLA2R) was detected (1:320). A percutaneous nephrectomy biopsy was performed under ultrasound guidance, and the postoperative pathology was consistent with stage I membranous nephropathy (Figure 3).

FINAL DIAGNOSIS

Combined with the patient's medical history, the final diagnosis was primary membranous nephrotic syndrome with chylothorax and chylous urine.

TREATMENT

Approximately 500 mL of fluid was drained per day *via* a closed chest drainage tube, and the patient was given a low-salt, low-fat, and low-protein diet, diuretic therapy, and other symptomatic supportive treatment. After the diagnosis was confirmed, he was treated with oral methylprednisolone and cyclosporine A.

OUTCOME AND FOLLOW-UP

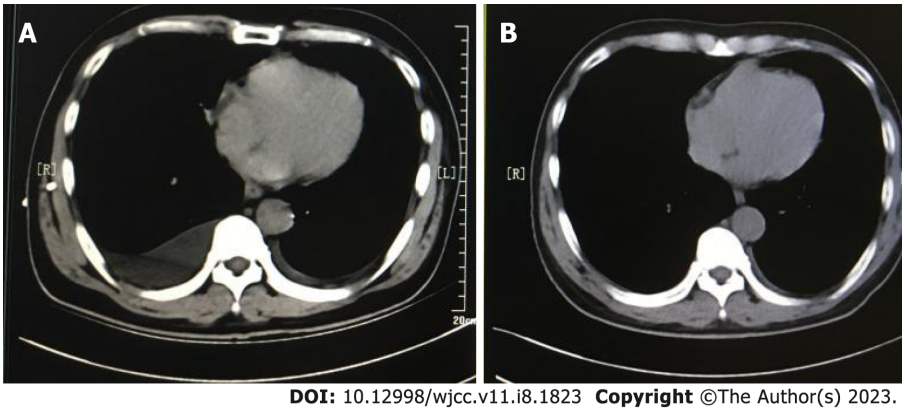
After 1 wk, the patient's oedema had subsided, the pleural effusion had disappeared, and the dyspnoea had improved significantly (Figure 1B). A review of relevant laboratory tests showed blood total cholesterol of 10.04 mmol/L, blood triglycerides of 3.78 mmol/L, urine protein concentration of 4730 mg/L, and total urine protein of 9460 mg/24 h, and the urinary chyle qualitative test was negative. The patient was discharged in better condition and remains in follow-up.

DISCUSSION

Membranous nephropathy (MN) is a common pathological type of primary nephrotic syndrome in adults[1]. MN is an autoimmune disease caused by an autoantibody attack against podocyte antigens that results in the production of *in situ* immune complexes, mediated primarily by anti-PLA2R (85%), antibodies to the thrombospondin type 1 structural domain containing 7A (3%-5%), or other unknown mechanisms (10%)[2]. Most adults (80%) with primary membranous nephropathy present with nephrotic syndrome, with the remainder presenting with nephrotic proteinuria[2].

In contrast, chylothorax is a rare complication of primary nephrotic syndrome first reported in 1989 by Moss Retal[3]. Chylothorax is usually caused by injury to the thoracic duct and chyle leakage from the lymphatic system into the pleural cavity. Most chylothorax-inducing injuries are caused by medical trauma and surgery[4-6]. Apart from those main causes, tuberculous lymphadenitis, autoimmune diseases, malignancies, and congenital ductal abnormalities may also induce chylothorax[7-9].

A literature review was performed through April 2022; the Chinese Biomedical Literature Database, PubMed, and other national and international databases were searched using the term "nephrotic syndrome, chylothorax" without date or language restrictions. All the relevant literature and cross-references were checked to ensure that all eligible cases were included in the statistical analysis. Fourteen foreign papers were reviewed[2,10-22], and the majority of cases were individual case reports [23-30]. Four of the cases were diagnosed with microscopic nephrotic syndrome (3 foreign and 1 domestic); 3 with membranous nephrotic syndrome (3 foreign); 3 with focal segmental glomerulosclerotic nephrotic syndrome (all foreign); 3 with membranoproliferative nephrotic syndrome (2 foreign and 1 domestic); 1 with membranoproliferative glomerulonephritis (all domestic); and 9 with undetermined pathology. Most of the patients, of which 10 were children, were admitted with facial and



DOI: 10.12998/wjcc.v11.i8.1823 **Copyright** ©The Author(s) 2023.

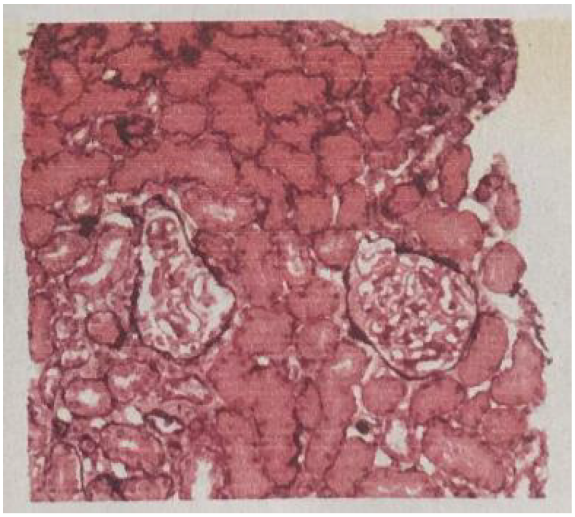
Figure 1 Patient's chest computed tomography on admission and at discharge. A: Chest computed tomography showed bilateral pleural effusion; B: The effusion gradually resolved after 1 wk of treatment.

DOI: 10.12998/wjcc.v11.i8.1823 **Copyright** ©The Author(s) 2023.

Figure 2 Fluid from the closed thoracic drainage. The pleural effusion was milky white.

bilateral lower limb oedema; the youngest patient was 2.5 years old and the oldest was 66 years old. There were 15 males and 8 females. Pleural effusion was mostly bilateral, predominantly on the right side and with a smaller amount on the left. Ten of the patients had celiac effusion, and 6 had thrombosis (not available in detail).

The specific pathogenesis of primary nephrotic syndrome complicated by chylothorax remains unclear. An analysis of this case in combination with previous literature reports reveals that the pathogenesis may be related to the following mechanisms. First, nephrotic syndrome leads to hypoproteinaemia and severe systemic tissue oedema, and lymphatic vascular oedema increases the permeability of the intestinal mucosa and lymphatic vessels, causing celiac particle leakage and celiac pleural effusion. Second, severe tissue oedema increases the pressure in the capillaries and lymphatic vessels, leading to the rupture of lymphatic vessels and the leakage of celiac fluid. In addition, it has also been reported that in membranous nephropathy with chylous ascites, negative intrapleural pressure causes celiac ascites to enter the pleural cavity through the diaphragmatic defect. In the case of massive ascites, the intraperitoneal pressure increases, and the peritoneum thins and folds back upwards through the transverse septal fissure to form large vesicles. The continuous increase in pressure in the abdomen causes large vesicles to rupture and chylous ascites to enter the pleural cavity to form chylothorax[11,19,31]. Rathore *et al*[18] reported a case of chylothorax in an 8-year-old child and found that the hypercoagulable state of the blood in nephrotic syndrome could lead to venous thrombosis (superior vena cava and subclavian vein thrombosis), as it causes impaired lymphatic return and increased pressure in the lymphatic vessels. When the pressure in the lymphatic vessels exceeds the drainage capacity of the thoracic duct, the pleural lymphatic vessels dilate, stagnate, and rupture, resulting in the overflow of lymphatic fluid to form chylothorax. More research is needed to confirm whether there are other mechanisms involved in nephrotic syndrome and chylothorax, and whether



DOI: 10.12998/wjcc.v11.i8.1823 **Copyright** ©The Author(s) 2023.

Figure 3 Renal biopsy results. Biopsy revealed mild glomerular mesangium and stromal hyperplasia, focal segmental sclerosis, diffuse globular thickening of the basement membrane, diffuse segmental pegging, and unremarkable intracapillary hyperplasia. Mild tubular atrophy, extensive oedema, and unremarkable interstitial and vascular lesions were also present.

they are related to the type of pathology.

Clinically, the diagnosis of primary nephrotic syndrome with chylothorax is based on past medical history, clinical symptoms and signs, and laboratory and imaging tests. The clinical symptoms of primary nephrotic syndrome with chylothorax are atypical. In addition to the manifestations of the primary disease, the symptoms mostly include dyspnoea, shortness of breath, and cough caused by pleural effusion, and the diagnosis is not specific. In contrast, thoracentesis and laboratory tests are often used as the preferred diagnostic methods for chylothorax. Laboratory tests for chylothorax often have the following characteristics for its diagnosis: (1) The fluid is white, milky or cloudy in appearance, and liquid stratification occurs after resting; (2) The fluid is rich in lymphocytes, often polyclonal T-cell populations, and is usually alkaline, with a pH value between 7.4 and 7.8; (3) Thoracic effusion triglyceride levels are specific for the diagnosis of chylothorax. Chylothorax is diagnosed when triglycerides are > 110 mg/dL, cholesterol is < 200 mg/dL and celiac particles are microscopically visible. Thoracic effusion with a triglyceride value < 50 mg/dL usually rules out chylothorax. Triglyceride levels between 55 and 110 mg/dL require lipoprotein electrophoresis analysis to detect chyle particles. In patients who are fasting or malnourished, lipoprotein electrophoresis analysis is recommended even if triglycerides are < 50 mg/dL; and (4) A thoracic effusion-to-serum triglyceride ratio > 1, a thoracic effusion-to-serum cholesterol ratio < 1, and a thoracic effusion triglyceride-to-cholesterol ratio > 1 may also aid in the diagnosis of chylothorax. X-rays, ultrasound, CT, magnetic resonance imaging, lymphography, and nuclear lymphography can also clarify the cause of chylothorax, and if necessary, histopathological biopsy or excision of the positive lesions on imaging may be performed as appropriate.

The treatment of nephrotic syndrome with chylothorax should be individualised and combined, *i.e.*, with active treatment of the primary disease and simultaneous treatment of chylothorax to achieve a faster cure or remission. Therefore, the basic treatment of chylothorax lies in symptomatic supportive treatment.

The patient presented to the Shaanxi Provincial People's Hospital with a complaint of dyspnoea for the preceding 12 d. Laboratory tests suggested hypoproteinaemia, hyperlipidaemia, and massive proteinuria, consistent with nephrotic syndrome. The patient had no history of recent surgery, catheter insertion or trauma, recurrent respiratory infections, or chemical or toxic exposure, and laboratory and imaging tests ruled out chylothorax due to tuberculosis, a fungus, or a tumour. The patient had no history of nonsteroidal anti-inflammatory drug abuse, and secondary membranous nephropathy was excluded. The diagnosis of primary membranous nephropathy syndrome with chylothorax was clear, taking into account the pathological findings of the renal biopsy, the clinical symptoms and signs, all test results, and the effectiveness of various drugs during the course of treatment.

For this patient, we administered conservative symptomatic supportive treatment, reduced cholesterol intake through a low-salt, low-fat and low-protein diet, and increased physical activity to reduce weight. Symptomatic treatment, such as diuresis and albumin supplementation, can relieve tissue oedema and pleural effusion, and growth inhibitors as well as omeprazole can reduce chylous fluid production. In this case, the pleural effusion was significantly reduced after aggressive treatment, and the patient's shortness of breath was relieved.

CONCLUSION

Chylothorax is a rare complication of primary nephrotic syndrome, and a systematic differential diagnosis should be made clinically. Furthermore, a pathological biopsy should be performed when the diagnosis is unclear. By reporting this case, we hope that clinicians can improve their understanding of primary nephrotic syndrome and chylothorax, enriching their clinical knowledge, and provide new ideas for future clinical treatment.

FOOTNOTES

Author contributions: Feng LL was involved in data collection and analysis, and writing of the manuscript; Du J and Wang C were involved in data verification, student supervision, and manuscript editing; all authors have read and approved the final manuscript.

Supported by the Shaanxi Provincial People's Hospital Science and Technology Development Incubation Fund Project, No. 2021YJY-33.

Informed consent statement: Written informed consent was obtained from the patient for the publication of this report and any accompanying images.

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

CARE Checklist (2016) statement: All authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Le-Le Feng 0000-0003-0864-2529; Shui-Li Wang 0000-0001-6303-8303.

S-Editor: Wang LL
L-Editor: Wang TQ
P-Editor: Wang LL

REFERENCES

1 **Ayalon R**, Beck LH Jr. Membranous nephropathy: not just a disease for adults. *Pediatr Nephrol* 2015; **30**: 31-39 [PMID: 24375012 DOI: 10.1007/s00467-013-2717-z]
2 **Couser WG**. Primary Membranous Nephropathy. *Clin J Am Soc Nephrol* 2017; **12**: 983-997 [PMID: 28550082 DOI: 10.2215/CJN.11761116]
3 **Moss R**, Hinds S, Fedullo AJ. Chylothorax: a complication of the nephrotic syndrome. *Am Rev Respir Dis* 1989; **140**: 1436-1437 [PMID: 2817608 DOI: 10.1164/ajrccm/140.5.1436]
4 **Liu YM**, Wei YJ, Lu XQ, Wang YF, Wang P, Liang XH. Catheter-related superior vena cava obstruction: A rare cause of chylothorax in maintenance hemodialysis patients. *J Vasc Access* 2022; 11297298211073425 [PMID: 35090360 DOI: 10.1177/11297298211073425]
5 **Ruggiero RP**, Caruso G. Chylothorax--a complication of subclavian vein catheterization. *JPEN J Parenter Enteral Nutr* 1985; **9**: 750-753 [PMID: 3934410 DOI: 10.1177/0148607185009006750]
6 **Zheng XD**, Li SC, Lu C, Zhang WM, Hou JB, Shi KF, Zhang P. Safety and efficacy of minimally invasive McKeown esophagectomy in 1023 consecutive esophageal cancer patients: a single-center experience. *J Cardiothorac Surg* 2022; **17**: 36 [PMID: 35292067 DOI: 10.1186/s13019-022-01781-2]
7 **Kutlu O**, Demirbas S, Sakin A. Chylothorax due to tuberculosis lymphadenitis. *North Clin Istanb* 2016; **3**: 225-228 [PMID: 28275756 DOI: 10.14744/nci.2015.52714]
8 **Takano H**, Taoka K, Hayashida H, Tsushima T, Sugimura H, Yamazaki I, Hara H, Mihara M, Yamamoto M, Shimura A, Masamoto Y, Kurokawa M. [Successful treatment of refractory chylothorax associated with diffuse large B-cell lymphoma by multidisciplinary care]. *Rinsho Ketsueki* 2021; **62**: 1623-1627 [PMID: 34866086 DOI: 10.11406/rinketsu.62.1623]
9 **Tang X**, Chen Z, Shen X, Xie T, Wang X, Liu T, Ma X. Refractory thrombocytopenia could be a rare initial presentation of Noonan syndrome in newborn infants: a case report and literature review. *BMC Pediatr* 2022; **22**: 142 [PMID: 35300644 DOI: 10.1186/s12887-021-02909-4]
10 **Bonnin Vilaplana M**, Pelegrí Santos A, Parra Ordaz O. [Chylotorax and chylose ascites: initial manifestation of a

nephrotic syndrome]. *Med Clin (Barc)* 2006; **127**: 718 [PMID: 17169306 DOI: 10.1157/13095104]

11 **Chen YC**, Kuo MC, Chen HC, Liu MQ, Hwang SJ. Chylous ascites and chylothorax due to the existence of transdiaphragmatic shunting in an adult with nephrotic syndrome. *Nephrol Dial Transplant* 2005; **20**: 1501-1502 [PMID: 15784634 DOI: 10.1093/ndt/gfh791]

12 **Cogar BD**, Groshong TD, Turpin BK, Guajardo JR. Chylothorax in Henoch-Schonlein purpura: a case report and review of the literature. *Pediatr Pulmonol* 2005; **39**: 563-567 [PMID: 15830386 DOI: 10.1002/ppul.20203]

13 **Hanna J**, Truemper E, Burton E. Superior vena cava thrombosis and chylothorax: relationship in pediatric nephrotic syndrome. *Pediatr Nephrol* 1997; **11**: 20-22 [PMID: 9035166 DOI: 10.1007/s004670050225]

14 **Kren L**, Rotterova P, Hermanova M, Krenova Z, Sterba J, Dvorak K, Goncharuk V, Wilner GD, McKenna BJ. Chylothorax as a possible diagnostic pitfall: a report of 2 cases with cytologic findings. *Acta Cytol* 2005; **49**: 441-444 [PMID: 16124177 DOI: 10.1159/000326181]

15 **Lin SH**, Lin YF, Shih YL. An unusual complication of nephrotic syndrome: chylothorax treated with hemodialysis. *Nephron* 2001; **87**: 188-189 [PMID: 11244317 DOI: 10.1159/000045911]

16 **Lin WY**, Lin GM, Wu CC. Coexistence of non-communicated chylothorax and chylous ascites in nephrotic syndrome. *Nephrology (Carlton)* 2009; **14**: 700 [PMID: 19796031 DOI: 10.1111/j.1440-1797.2008.01078.x]

17 **Poswal L**, Dhyani A, Malik P, Ameta P. Bilateral Chylothorax due to Brachiocephalic Vein Thrombosis in Relapsing Nephrotic Syndrome. *Indian J Pediatr* 2015; **82**: 1181-1182 [PMID: 25952663 DOI: 10.1007/s12098-015-1769-4]

18 **Rathore V**, Bhattacharya D, Pandey J, Bhatia A, Dawman L, Tiewsoh K. Chylothorax in a Child with Nephrotic Syndrome. *Indian J Nephrol* 2020; **30**: 32-34 [PMID: 32015598 DOI: 10.4103/ijn.IJN_24_19]

19 **Singh SK**, Chauhan A, Swain B. A rare case of nephrotic syndrome with chylothorax. *J Family Med Prim Care* 2021; **10**: 3498-3501 [PMID: 34760780 DOI: 10.4103/jfmpc.jfmpc_2605_20]

20 **Suri D**, Gupta N, Morigeri C, Saxena A, Manoj R. Chylopericardial tamponade secondary to superior vena cava thrombosis in a child with nephrotic syndrome. *Pediatr Nephrol* 2009; **24**: 1243-1245 [PMID: 19189135 DOI: 10.1007/s00467-008-1115-4]

21 **Voudiclari S**, Sonikian M, Kallivretakis N, Pani I, Kakavas I, Papageorgiou K. Chylothorax and nephrotic syndrome. *Nephron* 1994; **68**: 388 [PMID: 7838267 DOI: 10.1159/000188407]

22 **Xu Y**, Shi J, Xu S, Cui C. Primary nephrotic syndrome complicated by chylothorax: a case report. *Ann Palliat Med* 2022; **11**: 2523-2528 [PMID: 34775776 DOI: 10.21037/apm-21-1872]

23 **Dong JX**. One1 case of nephrotic syndrome with chylothoracic ascites. *Journal of Suzhou Medical College* 1995; 648

24 **Fu Q**, Fan JF, Zhou N, Chen Z, Liu XR. Childhood nephrotic syndrome and true chylothorax in one case. *The Chinese Clinical Journal of Practical Pediatrics* 2020; 469-471 [DOI: 10.3760/cma.j.cn101070-20190130-00076]

25 **Li XM**, Chen BW. Nnephrotic syndrome and large chylothorax ascites one case. *Journal of Rare Diseases* 2003; 51-52 [DOI: 10.3969/j.issn.1009-3257.2003.01.037]

26 **Wang P**, Jun ZJ. One case with chylothoracic water was reported. *Chinese and Foreign Medical Treatment* 2008; 71 [DOI: 10.3969/j.issn.1674-0742.2008.04.064]

27 **Wu LR**. Two cases with nephrotic syndrome and chylothorax. *Guangdong Medicine* 1994; 138-139

28 **Xu YY**. Nephrotic syndrome complicated with chylothorax and ascites. *Jiangsu Medicine* 1989; 8

29 **Yang YJ**, Zhang SP, Gao ZY. One case of chylous pleural effusion caused by primary nephrotic syndrome. *Clinical meta-study* 2007; 894 [DOI: 10.3969/j.issn.1004-583X.2007.12.038]

30 **Zhou LM**, Zhu L, Wang P. Primary nephrotic syndrome complicated with chylothor ax in 1 case. *Journal of Medical College of Qingdao University* 2008; 98

31 **Liu X**, Xu Y, Wu X, Liu Y, Wu Q, Wu J, Zhang H, Zhou M, Qu J. Soluble Immune-Related Proteins as New Candidate Serum Biomarkers for the Diagnosis and Progression of Lymphangioleiomyomatosis. *Front Immunol* 2022; **13**: 844914 [PMID: 35300340 DOI: 10.3389/fimmu.2022.844914]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1830-1836

DOI: 10.12998/wjcc.v11.i8.1830

ISSN 2307-8960 (online)

CASE REPORT

Continuous positive airway pressure for treating hypoxemia due to pulmonary vein injury: A case report

Chao Zhou, Shan Song, Jian-Feng Fu, Xue-Lian Zhao, Hua-Qin Liu, Huan-Shuang Pei, Hong-Bo Guo

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

P-Reviewer: Dilek ON, Turkey; Hu JW, China; Tsujinaka S, Japan

Received: December 15, 2022
Peer-review started: December 15, 2022
First decision: January 17, 2023
Revised: February 25, 2023
Accepted: February 22, 2023
Article in press: February 22, 2023
Published online: March 16, 2023

Chao Zhou, Jian-Feng Fu, Xue-Lian Zhao, Hua-Qin Liu, Huan-Shuang Pei, Hong-Bo Guo, Department of Anesthesiology, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050001, Hebei Province, China

Shan Song, Department of Respiratory, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, Hebei Province, China

Corresponding author: Jian-Feng Fu, MS, Chief Physician, Department of Anesthesiology, The Fourth Hospital of Hebei Medical University, No. 12 Jiankang Road, Shijiazhuang 050011, Hebei Province, China. fffjf2008@sohu.com

Abstract

BACKGROUND

Vascular injury during thoracoscopic surgery for esophageal cancer is a rare but life-threatening complication that can lead to severe hypotension and hypoxemia. Anesthesiologists need to provide rapid and effective treatment to save patients' lives.

CASE SUMMARY

A 54-year-old male patient was scheduled to undergo a thoracoscopic-assisted radical resection of esophageal cancer through the upper abdomen and right chest. While dissociating the esophagus from the carina through the right chest, unexpected profuse bleeding occurred from a suspected pulmonary vascular hemorrhage. While the surgeon attempted to achieve hemostasis, the patient developed severe hypoxemia. The anesthesiologist implemented continuous positive airway pressure (CPAP) using a bronchial blocker (BB), which effectively improved the patient's oxygenation and the operation was completed successfully.

CONCLUSION

CPAP using a BB can resolve severe hypoxemia caused by accidental injury of the left inferior pulmonary vein during surgery.

Key Words: Vascular injury; Continuous positive airway pressure; Hypoxemia; Bronchial blocker; Esophageal carcinoma resection; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Although hypoxemia caused by pulmonary vein injury is a rare complication, it is life-threatening. We report such a rare case, successfully managed by continuous positive airway pressure using a bronchial blocker. We hope that this case report helps other specialists to promptly manage similar incidents and avoid treatment delays and death.

Citation: Zhou C, Song S, Fu JF, Zhao XL, Liu HQ, Pei HS, Guo HB. Continuous positive airway pressure for treating hypoxemia due to pulmonary vein injury: A case report. *World J Clin Cases* 2023; 11(8): 1830-1836
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1830.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1830

INTRODUCTION

The esophagus is adjacent to major blood vessels such as the aorta and pulmonary vessels. Injury to these blood vessels during thoracoscopic surgery for esophageal cancer is a rare but life-threatening complication[1], which can lead to severe hypotension and hypoxemia. Thus, anesthesiologists need to provide rapid and effective treatment to save the affected patient's life. Here, we report a special case wherein the surgeon accidentally injured the left inferior pulmonary vein while dissociating the esophagus during thoracoscopic surgery for esophageal cancer. The patient developed severe hypoxemia during hemostasis. Continuous positive airway pressure (CPAP) was administered through a bronchial blocker (BB), significantly improving oxygenation, and thereby preventing life-threatening complications.

CASE PRESENTATION

Chief complaints

A 54-year-old man undergoing elective resection of esophageal cancer.

History of present illness

The patient was diagnosed with middle thoracic esophageal cancer in January 2022 after presenting to the hospital with dysphagia. He underwent two cycles of neoadjuvant chemotherapy and was scheduled for esophageal cancer resection.

History of past illness

The patient had no previous history of any major illness and no other underlying illnesses.

Personal and family history

The patient denied any family or genetic history of similar diseases.

Physical examination

173 cm tall, weighing 72 kg, ASA II.

Laboratory examinations

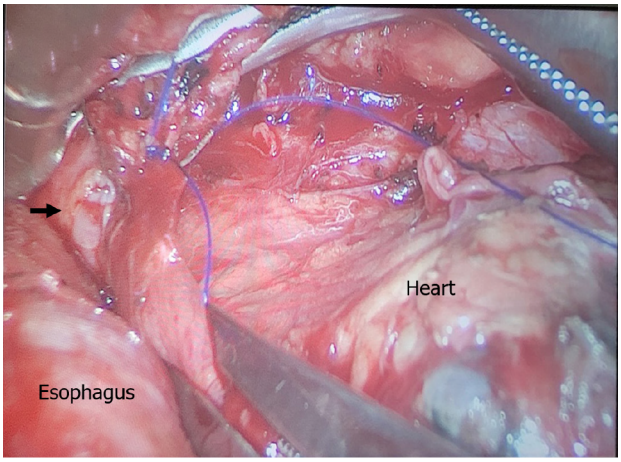
The patient's laboratory test results, including the full blood count and liver and renal function tests, were normal.

Imaging examinations

Electronic gastroscope results: Canker-like new organisms were observed 30-37 cm away from the local incisors. Pathology results: Squamous cell carcinoma. Chest computed tomography results: Thickening of the middle and lower esophageal wall.

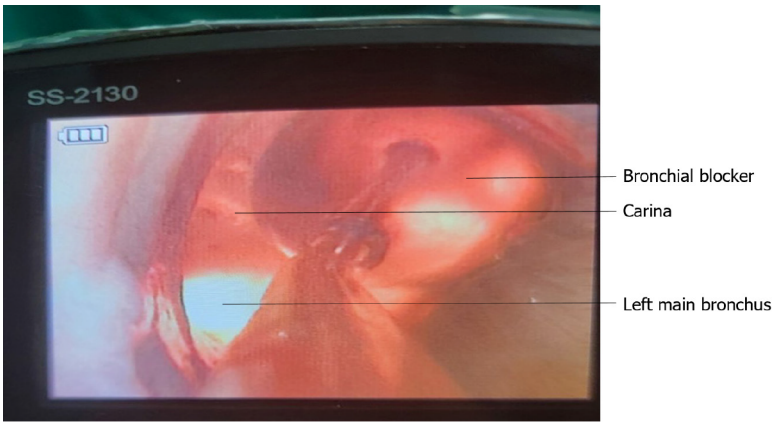
SURGERY

The patient was scheduled to undergo thoracoscopic-assisted radical resection of esophageal cancer through the upper abdomen and right chest. The abdominal operation was successful, after which the patient was placed in the supine position on his left side, and a BB was inserted into the right main bronchus. While dissociating the esophagus from the carina through the right chest, unexpected profuse bleeding occurred, which resulted in an emergency thoracotomy due to a possible pulmonary vascular



DOI: 10.12998/wjcc.v11.i8.1830 **Copyright** ©The Author(s) 2023.

Figure 1 After occlusion of the left inferior pulmonary vein. The arrow indicates the vascular rupture.



DOI: 10.12998/wjcc.v11.i8.1830 **Copyright** ©The Author(s) 2023.

Figure 2 Bronchial blocker in the correct position.

hemorrhage. The rate of blood loss from an unknown source was approximately 1000 mL/3 min.

After finger pressure suppressed the bleeding, the surgeon dissected the structures around the bleeding source with the aid of video-assisted thoracoscopy. Rapid fluid replacement and vasoactive drugs were administered to maintain blood pressure, along with other treatments, while 2 units of red blood cells were being prepared.

Following dissection, the surgeon clamped both ends of the ruptured blood vessel in preparation for suturing (Figure 1). Following vascular occlusion, the patient's pulse oxygen saturation (SpO_2) suddenly decreased from 97% to 87% over 5 min, followed by a further decrease from 87% to 66% over the next 10 min (Table 1). We quickly ruled out possible anesthesia-related factors, including the respiratory circuit falling off and BB displacement. Manual ventilation was concurrently initiated to increase the respiratory rate and improve blood oxygenation. Additionally, correct BB positioning was confirmed using a fiberoptic bronchoscope (Figure 2). The surgeon confirmed that the rupture was located in the left inferior pulmonary vein, thereby identifying the cause of the patient's hypoxemia. The patient's respiratory status was as follows: the right lung was unable to complete gas exchange as there was blood flow without ventilation during the time in which the BB was inserted into the right main bronchus; whilst for the left lung, only the upper lobe could complete gas exchange as the lower lobe was ventilated without blood flow while the left lower pulmonary vein was clamped (Figure 3).

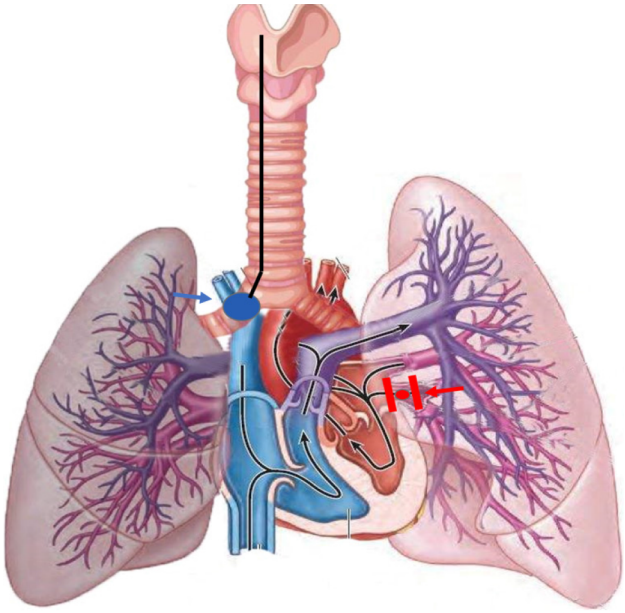
FINAL DIAGNOSIS

Hypoxemia secondary to injury of the left inferior pulmonary vein during thoracoscopic surgery for esophageal cancer.

Table 1 Oxygenation status of the patient at different time points

	Immediately after blocking the pulmonary vein	5 min after blocking the pulmonary vein	10 min after blocking the pulmonary vein, start CPAP	5 min after CPAP	25 min after CPAP
SpO_2, %	97	87	66	84	90
PaO_2 (mmHg)	-	-	-	63.4	79.2
$PaCO_2$ (mmHg)	-	-	-	63.2	71
$PETCO_2$ (mmHg)	34	32	39	31	43

CPAP: Continuous positive airway pressure; SpO_2: Pulse oxygen saturation; PaO_2: Partial pressure of oxygen in artery; $PaCO_2$: Partial pressure of carbon dioxide in artery; $PETCO_2$: End tidal carbon dioxide.



DOI: 10.12998/wjcc.v11.i8.1830 **Copyright** ©The Author(s) 2023.

Figure 3 The blue arrow indicates the bronchial blocker and the red arrow the bleeding point and forceps.

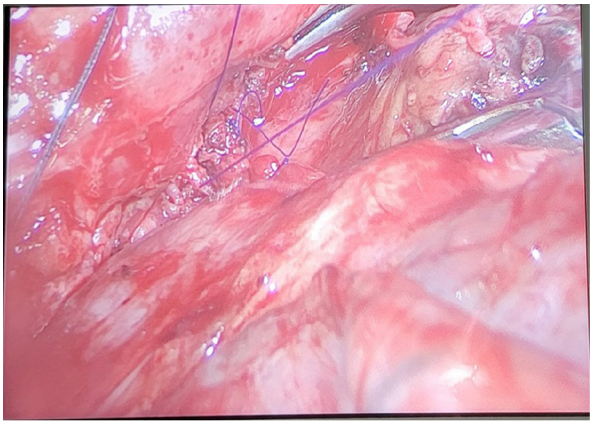
TREATMENT

There was a challenge: If the clamp was released, the blood supply to the left lung would be restored, allowing the patient to be ventilated; however, bleeding would resume. Due to the position of the rupture on the left side of the protuberance, ventilation of the right lung would affect the surgeon's ability to conduct the operation.

After consultation, we decided to administer 5 mmHg CPAP to the right lung to improve oxygenation by precisely controlling the CPAP pressure through the BB suction hole. After administering CPAP, the patient's SpO_2 increased gradually, from 66% to 84% over 5 min, and the blood SpO_2 gradually increased to 90%. After the patient was stabilized, the surgeon anastomosed the blood vessels (Figure 4) and the patient underwent ventilation for both lungs. The respiratory parameters were then adjusted, and the end tidal carbon dioxide decreased to 33 mmHg, with a partial pressure of carbon dioxide in the artery ($PaCO_2$) of 40 mmHg.

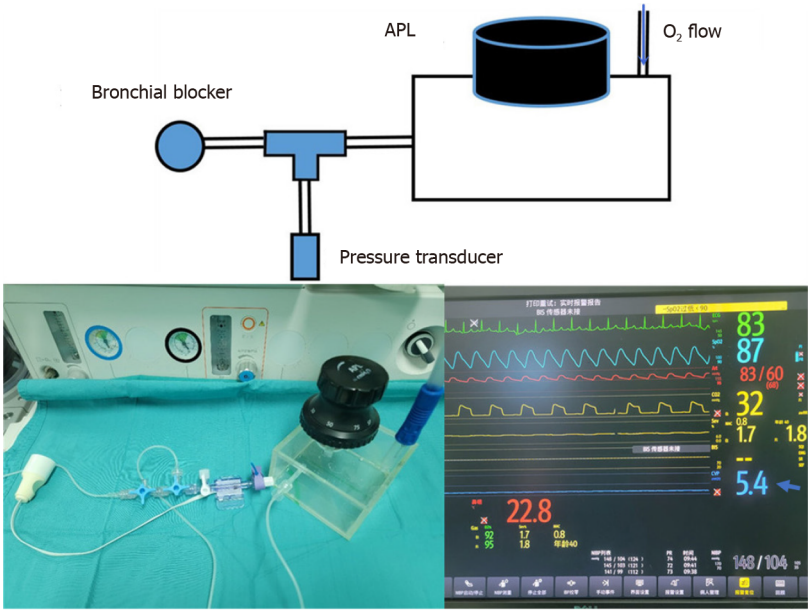
OUTCOME AND FOLLOW-UP

The endotracheal tube was removed 15 min after surgery and the patient was discharged seven days later with no further complications.



DOI: 10.12998/wjcc.v11.i8.1830 **Copyright** ©The Author(s) 2023.

Figure 4 Blood vessels after suture.



DOI: 10.12998/wjcc.v11.i8.1830 **Copyright** ©The Author(s) 2023.

Figure 5 Accurate control of the continuous positive airway pressure and physical diagrams. The blue arrow indicates the continuous positive airway pressure displayed in the monitor.

DISCUSSION

In the present case, common hypoxemia management methods would not have been able to improve the patient's oxygenation levels (Table 2). Although the use of CPAP through a BB to treat hypoxemia during one-lung ventilation has been reported[2,3], a system to monitor and accurately adjust CPAP pressure in real time has not been reported. This case required accurate control of CPAP pressure due to the fact that excessively low CPAP pressure would not have improved oxygenation and excessively high CPAP would have caused lung expansion, affecting the surgical procedure[4]. The anesthetic machine APL valve was used for pressure adjustment and a pressure sensor was added to continuously monitor the CPAP in real-time (Figure 5).

During vascular anastomosis, only the left upper lobe of the lung could exchange gas. The decrease in the lung ventilation area leads to an increased $PaCO_2$ and a higher level of $PaCO_2$ than the pressure of endtidal CO_2. Foreseeing this possibility, we closely monitored the patient's vital signs and increased the frequency of blood gas analyses. Patients with pulmonary artery occlusion or severe chronic obstructive pulmonary disease may have similar problems[5,6]. After completion of vascular anastomosis, the patient was adequately ventilated, releasing CO_2, and his $PaCO_2$ returned to normal when he awoke.

We believe that the blood supply of the left lower lobe bronchial artery is involved in oxygenation. The lung has a dual blood supply from the bronchial and pulmonary arteries. The bronchial artery

Table 2 Common hypoxemia management methods

Ensure that $FiO_2 = 1$	Already used, but unable to improve
Check BB position with a fiberoptic bronchoscope	Already used, but unable to improve
Ensure optimal cardiac output and reduce volatile anesthetics (< 1MAC)	Already used, but unable to improve
Apply recruitment maneuver to the ventilated lung	Already used, but unable to improve
Apply PEEP (5 cmH_2O) to the ventilated lung	Already used, but unable to improve
Perform intermittent re-expansion on the non-ventilated lung	Unable to apply
Mechanically restrict blood flow of the non-ventilated lung	Unable to apply

FiO2: Fraction of inspired oxygen; BB: Bronchial blocker; MAC: Minimum alveolar concentration; PEEP: Positive end-expiratory pressure.

generally originates from the thoracic aorta or aortic arch, with two left and right sides, and supplies all bronchus levels above the respiratory bronchus, anastomosing with the capillaries at the end of the pulmonary artery. The bronchial artery accounts for 1%-3% of the pulmonary blood supply[7]. If the left inferior pulmonary vein is blocked, the bronchial artery blood supply may increase and significantly contribute to oxygenation. This has been confirmed in patients with bronchiectasis and other diseases [8].

CONCLUSION

In conclusion, precise CPAP implementation using a BB could effectively treat severe hypoxemia due to accidental injury of the left inferior pulmonary vein during resection of esophageal cancer.

FOOTNOTES

Author contributions: Zhou C and Guo HB wrote the manuscript; Song S finished the literature review; Zhao XL, Liu HQ provided revision suggestions; Pei HS contributed to the redaction of this manuscript and proof reading; Fu JF contributed to manuscript finalizing.

Informed consent statement: Written informed consent was obtained from the patient for publication of this case.

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).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Chao Zhou 0000-0001-8883-6141; Shan Song 0000-0002-1865-4585; Jian-Feng Fu 0000-0002-3637-1474; Xue-Lian Zhao 0000-0001-5712-677X; Hua-Qin Liu 0000-0001-5105-5333; Huan-Shuang Pei 0000-0002-9064-0233; Hong-Bo Guo 0000-0002-0878-1011.

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

REFERENCES

1 **Javed A**, Pal S, Chaubal GN, Sahni P, Chattopadhyay TK. Management and outcome of intrathoracic bleeding due to vascular injury during transhiatal esophagectomy. *J Gastrointest Surg* 2011; **15**: 262-266 [PMID: 21116730 DOI: 10.1007/s11605-010-1375-8]

2 **Benumof JL**, Gaughan S, Ozaki GT. Operative lung constant positive airway pressure with the Univent bronchial blocker tube. *Anesth Analg* 1992; **74**: 406-410 [PMID: 1539822 DOI: 10.1213/00000539-199203000-00015]

3 **Sasano H**, Sasano N, Ito S, Fujita Y, Sugiura T, Morita M, Sobue K. Continuous positive airway pressure applied through a bronchial blocker as a treatment for hypoxemia due to stenosis of the left main bronchus. *Anesthesiology* 2009; **110**: 1199-1200 [PMID: 19387199 DOI: 10.1097/ALN.0b013e3181a10969]

4 **El-Tahan MR**, Doyle DJ, Hassieb AG. High-frequency jet ventilation using the Arndt bronchial blocker for refractory hypoxemia during one-lung ventilation in a myasthenic patient with asthma. *J Clin Anesth* 2014; **26**: 570-573 [PMID: 25439421 DOI: 10.1016/j.jclinane.2014.04.009]

5 **Ward KR**, Yealy DM. End-tidal carbon dioxide monitoring in emergency medicine, Part 2: Clinical applications. *Acad Emerg Med* 1998; **5**: 637-646 [PMID: 9660293 DOI: 10.1111/j.1553-2712.1998.tb02474.x]

6 **Kartal M**, Goksu E, Eray O, Isik S, Sayrac AV, Yigit OE, Rinnert S. The value of ETCO2 measurement for COPD patients in the emergency department. *Eur J Emerg Med* 2011; **18**: 9-12 [PMID: 20224417 DOI: 10.1097/MEJ.0b013e328337b9b9]

7 **Walker CM**, Rosado-de-Christenson ML, Martínez-Jiménez S, Kunin JR, Wible BC. Bronchial arteries: anatomy, function, hypertrophy, and anomalies. *Radiographics* 2015; **35**: 32-49 [PMID: 25590386 DOI: 10.1148/rg.351140089]

8 **Rojas S**, Quintana E, Ortega M, Rodríguez-Baeza A. A case of unusual configuration of the right bronchial arteries combined with cryptogenic severe bilateral hypertrophy. *Surg Radiol Anat* 2017; **39**: 1049-1052 [PMID: 28132091 DOI: 10.1007/s00276-017-1816-0]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1837-1846

DOI: 10.12998/wjcc.v11.i8.1837

ISSN 2307-8960 (online)

CASE REPORT

False positive detection of serum cryptococcal antigens due to insufficient sample dilution: A case series

Wen-Yu Chen, Cheng Zhong, Jian-Ying Zhou, Hua Zhou

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Hasan S, India; Papazafiropoulou A, Greece; Yoshimatsu K, Japan

Received: December 6, 2022
Peer-review started: December 6, 2022
First decision: January 17, 2023
Revised: February 2, 2023
Accepted: February 17, 2023
Article in press: February 17, 2023
Published online: March 16, 2023

Wen-Yu Chen, Cheng Zhong, Jian-Ying Zhou, Hua Zhou, Department of Respiratory, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 314000, Zhejiang Province, China

Wen-Yu Chen, Department of Respiratory, The Affiliated Hospital of Jiaxing University, Jiaxing 314000, Zhejiang Province, China

Corresponding author: Hua Zhou, PhD, Doctor, Department of Respiratory, The First Affiliated Hospital, Zhejiang University School of Medicine, No. 1882 Zhonghuan South Road, Jiaxing 314000, Zhejiang Province, China. zhouhua1@zju.edu.cn

Abstract

At present, with the development of technology, the detection of cryptococcal antigen (CRAG) plays an increasingly important role in the diagnosis of cryptococcosis. However, the three major CRAG detection technologies, latex agglutination test (LA), lateral flow assay (LFA) and Enzyme-linked Immunosorbent Assay, have certain limitations. Although these techniques do not often lead to false-positive results, once this result occurs in a particular group of patients (such as human immunodeficiency virus patients), it might lead to severe consequences.

Key Words: Cryptococcosis; Capsular antigen detection; False positive; Tissue; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Cryptococcosis is a pulmonary or disseminated infectious disease caused by Cryptococcus, which mainly causes pneumonia and meningitis, but also skin, bone or internal organs infection. the three major cryptococcal antigen detection technologies, latex agglutination test, lateral flow assay and Enzyme-linked Immunosorbent Assay, have certain limitations. Although these techniques do not often lead to false-positive results, once this result occurs in a particular group of patients (such as human immunodeficiency virus patients), it might lead to severe consequences. Therefore, once the test results are inconsistent with the clinical symptoms, it is necessary to reexamine the samples carefully.

Citation: Chen WY, Zhong C, Zhou JY, Zhou H. False positive detection of serum cryptococcal antigens due to insufficient sample dilution: A case series. *World J Clin Cases* 2023; 11(8): 1837-1846
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1837.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1837

INTRODUCTION

Cryptococcosis is a pulmonary or disseminated infectious disease caused by Cryptococcus, which mainly causes pneumonia and meningitis, but also skin, bone or internal organs infection. Clinically, combined with clinical manifestations and microscopic examination results, the diagnosis was made, and then confirmed by fungal culture or tissue staining. Infection is caused by inhalation of Cryptococcus in human respiratory tract, and the primary infection focus is mostly lung, which causes Pulmonary cryptococcosis (PC)[1-3]. However, immunocompetent people who are infected with cryptococcosis often have insidious onset, usually without typical clinical symptoms, mostly of which are found in physical examination, and the imaging manifestations are diverse which cause trouble in the diagnosis of PC in normal population[4-6]. At present, the diagnosis of PC mainly includes three methods: Pathogen detection, immunologic test and molecular biological detection. The detection of cryptococcal capsular polysaccharide antigen (CRAG) is considered to be the most valuable and rapid serological diagnosis methods in routine examination of cryptococcosis[7]. There are three major CRAG detection technologies for now, atex agglutination test (LA), lateral flow assay (LFA) and Enzyme-linked Immunosorbent Assay. Generally speaking, CRAG titer > 1:4 indicates cryptococcal infection, and the higher the titer, the greater the diagnostic value. Current researches suggest that CRAG test has higher sensitivity and diagnostic specificity than traditional immunodiagnostic methods and is widely applied in clinic[8-10].

However, recently, our team found 3 false positive detection cases of serum CRAG in immunocompetent patients with pulmonary lesions. One of the patients was diagnosed as PC, but the anti-cryptococcosis treatment was ineffective, and finally the patient was found to be misdiagnosed by tissue culture after lung puncture biopsy. The other two patients were detected by lung puncture and continuous re-examination of CRAG to exclude diagnosis of PC with negative results. In order to summarize the diagnosis and treatment experience of these three cases and enhance the diagnosis and treatment level of PC, the clinical data are shared as follows.

CASE PRESENTATION

Chief complaints

Case 1: A 53-year-old man, half a month ago, the chest computed tomography (CT) suggested a thick-walled cavity shadow in inferior lobe of left lung.

Case 2: A 67-year-old woman developed a cough without obvious inducement, accompanied by chest muffling and shortness of breath. These symptoms lasted for 2 wk.

Case 3: A 67-year-old male patient, was found to have new solid nodules in the middle lobe of the right lung during routine review.

History of present illness

Case 1: The patient, was found to have nodules in inferior lobe of left lung during physical examination one year ago. Half a month ago, the chest CT review of the man suggested a thick-walled cavity shadow in inferior lobe of left lung. The patient came to our hospital for further diagnosis.

Case 2: The patient developed a cough without obvious inducement, presenting paroxysmal coughing without sputum and accompanied by chest muffling and shortness of breath. These symptoms lasted for 2 wk, during which the patient had received antimicrobial therapy with oral administration of Moxifloxacin 0.5 g once a day for 5 d in the outer court, but the symptoms were still not relieved, and even aggravated. On December 19, 2018, the patient checked the lung CT examination and found that there were nodules in inferior lobe of left lung and multiple enlarged lymph nodes in mediastinum. The patient with left lung infection was further diagnosed in our hospital.

Case 3: The patient with liver transplantation two years before and had been treated with oral tacrolimus anti-rejection after liver transplantation. The patient was found to have new solid nodules in the middle lobe of the right lung during routine review and had no chief complaint. The patient came to our hospital for further diagnosis.

History of past illness

Case 1: A history of nodules in inferior lobe of left lung during physical examination one year ago, general health good.

Case 2: A history of asthma.

Case 3: A history of liver transplantation two years before and had been treated with oral tacrolimus anti-rejection after liver transplantation.

Physical examination

Case 1: The patient underwent a preliminary examination with the results of a body temperature of 36.2 ℃, blood pressure of 137/86 mmHg, pulse rate of 91 beats/min, respiratory rate of 20 beats/min and oxygen saturation of 98%. Lung auscultation suggested clear respiratory sounds in both lungs, no rales were heard, and other examinations showed no obvious abnormality.

Case 2: The patient underwent a preliminary examination with the results of a body temperature of 37.2 ℃, blood pressure of 119/73 mmHg, pulse rate of 100 beats/min, respiratory rate of 21 beats/min and oxygen saturation of 96% with two nasal cathedrals of 2L/ min. Further physical examination revealed that an enlarged lymph node about 1 cm × 2 cm in size could be touched in the left neck, which was soft with moderately activity. Lung auscultation suggested heavy respiratory sounds in both lungs, but no rales were heard, and other examinations showed no obvious abnormality.

Case 3: The patient underwent a preliminary examination with the results of a body temperature of 36.7 ℃, blood pressure of 126/75 mmHg, pulse rate of 83 beats/min, respiratory rate of 18 beats/min and oxygen saturation of 99%. Lung auscultation suggested clear respiratory sounds in both lungs, no rales were heard, and other examinations showed no obvious abnormality.

Laboratory examinations

Case 1: After admission, the CRAG detection was positive, and no other major were found in other items. The results of cerebrospinal fluid (CSF) were all negative. After 19 days of treatment, the detection of CRAG was negative.

Case 2: After admission, in routine hematology and biochemical laboratory examinations, tests for CRAG and T-cell detection of tuberculosis infection were positive, and no other major findings were found in other items.

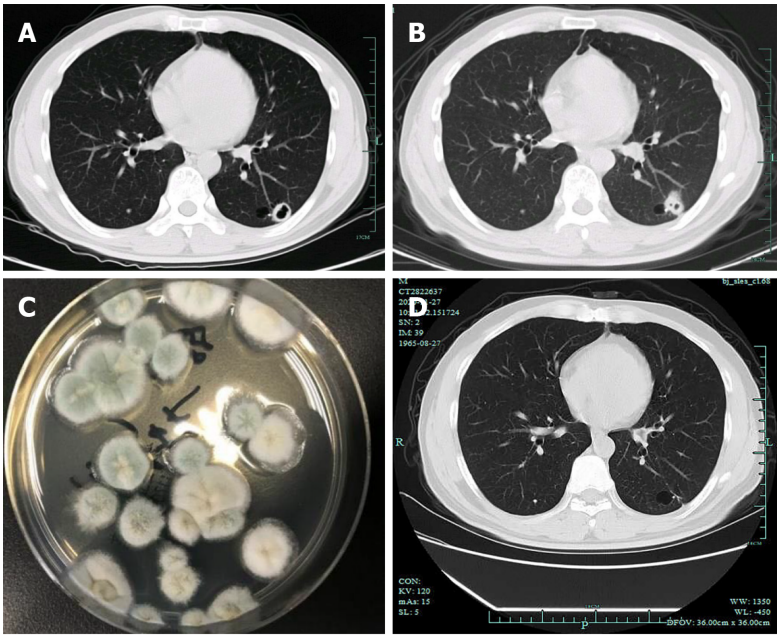
Case 3: After admission, routine hematology and biochemical laboratory tests showed that the detection of CRAG was positive with no other major findings were found in other items. Before the treatment, the local hospital rechecked the test of CRAG and the result was negative. Three months later, the detection of serum CRAG showed a negative result.

Imaging examinations

Case 1: Half a month ago, the chest CT review of the man suggested a thick-walled cavity shadow in inferior lobe of left lung. After admission, high resolution CT (HRCT) examination of the patient indicated multiple nodules in inferior lobe of left lung, one with a thick-walled cavity and one with nodules, suggesting granulomatous inflammation and the possibility of cryptococcus (Figure 1A). After 19 d of treatment, chest CT reexamination, which revealed the formation of nodules with cavities in the left lower lobe. The lesions were enlarged, and internal cavity was narrowed compared to old CT photos (Figure 1B). The patient had three times of chest CT reexamination later, all of which indicated that the infection lesions in inferior lobe of left lung were shrinking.

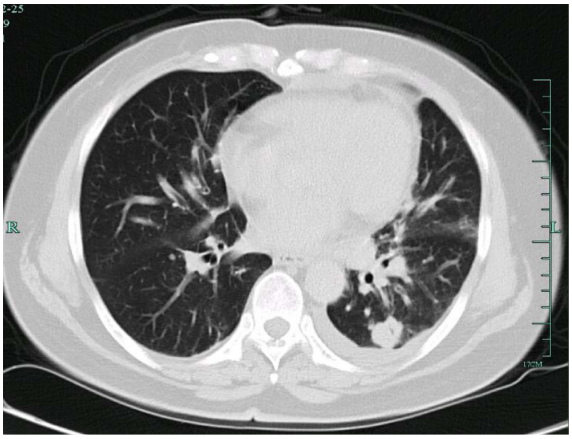
Case 2: On December 19, 2018, the lung CT examination found that there were nodules in inferior lobe of left lung and multiple enlarged lymph nodes in mediastinum. After admission, the chest HRCT of the patient indicated left inferior lobe lung cancer, multiple mediastinal lymph node metastasis, and pleural effusion with a small amount of pericardial effusion (Figure 2). Attachment: cysts in pancreatic body. B-ultrasound examination presented that there were multiple TI-RADS2 types of nodules in right thyroid, multiple lymph nodes enlargement in the IV region of bilateral neck, fatty liver, no obvious abnormality in bilateral adrenal scanning and retroperitoneal scanning. After the treatment, two chest CT reexaminations later, both indicated that the left lower pulmonary lesions were continuously shrinking.

Case 3: After admission, the chest HRCT reexamination of the patient suggested nodules in the right middle lobe and bilateral lower lobe and proliferative lesions were considered (Figure 3A). Three months later, chest CT examination of the patient in local hospital revealed the absorption of lesions in right lung.



DOI: 10.12998/wjcc.v11.i8.1837 **Copyright** ©The Author(s) 2023.

Figure 1 High resolution computed tomography examination. A: High resolution computed tomography (CT) examination of the patient indicated multiple nodules in inferior lobe of left lung, one with a thick-walled cavity and one with nodules, suggesting granulomatous inflammation and the possibility of Cryptococcus; B: The lesions were enlarged, and internal cavity was narrowed compared to old CT photos; C: Tissue culture suggested Aspergillus spp.; D: The three times of chest CT reexamination after the treatment, all of which indicated that the infection lesions in inferior lobe of left lung were shrinking, suggesting that the treatment was effective.



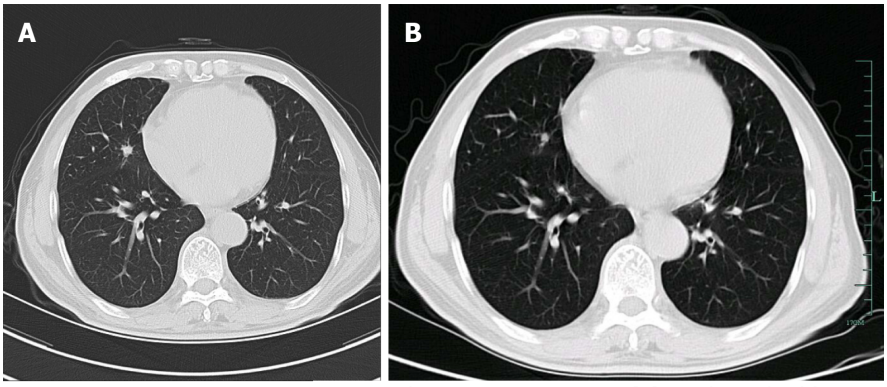
DOI: 10.12998/wjcc.v11.i8.1837 **Copyright** ©The Author(s) 2023.

Figure 2 Multiple mediastinal lymph node metastasis, and pleural effusion with a small amount of pericardial effusion.

Pathological examinations

Case 1: Half a month ago, no significant abnormality was observed in bronchoscopy. After 19 days of treatment, the patient underwent CT-guided puncture biopsy of the left pulmonary lesions. Tissue culture suggested Aspergillus spp. (Figure 1C).

Case 2: On December 25, 2018, tracheoscopy suggested mucosal swelling of the left upper lobe bronchus. Intraoperative EBUS detected lymph node enlargement in the seventh and eleventh groups, and EBUS-TBA was performed in the seventh group. At the same time, the patient also underwent CT-guided lung puncture and left supraclavicular lymph node puncture biopsy. Pathological prompts of three above examinations were as follows, EBUS-TBNA: adenocarcinoma CK7 (+), TTF-1 (+), NapsinA (+), CK5/6 (-), P63 (-), CgA (-), ALK-Lung (-); left lung puncture: adenocarcinoma CK7 (+), TTF-1 (+), NapsinA (+), CK5/6 (-), ALK-Lung (-), P63 (-), Ki-67 (25%); left supraclavicular lymph node puncture: metastasis of lung adenocarcinoma CK(pan) (+), CK7 (+), TTF-1 (+), NapsinA (+), CDX2 (-), GATA-3 (-), CK20 (+). Further genetic testing suggested a mutation in L858R.



DOI: 10.12998/wjcc.v11.i8.1837 **Copyright** ©The Author(s) 2023.

Figure 3 High resolution computed tomography reexamination. A: The chest high resolution computed tomography reexamination of the patient suggested nodules in the right middle lobe and bilateral lower lobe and proliferative lesions were considered; B: the detection of serum cryptococcal antigen showed a negative result, suggesting that the treatment was effective.

Case 3: No evidence.

FINAL DIAGNOSIS

Depending on laboratory, radiological and pathological findings, Patient 1 was diagnosed as pulmonary aspergillosis.

According to laboratory, imaging and pathological examination, Patient 2 was diagnosed with lung adenocarcinoma in stage IV (cT2aN3M1c), and basically ruling out the possibility of cryptococcus infection.

Following the radiographic, clinical and laboratory examination, Patient 3 was diagnosed as community-acquired pneumonia.

TREATMENT

Case 1

The treatment regimen was Diflucan at a dosage of 400 mg intravenously once a day, and three d later the patient switched to oral administration and was discharged with medication. After 19 d oral administration of Diflucan (400 mg orally once a day), the lesions were still progressing after oral administration of Diflucan with the negative result of CRAG detection, the diagnosis of PC should be further verified and the treatment program was modified to Voriconazole 200mg orally twice a day, and the patient was discharged with medication.

Case 2

According to the genetic testing results, we developed an oral Conmana 125mg tid targeted therapy regimen.

Case 3

Since the patient had been treated with oral tacrolimus anti-rejection after liver transplantation and had the basis of immune injury, the possibility of PC was considered as the preliminary diagnosis combined with the imaging examination and the positive detection of CRAG. The treatment of Diflucan by oral administration was recommended. The patient then returned to the local hospital for treatment, but before the treatment, the local hospital rechecked the test of CRAG and the result was negative. After contacting our hospital, a consensus was reached that anti-cryptococcal therapy should be replaced with antimicrobial therapy.

OUTCOME AND FOLLOW-UP

Case 1

The three times of chest CT reexamination after the treatment, all of which indicated that the infection

lesions in inferior lobe of left lung were shrinking, suggesting that the treatment was effective (Figure 1D).

Case 2

The two chest CT reexaminations after the treatment, both indicated that the left lower pulmonary lesions were continuously shrinking, suggesting effective treatment and basically ruling out the possibility of cryptococcus infection.

Case 3

Three months after the treatment, chest CT examination of the patient in local hospital revealed the absorption of lesions in right lung, and the detection of serum CRAG showed a negative result, suggesting that the treatment was effective (Figure 3B).

DISCUSSION

Since the above three cases all showed false positive detection of serum CRAG in the same period, our team attached great importance to it. We reviewed the examination results of the three patients and checked the possible factors one by one. Finally, we found that the false positive in this batch of specimens was caused by improper handling by technicians. Common methods for detection of CRAG includes LA, LFA and Enzyme-linked Immunosorbent Assay (ELISA). While we used LFA for detection, which is a simple and effective laboratory method for qualitative and semi-quantitative detection of the polysaccharide antigen in serum, plasma, whole blood and CSF by immunochromatography. The principle of LFA is essentially a "sandwich" immunochromatographic strip test, which requires adding the sample and sample dilution to a suitable container (such as a test tube), and the test strip is also placed in the container. During the test, the sample is chromatographed to the gold labelled anti-Cryptococcus antigen capture monoclonal antibody and the gold labelled control antibody located on the detection membrane. If there is a CRAG in the sample, it will bind to the gold labelled anti-cryptococcus antibody. The bound gold labelled antibody (GAB) antigen complex continues to be chromatographed on the membrane by capillarity and reacts with detection strips containing immobilized anticryptococcal monoclonal antibodies. The GAB antigen complex forms a "sandwich" structure at the detection strips and displays a visible detection strip. As long as there is normal chromatography and reagent reaction, the chromatography of any positive or negative samples will cause the gold labelled control antibody to move to the control strip, and the immobilized antibody will combine with the gold labelled control antibody to form a visible control strip. Positive test results will show two bands (test band and control band) and negative test results will show only one band (control strip). If no control strip appears, the test is invalid[8,11,12].

The kit used in our hospital is IMMY's CrAg Lateral Flow Assay (colloidal gold immunochromatography). First, add a drop of sample dilution to the microcentrifuge tube, then add 40 μL of sample. Next the white end of the CRAG test strip was immersed in the sample solution, and the result was read after 10 minutes. Diluting the sample is a critical step and usually about 50 μL of sample dilution is needed. Although this is not emphasized in the product specification, studies have shown that insufficient sample dilution is an important cause of false negative or false positives in test results[13,14]. According to the investigation, these three cases were caused by a newly employed technician who did not add enough sample diluent during the operation, which resulted in false positive in the test.

LITERATURE REVIEW

Although the detection of CRAG has high clinical value in the rapid diagnosis of cryptococcosis, we still cannot ignore the false positive results that may occur in the detection process. For once the above results are misjudged, it is easy to cause misdiagnosis. We searched on Pubmed with terms such as "cryptococcosis", "cryptococcal capsular antigen detection", "latex agglutination test", "colloidal gold immunochromatography", "enzyme-linked immunosorbent assay", and "false positive", and excluding the literature that simply discuss the "false-negative" of the above three techniques and the literature that study other methods for diagnosing cryptococcal. Only the reports on false positive results of CRAG detected by LA, LFA and ELISA were considered, including main clinical features and detection methods. A total of 4 cases were included (Table 1), as well as 8 other related studies. After reviewing the literature, we found that the three commonly used CRAG technologies (LA, LFA, and ELISA) in the market have the possibility of false positive results. Among the 4 included cases and 3 cases we reported, 4 cases adopted LA and 3 cases adopted LFA. A recently reported case of false positive adopted LA was from systemic lupus erythematosus (SLE) patient in active phase and complicated with Libman-Sacks endocarditis[15]. The patient developed onset of sudden disturbance of consciousness, recovered consciousness after 16 h, and the neurological examination was essentially normal, but the

Table 1 Case reports of false positive cryptococcal antigen

Ref.	Age (yr)/gender	Country	Underlying disease (including Immunosupressive disease or drug use)	Sample source/Detection method/Reagent company	Basis of diagnosis	Possible causes	Outcome
Matsumoto *et al*[24], 2019	58/F	United States	SLE with secondary immune thrombocytopenic purpura	CSF/LA/CALAS® Meridian Bioscience Inc., Cincinnati, Ohio	(1) Reexamination of serum LA suggested negative; (2) Both CSF ink staining and culture results were negative; and (3) Head MRI showed abnormal signals in the left superior frontal cortex, consistent with subacute ischemia; Cardiac hypertrophy suggested Libman-Sack endocarditis. The final diagnosis was "thromboembolic cerebrovascular transient ischemia"	Nonspecific interference with the autoantibodies of SLE circulation in patients	Survived
Augeret al [25], 2019	26/M	United States	None	CSF/LA	Blood and CSF culture identified Df-2 infection	Common antigenic surface components may exist in DF-2	
Volozhantsev *et al*[26], 2020	33/M	United States	Aplastic anemia; after bone marrow transplantation	Serum/LA/ IM Inc, American Microscan	The autopsy confirmed Trichosporon asahiti infection	Similar structures of polysaccharides may exist in Trichosporon asahiti	Died
Zhu *et al*[27], 2018	29/F	United States	Non-Hodgkin's lymphoma	CSF/LA/CALAS, Meridian Diagnostics, Cincinnati, Ohio, and CRYPTO-LA, International Biological Laboratories, Cranbury, New Jersey	CSF culture indicated Stomatococcus infection	Stomatococcus infection may cross-react with LA	Died
This case 1	53/M	China	None	Serum/LFA/ IMMY Immuno-Mycologics, Norman, Oklahoma, United States	(1) Anticryptococcal treatment failed; and (2) Lung puncture tissue culture suggested aspergillus	Insufficient sample dilution	Survived
Case 2	67/F	China	Bronchial asthma	Serum/LFA/ IMMY Immuno-Mycologics, Norman, Oklahoma, United States	Lung biopsy and left supraclavicular lymph node biopsy indicated lung adenocarcinoma	Insufficient sample dilution	Survived
Case 3	67/M	China	Post-orthotopic liver transplantation	Serum/LFA/ IMMY Immuno-Mycologics, Norman, Oklahoma, United States	(1) The local hospital reexamination of CRAG was negative; and (2) Antibacterial therapy was effective	Insufficient sample dilution	Survived

SLE: Systemic lupus erythematosus; CSF: Cerebrospinal fluid; LA: Latex agglutination; MRI: Magnetic resonance imaging; CRAG: Cryptococcal antigen.

initial CRAG of CSF was positive. Then the patient began to receive anti- cryptococcal therapy. CSF ink staining and culture results were both negative after 3 days, and the CRAG of CSF was negative after reexamination. The first positive result was considered unreliable, so the anti-cryptococcal treatment was suspended. The reason for this false positive result may be caused by the non-specific interference of circulating autoantibodies in active SLE patients, especially when the titer of serum anti-nuclear antibodies was high[15]. In addition, it has been reported that fungal infection caused by Trichosporon asahii or bacterial infection caused by Stomatococcus or Capnocytophaga can lead to false positive results in the detection of CRAG, and these positive results usually show low titer[16-18]. Besides, there are some rare cases of false positives adopted LA, including contamination of samples by substances in the BBL Port-A-cul specimen transport bottle and the inactivation of invertase vials of the test kits[19, 20].

LFA is considered to have better operability and stability than LA and the Chinese consensus believes that LFA method has a low probability of false positive, and has replaced the traditional screening method for cryptococcal infection, due to its simple operation, fast detection speed (< 15min), simple technology, less experimental instruments, and no need for refrigerated reagents[14-17]. Some studies

Table 2 Possible causes of false positive results in three cryptococcal antigen detection techniques

Detection method	LA	LFA	ELISA
Sample	Cerebrospinal fluid/Serum	Cerebrospinal fluid/Serum/Plasma /Whole blood	Cerebrospinal fluid/Serum
Possible causes of false positive	Serum of rheumatoid factor, agarose dehydration, hydroxyethyl starch, and containing Fe^{3+}/dL > 200 mg was present, Circular slides are not properly washed, the inactivation of Streptomyces protease in the kit and some nonspecific reactions in patients with HIV infection occur	LFA has antigenic cross-reaction with aspergillus which may lead to false positive results[1]; Sample dilution is insufficient[2]	Samples are Infected with other microbial infections, such as Trichosporon[1]; Reagents and samples to be tested are contaminated[2]

[1]Lateral flow assay (LFA) should not be used as a screening test for the general population, but only should be performed when clinical evidence suggests the possibility of cryptococcosis.
[2]LFA may also have potential interference factors, including samples pretreated with 2-mercaptoethanol or those containing vaginal ointment, caffeine, ascorbic acid, itraconazole, amphotericin B, acetaminophen or acetylsalicylic acid. However, the above factors have not been systematically evaluated.
LA: Latex agglutination; LFA: Lateral flow assay; ELISA: Enzyme linked immunosorbent assay; HIV: Human immunodeficiency virus.

have found that when the antigen titer in the sample is too high or the sample is not diluted enough, a post-zone phenomenon, also known as Prozone phenomenon (It is also called HOOK effect in the kit instruction), may occur which will interfere with the antigen-antibody reaction necessary for the display of positive test, resulting in false negative results[21-23]. But, accoeding to the investigation, it is puzzling that the three cases we reported had false positive results due to insufficient dilution of samples. This phenomenon is extremely rare, and only a few literatures have mentioned it, but its mechanism has never been discussed in depth. We proposed a relatively reasonable explanation. LFA detection of CRAG is achieved by capturing cryptococcal capsular polysaccharide components in serum or CSF samples with antibodies against cryptococcal capsular polysaccharide. This polysaccharide component is not unique to Cryptococcus, many microorganisms in nature secrete capsular polysaccharides (such as Streptococcus pneumoniae, Streptococcus group B, Streptococcus suis, *etc.*)[24-26]. Although LFA can detect CRAG of four major cryptococcus serotypes (type A and D are cryptococcus neoformans, type B and C are Cryptococcus Gattinii), capsular polysaccharides produced by other microorganisms are likely to be associated with CRAG in a cross-structure. False positive results may occur when the sample is not sufficiently diluted and there is a similar structure of CARG in the patient. As mentioned above, this may be the cause of false-positive capsular antigen results after certain fungal or bacterial infections.

In addition, through literature review, we found that with the progress and promotion of LFA and LA in recent years, ELISA was rarely used to detect CRAG in clinical diagnosis of cryptococcosis, but there were still reports on the comparison of three detection technologies[27-32]. Through these reports and some related works, we summarize the limitations of the three techniques in detecting CRAG (Table 2).

CONCLUSION

At present, with the development of technology, the detection of CRAG plays an increasingly important role in the diagnosis of cryptococcosis. However, the three major CRAG detection technologies have certain limitations. Although these techniques do not often lead to false positive results, once this result occurs in a special group of patients (such as human immunodeficiency virus patients), it might lead to serious consequences. Therefore, once the test results are inconsistent with the clinical symptoms, it is necessary to carefully reexamine the samples. Especially for LFA and LA, the samples can be fully diluted or segmented dilution to avoid false positive results. It is certainly that in the diagnosis, fluid and tissue culture should also be improved, combined with imaging, ink staining and other methods to further improve the accuracy of the diagnosis.

FOOTNOTES

Author contributions: Chen YW and Zhong C contributed equally to this work and should be considered as co-first authors; Chen YW conceptualized, drafted, and led the writing of the manuscript; Zhou H and Zhou JY provided overall conceptual guidance for the study; Chen YW closely worked with Zhong C to develop the article; all authors have contributed to the writing and reviewed and approved the final manuscript.

Supported by the Key Discipline of Jiaxing Respiratory Medicine Construction Project, No. 2019-zc-04.

Informed consent statement: The ethics committee approved the exemption of informed consent, and the ethics review approval document has been uploaded.

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

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).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Wen-Yu Chen 0000-0003-0412-2913; Cheng Zhong 0000-0002-1936-3448; Jian-Ying Zhou 0000-0002-8924-935X; Hua Zhou 0000-0001-6397-3203.

S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

REFERENCES

1 **García J**, Pemán J. [Microbiological diagnosis of invasive mycosis]. *Rev Iberoam Micol* 2018; **35**: 179-185 [PMID: 30471895 DOI: 10.1016/j.riam.2018.05.003]
2 **Hevey MA**, George IA, Raval K, Powderly WG, Spec A. Presentation and Mortality of Cryptococcal Infection Varies by Predisposing Illness: A Retrospective Cohort Study. *Am J Med* 2019; **132**: 977-983.e1 [PMID: 31077652 DOI: 10.1016/j.amjmed.2019.04.026]
3 **Bruner KT**, Franco-Paredes C, Henao-Martínez AF, Steele GM, Chastain DB. Cryptococcus gattii Complex Infections in HIV-Infected Patients, Southeastern United States. *Emerg Infect Dis* 2018; **24**: 1998-2002 [PMID: 30334702 DOI: 10.3201/eid2411.180787]
4 **Zhou Y**, Lin PC, Ye JR, Su SS, Dong L, Wu Q, Xu HY, Xie YP, Li YP. The performance of serum cryptococcal capsular polysaccharide antigen test, histopathology and culture of the lung tissue for diagnosis of pulmonary cryptococcosis in patients without HIV infection. *Infect Drug Resist* 2018; **11**: 2483-2490 [PMID: 30555247 DOI: 10.2147/idr.S178391]
5 **Eshwara VK**, Garg R, Chandrashekhar GS, Shaw T, Mukhopadhyay C. Fatal Cryptococcus gattii meningitis with negative cryptococcal antigen test in a HIV-non-infected patient. *Indian J Med Microbiol* 2018; **36**: 439-440 [PMID: 30429403 DOI: 10.4103/ijmm.IJMM_18_164]
6 **Ni LF**, Wang H, Li H, Zhang ZG, Liu XM. [Clinical analysis of pulmonary cryptococcosis in non-human immunodeficiency virus infection patients]. *Beijing Da Xue Xue Bao Yi Xue Ban* 2018; **50**: 855-860 [PMID: 30337748]
7 **Setianingrum F**, Rautemaa-Richardson R, Denning DW. Pulmonary cryptococcosis: A review of pathobiology and clinical aspects. *Med Mycol* 2019; **57**: 133-150 [PMID: 30329097 DOI: 10.1093/mmy/myy086]
8 **Kozel TR**, Bauman SK. CrAg lateral flow assay for cryptococcosis. *Expert Opin Med Diagn* 2012; **6**: 245-251 [PMID: 23480688 DOI: 10.1517/17530059.2012.681300]
9 **Cáceres DH**, Zuluaga A, Tabares ÁM, Chiller T, González Á, Gómez BL. Evaluation of a Cryptococcal antigen Lateral Flow Assay in serum and cerebrospinal fluid for rapid diagnosis of cryptococcosis in Colombia. *Rev Inst Med Trop Sao Paulo* 2017; **59**: e76 [PMID: 29267584 DOI: 10.1590/s1678-9946201759076]
10 **Jitmuang A**, Panackal AA, Williamson PR, Bennett JE, Dekker JP, Zelazny AM. Performance of the Cryptococcal Antigen Lateral Flow Assay in Non-HIV-Related Cryptococcosis. *J Clin Microbiol* 2016; **54**: 460-463 [PMID: 26607986 DOI: 10.1128/jcm.02223-15]
11 **Alves Soares E**, Lazera MDS, Wanke B, Faria Ferreira M, Carvalhaes de Oliveira RV, Oliveira AG, Coutinho ZF. Mortality by cryptococcosis in Brazil from 2000 to 2012: A descriptive epidemiological study. *PLoS Negl Trop Dis* 2019; **13**: e0007569 [PMID: 31356603 DOI: 10.1371/journal.pntd.0007569]
12 **Marr KA**, Sun Y, Spec A, Lu N, Panackal A, Bennett J, Pappas P, Ostrander D, Datta K, Zhang SX, Williamson PR; Cryptococcus Infection Network Cohort Study Working Group. A Multicenter, Longitudinal Cohort Study of Cryptococcosis in Human Immunodeficiency Virus-negative People in the United States. *Clin Infect Dis* 2020; **70**: 252-261 [PMID: 30855688 DOI: 10.1093/cid/ciz193]
13 **Santos-Gandelman J**, Rodrigues ML, Machado Silva A. Future perspectives for cryptococcosis treatment. *Expert Opin Ther Pat* 2018; **28**: 625-634 [PMID: 30084284 DOI: 10.1080/13543776.2018.1503252]
14 **Liu ZY**, Wang GQ, Zhu LP, Lyu XJ, Zhang QQ, Yu YS, Zhou ZH, Liu YB, Cai WP, Li RY, Zhang WH, Zhang FJ, Wu H, Xu YC, Lu HZ, Li TS; Society of Infectious Diseases, Chinese Medical Association. [Expert consensus on the diagnosis and treatment of cryptococcal meningitis]. *Zhonghua Nei Ke Za Zhi* 2018; **57**: 317-323 [PMID: 29747285 DOI: 10.3760/cma.j.issn.0578-1426.2018.05.003]
15 **Isseh IN**, Bourgi K, Nakhle A, Ali M, Zervos MJ. False-positive cerebrospinal fluid cryptococcus antigen in Libman-Sacks

endocarditis. *Infection* 2016; **44**: 803-805 [PMID: 27246719 DOI: 10.1007/s15010-016-0909-8]
16 **Westerink MA**, Amsterdam D, Petell RJ, Stram MN, Apicella MA. Septicemia due to DF-2. Cause of a false-positive cryptococcal latex agglutination result. *Am J Med* 1987; **83**: 155-158 [PMID: 3605167 DOI: 10.1016/0002-9343(87)90512-2]
17 **McManus EJ**, Jones JM. Detection of a Trichosporon beigelii antigen cross-reactive with Cryptococcus neoformans capsular polysaccharide in serum from a patient with disseminated Trichosporon infection. *J Clin Microbiol* 1985; **21**: 681-685 [PMID: 3889042 DOI: 10.1128/jcm.21.5.681-685.1985]
18 **Chanock SJ**, Toltzis P, Wilson C. Cross-reactivity between Stomatococcus mucilaginosus and latex agglutination for cryptococcal antigen. *Lancet* 1993; **342**: 1119-1120 [PMID: 8105345 DOI: 10.1016/0140-6736(93)92106-4]
19 **Wilson DA**, Sholtis M, Parshall S, Hall GS, Procop GW. False-positive cryptococcal antigen test associated with use of BBL Port-a-Cul transport vials. *J Clin Microbiol* 2011; **49**: 702-703 [PMID: 21159939 DOI: 10.1128/jcm.01169-10]
20 **Stoeckli TC**, Burman WJ. Inactivated pronase as the cause of false-positive results of serum cryptococcal antigen tests. *Clin Infect Dis* 2001; **32**: 836-837 [PMID: 11229857 DOI: 10.1086/319212]
21 **Yadava SK**, Fazili T. Postzone phenomenon resulting in a false-negative cerebral spinal fluid cryptococcal antigen lateral flow assay. *AIDS* 2019; **33**: 1099-1100 [PMID: 30946166 DOI: 10.1097/qad.0000000000002157]
22 **Lee GH**, Arthur I, Leung M. False-Negative Serum Cryptococcal Lateral Flow Assay Result Due to the Prozone Phenomenon. *J Clin Microbiol* 2018; **56** [PMID: 29367291 DOI: 10.1128/jcm.01878-17]
23 **Kojima N**, Chimombo M, Kahn DG. False-negative cryptococcal antigen test due to the postzone phenomenon. *AIDS* 2018; **32**: 1201-1202 [PMID: 29746320 DOI: 10.1097/qad.0000000000001805]
24 **Matsumoto Y**, Miyake K, Ozawa K, Baba Y, Kusube T. Bicarbonate and unsaturated fatty acids enhance capsular polysaccharide synthesis gene expression in oral streptococci, Streptococcus anginosus. *J Biosci Bioeng* 2019; **128**: 511-517 [PMID: 31130336 DOI: 10.1016/j.jbiosc.2019.04.010]
25 **Auger JP**, Payen S, Roy D, Dumesnil A, Segura M, Gottschalk M. Interactions of Streptococcus suis serotype 9 with host cells and role of the capsular polysaccharide: Comparison with serotypes 2 and 14. *PLoS One* 2019; **14**: e0223864 [PMID: 31600314 DOI: 10.1371/journal.pone.0223864]
26 **Volozhantsev NV**, Shpirt AM, Kislichkina AA, Shashkov AS, Verevkin VV, Fursova NK, Knirel YA. Structure and gene cluster of the capsular polysaccharide of multidrug resistant carbapenemase OXA-48-producing Klebsiella pneumoniae strain KPB536 of the genetic line ST147. *Res Microbiol* 2020; **171**: 74-79 [PMID: 31606486 DOI: 10.1016/j.resmic.2019.10.001]
27 **Zhu T**, Luo WT, Chen GH, Tu YS, Tang S, Deng HJ, Xu W, Zhang W, Qi D, Wang DX, Li CY, Li H, Wu YQ, Li SJ. Extent of Lung Involvement and Serum Cryptococcal Antigen Test in Non-Human Immunodeficiency Virus Adult Patients with Pulmonary Cryptococcosis. *Chin Med J (Engl)* 2018; **131**: 2210-2215 [PMID: 30203796 DOI: 10.4103/0366-6999.240815]
28 **Kumari S**, Verma RK, Singh DP, Yadav R. Comparison of Antigen Detection and Nested PCR in CSF Samples of HIV Positive and Negative Patients with Suspected Cryptococcal Meningitis in a Tertiary Care Hospital. *J Clin Diagn Res* 2016; **10**: DC12-DC15 [PMID: 27190801 DOI: 10.7860/jcdr/2016/18322.7619]
29 **Tintelnot K**, Hagen F, Han CO, Seibold M, Rickerts V, Boekhout T. Pitfalls in Serological Diagnosis of Cryptococcus gattii Infections. *Med Mycol* 2015; **53**: 874-879 [PMID: 26337090 DOI: 10.1093/mmy/myv061]
30 **Huang HR**, Fan LC, Rajbanshi B, Xu JF. Evaluation of a new cryptococcal antigen lateral flow immunoassay in serum, cerebrospinal fluid and urine for the diagnosis of cryptococcosis: a meta-analysis and systematic review. *PLoS One* 2015; **10**: e0127117 [PMID: 25974018 DOI: 10.1371/journal.pone.0127117]
31 **Hansen J**, Slechta ES, Gates-Hollingsworth MA, Neary B, Barker AP, Bauman S, Kozel TR, Hanson KE. Large-scale evaluation of the immuno-mycologics lateral flow and enzyme-linked immunoassays for detection of cryptococcal antigen in serum and cerebrospinal fluid. *Clin Vaccine Immunol* 2013; **20**: 52-55 [PMID: 23114703 DOI: 10.1128/cvi.00536-12]
32 **Binnicker MJ**, Jespersen DJ, Bestrom JE, Rollins LO. Comparison of four assays for the detection of cryptococcal antigen. *Clin Vaccine Immunol* 2012; **19**: 1988-1990 [PMID: 23081814 DOI: 10.1128/cvi.00446-12]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1847-1856

DOI: 10.12998/wjcc.v11.i8.1847

ISSN 2307-8960 (online)

CASE REPORT

Lactation breast abscess treated with Gualou Xiaoyong decoction and painless lactation manipulation: A case report and review of literature

Li-Hua Jin, Hui-Ling Zheng, Yun-Xia Lin, Yi Yang, Jia-Li Liu, Rui-Lan Li, Hui-Jun Ye

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Mao ZM, China; Watanabe T, Japan

Received: December 8, 2022
Peer-review started: December 8, 2022
First decision: December 26, 2022
Revised: January 9, 2023
Accepted: February 7, 2023
Article in press: February 7, 2023
Published online: March 16, 2023

Li-Hua Jin, Hui-Ling Zheng, Yun-Xia Lin, Yi Yang, Jia-Li Liu, Rui-Lan Li, Hui-Jun Ye, Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Zhejiang Chinese Medical University, Xinhua Hospital of Zhejiang Province, Hangzhou 310005, Zhejiang Province, China

Corresponding author: Hui-Jun Ye, BM BCh, Chief Doctor, Professor, Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Zhejiang Chinese Medical University, Xinhua Hospital of Zhejiang Province, No. 318 Chaowang Road, Gongshu District, Hangzhou 310005, Zhejiang Province, China. 1320779970@qq.com

Abstract

BACKGROUND

Breast abscess during lactation is a severe complication of acute mastitis, which can lead to discomfort, high fever, breast fistula, sepsis, septic shock, breast damage, disease persistence and frequent hospitalization. Breast abscesses may also lead the mother to discontinue breastfeeding, thereby harming the infant's health. The predominant pathogenic bacteria are *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus*. The incidence of breastfeeding abscesses in breastfeeding women ranges between 4.0% and 11.0%. In cases of breast abscess, the rate of cessation of lactation is 41.0%. In instances of breast fistula, the rate of cessation of lactation is very high (66.7%). Furthermore, 50.0% of women with breast abscesses must be hospitalized and treated with intravenous antibiotics. Treatment includes antibiotics, abscess puncture and surgical incision and drainage. The patients suffer from stress, pain and easily induced breast scarring; the disease's progression is prolonged and recurrent, interfering with infant feeding. Consequently, it is crucial to discover an adequate cure.

CASE SUMMARY

A 28-year-old woman with a breast abscess was treated with Gualou Xiaoyong decoction and painless breast opening manipulation 24 d after cesarean delivery. On the 2nd d of treatment, the patient's breast mass was significantly reduced, the pain was significantly reduced, and the general asthenia was improved. All conscious symptoms disappeared after 3 d, breast abscesses faded after 12 d of treatment, inflammation images disappeared after 27 d, and normal lactation images were restored.

CONCLUSION
In treating breast abscesses during breastfeeding, the combination of Gualou Xiaoyong decoction and painless lactation provides a positive therapeutic impact. This disease's treatment offers the advantages of a short course of treatment, no need to discontinue breastfeeding and the ability to rapidly mitigate symptoms, which can be used as a reference in clinical practice.

Key Words: Lactation breast abscess; Gualou Xiaoyong decoction; Painless lactation manipulation; Literature review; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Breast abscess during lactation is a serious complication of acute mastitis, which can cause breast pain, fistula, sepsis, septic shock, breast destruction, disease persistence and discontinuation of lactation. Current treatment includes antibiotics, abscess puncture and surgical incision and drainage. Patients suffer from stress and discomfort, which readily induces breast scarring. Moreover, the disease's progression is prolonged and recurrent, interfering with newborn feeding. This article described a case of breast abscess that was cured with Gualou Xiaoyong decoction combined with painless breast opening therapy. The advantages are a short treatment course, no trauma, inexpensive, lactation continuation and rapid symptom improvement.

Citation: Jin LH, Zheng HL, Lin YX, Yang Y, Liu JL, Li RL, Ye HJ. Lactation breast abscess treated with Gualou Xiaoyong decoction and painless lactation manipulation: A case report and review of literature. *World J Clin Cases* 2023; 11(8): 1847-1856
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1847.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1847

INTRODUCTION

The World Health Organization (WHO) recommends 6 mo of exclusive breastfeeding following delivery[1,2]. However, mothers are unable to implement exclusive breastfeeding for various reasons, leaving their infants susceptible to respiratory and gastrointestinal diseases. Furthermore, the risk of noncommunicable diseases in childhood and adulthood, such as heart disease, obesity, diabetes, cancer, allergies, asthma and chronic lung, liver, and kidney diseases, also increases[1,2]. A quarter of lactating mothers believe that acute mastitis during lactation is the primary cause of their decision to wean. It is reported that the incidence rate of mastitis among breastfeeding women is as high as 33%, of which approximately 11% will be secondary to breast abscess[3]. Breast abscesses severely impact the physical and mental health of breastfeeding women, leading to the cessation of breastfeeding (41.0%), breast fistula (11.1%), readmission (50.0%) and even permanent breast deformity[4]. Here, we presented a case of breast abscess in lactation that was successfully treated with Gualou Xiaoyong decoction combined with painless breast opening therapy. It has the advantages of quick symptom alleviation, a short treatment duration, non-invasive, economical and does not require the cessation of breastfeeding.

CASE PRESENTATION

Chief complaints

On August 31, 2022, a 28-year-old Chinese female was initially diagnosed as "24 d after cesarean section, 9 d after breast swelling and pain".

History of present illness

The cesarean section was conducted 24 d before the diagnosis, and the operation was without incident. During the 9 d preceding the diagnosis, the patient experienced breast pain, lethargy, little aversion to colds, nausea and vomiting. On August 27, 2022, an ultrasound test in another hospital reported: "Left breast hypoechoic area, BI-RADS category 3, consider inflammation, right breast hyperechoic mass, consider milk accumulation," where BI-RADS is the abbreviation for Breast Imaging-Reporting and Data System. Oral consumption of Chinese medicine and cefuroxime axetil pills had no noticeable effect. On August 30, 2022, the other hospital conducted another ultrasound test that reported: "During lactation, several hypoechoic nodules were observed in the left breast, the larger ones were about 2.6 cm

× 1.2 cm (in the direction of 8 o'clock) and 1.3 cm × 1.0 cm (in the direction of 10 o'clock), the shape was irregular, the edges were blurry, and fine light spots were detected inside, the imaging behind remained unchanged, and there was no impact on the surrounding tissues. Color Doppler Flow Imaging (CDFI); no blood flow signal was found inside, considering breast abscess, breast cyst with infection." Under ultrasonography guidance, a fine needle puncture was performed, and 7 mL of purulent fluid was collected. The patient reported the pain and enlargement of both breasts to be excruciating. There was an absence of fever, but the patient experienced lethargy. The pain rating [visual analogue score (VAS) rating] was 7.

History of past illness

The patient reported no other known medical conditions or allergies.

Personal and family history

The patient was a non-smoker and a non-drinker with no family history; she also denied any interaction within epidemic areas.

Physical examination

Body temperature was 37 °C, multiple 4 cm × 4 cm sized masses were palpable in the left breast, and a 10 cm × 7 cm sized mass was palpable in the right breast, with obvious tenderness. The breast skin on the surface of the left breast lump was dark and about 2 cm × 2 cm in size.

Laboratory examinations

The white blood cell count (WBC) was 8.3 × 10^9/L, the neutrophil percentage was 69.8%, lymphocyte percentage was 22.8%, C-reactive protein (CRP) was 16.39 mg/L, procalcitonin (PCT) was 0.03 mg/L, and milk bacterial culture was positive for *Staphylococcus epidermidis*.

Imaging examinations

On August 30, 2022 in the lactating breast, several hypoechoic nodules were observed in the left breast. The larger nodules were about 2.6 cm × 1.2 cm (in the direction of 8 o'clock) and 1.3 cm × 1.0 cm (in the direction of 10 o'clock) (Figure 1A).The shape was irregular, the edge was fuzzy, and fine light spots were detected inside. CDFI revealed no blood flow signal inside, several cystic nodules were seen in the right breast, the largest nodule was 0.4 cm × 0.4 cm (in the direction of 10 o'clock) (Figure 1B), and the internal sound transmission was poor.

FINAL DIAGNOSIS

Cyst in right breast with infection and multiple abscesses in left breast.

TREATMENT

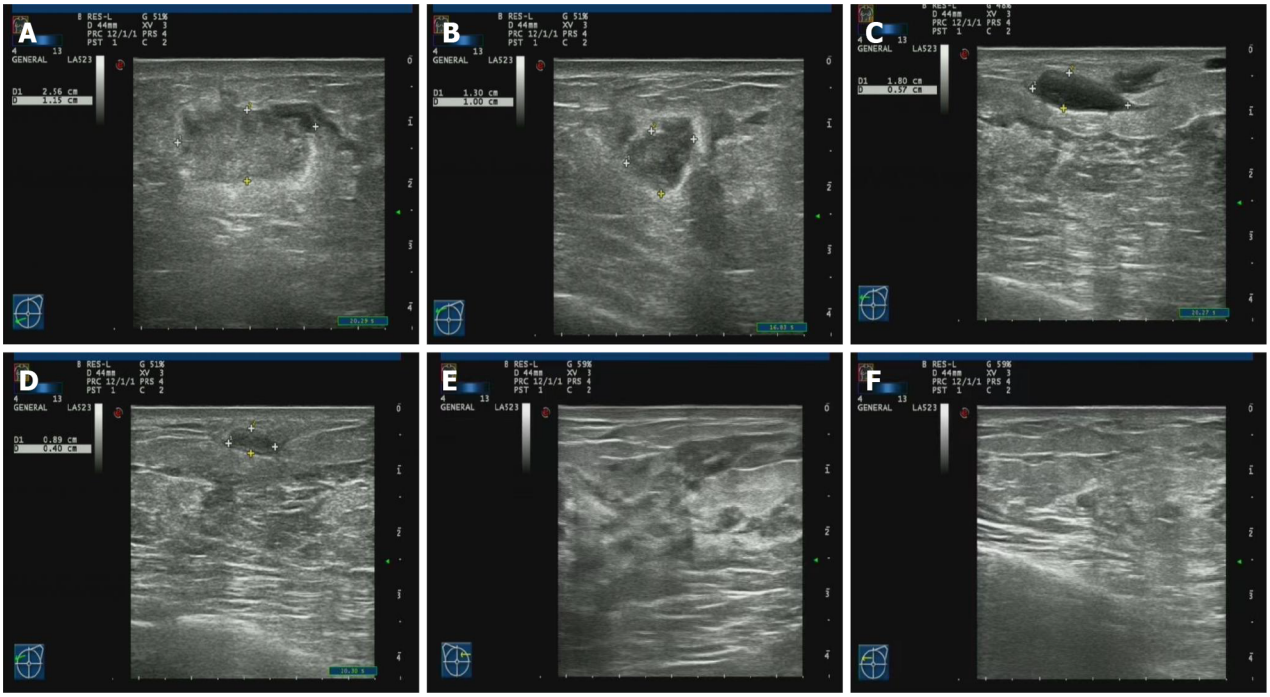
Oral Gualou Xiaoyong decoction was given. The milk from the left breast contained hints of blood, while the milk color of the right breast was normal. It was recommended to stop breastfeeding on the left breast for 1 d and regularly use a breast pump to express the milk on the left side. Continuation of breastfeeding from the right breast was recommended.

Chinese medicine

Gualou Xiaoyong decoction consisted of: Chaihu 9 g; gualou skin 15 g; luffa complex 15 g; lobelia lobata 15 g; dandelion 15 g; paeonia rubra 15 g; tongcao 6 g; peach kernel 10 g; fried coix seed 30 g; chixiaodou 20 g; angelica sinensis 15 g; fried atractylodes macrocephala 15 g; arctium lappa 15 g; honeysuckle 20 g; forsythia suspensa 15 g; poria cocos 15 g; lulutong 10 g; angelica dahurica dahurica 15 g; and saponin 15 g. To prepare the decoction, 400 mL of the medicinal solution was boiled. The decoction was consumed at a lukewarm temperature, 200 mL in the morning and in the afternoon for a total of 5 doses.

Painless lactation technique

Tanzhong, ruzhong, rugen, qimen, shaohai, chize, tianchi, tianxi, *etc* techniques can be used to massage the breast to remove the accumulated milk. Place the thumb and index finger of one hand at the junction of the black and white areola skin. Remove the front milk with the downward inward pressing method. Then apply massage oil to the hands, gently massage the milk block three times with the finger and towards to the nipple direction to discharge the milk. Massage each breast for 20-30 min using this method.



DOI: 10.12998/wjcc.v11.i8.1847 **Copyright** ©The Author(s) 2023.

Figure 1 Imaging examinations. A: August 30, 2022: Several hypoechoic nodules can be seen in the left breast, the larger ones are about 2.6 cm × 1.2 cm (in the direction of 8 points) and 1.3 cm × 1.0 cm (in the direction of 10 points); B: August 30, 2022: Several cystic nodules can be seen in the right breast, the larger size is about 0.4 cm × 0.4 cm (in the direction of 10 points), and the internal sound transmission is poor; C: September 5, 2022: Several hypoechoic masses can be seen in the left breast, the larger size is about 1.8 cm × 0.6 cm (in the direction of 10 points); D: September 12, 2022: Several hypoechoic masses can be seen in the left breast, the larger one is about 0.9 cm × 0.4 cm (in the direction of 10 points); E and F: September 27, 2022: Bilateral mammary glands have normal morphology.

OUTCOME AND FOLLOW-UP

On the return visit on September 1, 2022 the general fatigue had disappeared, and the patient's spirit improved significantly compared with the previous day. The swelling and pain of the left breast decreased significantly, and the pain of the right breast lump disappeared. The patient's VAS was 0. The patient's body temperature was 36.2 °C, and the left breast mass was significantly smaller than the previous day. Two hard masses with a size of about 2 cm × 2 cm were palpable, the skin was slightly red, and the right breast mass had disappeared. The patient received another painless lactation treatment, and no pyogenic milk was found in either breast. It was suggested that breastfeeding can be performed on both breasts. Another milk culture revealed *Staphylococcus epidermidis*.

On the follow-up visit on September 2, 2022 the swelling and pain of bilateral breasts mostly disappeared. The mass site on the left breast was slightly red, and there was no obvious fatigue or other discomforts. The patient's VAS was 0. The routine blood examination revealed WBC of 5.0 × 10^9/L, neutrophil percentage of 64.3%, lymphocyte percentage of 27.2%, CRP of 4.79 and PCT of < 0.02 mg/L. The bacterial milk culture was positive for *Staphylococcus epidermidis*.

Another ultrasound was conducted on September 5, 2022. Several hypoechoic masses were seen in the left breast, with a larger size of about 1.8 cm × 0.6 cm (in the direction of 10 o'clock) (Figure 1C). On September 9, 2022, the breast swelling and pain were barely noticeable. A 2 cm × 2 cm mass and a 1 cm × 1 cm mass were palpable on the left breast. The tenderness was not obvious, and the skin was slightly red. Seven doses of Chinese medicine were prescribed.

On September 12, 2022, a repeat ultrasound revealed several hypoechoic masses in the left breast, with a larger size of about 0.9 cm × 0.4 cm (in the direction of 10 o'clock) (Figure 1D). A return visit on September 16, 2022 (which was 40 d after the cesarean section), revealed that the breast pain disappeared (VAS 0). The patient's body temperature was 36.2 °C. A hard mass sized 1 cm × 1 cm was palpable in the left breast. No tenderness or color change were noticed. Seven more doses of Chinese medicine were prescribed.

At another return visit on September 23, 2022 (47 d after cesarean section), no breast pain or fatigue were reported (VAS 0). A mass sized 0.3 cm × 0.3 cm mass was palpable on the left breast, and it was soft and devoid of tenderness. The skin was not red. Five doses of traditional Chinese medicine were prescribed, and breast opening was performed once.

The ultrasound on September 27, 2022 revealed normal lactation (Figure 1E and F). At the return visit on September 30, 2022 (54 d after cesarean section), no discomfort such as breast swelling and pain were reported. The breast lump had disappeared, and there was no skin redness, swelling, heat or pain.

However, the patient had a common cold with a sore throat and coughing. Seven doses of Chinese medicine were subsequently prescribed. On October 7, 2022, the cold was cured, and there was no breast swelling, pain or lump.

Due to repeated positive bacterial culture findings, two boxes of azithromycin tablets and seven doses of traditional Chinese medicine were added. The return visit on October 17, 2022 revealed that the patient had no discomfort such as breast pain, fever and fatigue. The bacterial culture from the milk revealed *Staphylococcus epidermidis*. The treatment cycle was terminated because the patient had no symptoms and the routine blood test, CRP, PCT, and B-ultrasound were normal. See Table 1 for the results of bacteria culture in the milk.

After 2 mo of follow-up, the patient's condition had not relapsed. The infant did not suffer from fever, abdominal pain, diarrhea, abdominal distension, nausea, vomiting and other adverse reactions.

DISCUSSION

For the first 6 mo of life, the WHO recommends exclusive breastfeeding. Acute mastitis and breast abscess during lactation are regarded as the leading causes of unintentional weaning, preventing mothers from implementing exclusive nursing. Acute mastitis during lactation is a form of breast cellulitis affecting the interlobular connective tissue. The WHO defines the disease as "a state of breast inflammation, which may or may not be accompanied by infection"[1,5], which may lead to breast abscess and septic fever[6], and may directly lead to the cessation of breastfeeding. The disease can elicit breast pain locally and is frequently accompanied by fast developing systemic symptoms, such as fever, muscular pain, chills and fatigue[4].

In severe cases, the breast may be permanently scarred, and its occurrence rate ranges from 3% to 33%, with 4% to 11% developing breast abscesses[3]. If any of the following criteria is met, it is diagnosed as acute mastitis during lactation: (1) Local redness of breast, with or without temperature rise; (2) Systemic inflammatory reaction, such as chills, headache and fatigue; (3) Body temperature greater than 37.3 °C or the results of routine blood tests showed that WBC or neutrophils increased or the level of CRP increased; and (4) Patients with positive milk culture[7]. Breast abscess is defined as a local infection with fluid accumulation in breast tissue[8]. A physical examination can generally detect the pain, erythema and stiffness of the breast abscess. However, it is not always simple to palpate the lump, especially if it is positioned deep within a larger breast. Imaging studies are beneficial for breast abscess diagnosis, determining whether there are several small abscesses or a single defined cavity and determining whether the abscesses are located or separated so as to assist in treatment plan formulation [9].

A severe complication of acute mastitis during breastfeeding is breast abscess. The disease is associated with patient fatigue, pressure, blockage of the mammary duct, inadequate feeding times, oral abnormalities of infants (such as cleft lip or palate), local milk stasis, malnutrition of mothers, use of a manual breast suction device, community-acquired infection, breast injury and poor diet, as well as delayed treatment of acute mastitis[10]. It is usually caused by *Staphylococcus* infection caused by pathogenic bacteria such as *Streptococcus* and/or *Corynebacterium*[11]. Breastfeeding discontinuation (41.0%), breast fistula (11.1%) and readmission (50.0%) are prevalent among patients with the disease[4, 12]. In cases of breast abscess, the rate of cessation of nursing is 41.0%. In instances of breast fistula, the rate of cessation of nursing is very high (66.7%). In addition, 50% of postpartum *Staphylococcus aureus* breast abscess patients must be hospitalized again and administered intravenous antibiotics[12]. Consequently, the condition has a somewhat severe impact on mothers and infants and must be addressed promptly.

Breast abscess during lactation is often treated with antibiotics administered orally or intravenously, percutaneous aspiration (ultrasound-guided percutaneous puncture, fine needle puncture, vacuum-assisted biopsy, arthroscopic debridement and drainage, *etc.*[13-15]) and surgical incision and drainage [16] (Table 2). However, these procedures have limitations. Although antibiotics were empirically administered, it was later discovered that many isolated bacteria were antibiotic-resistant[17]; therefore, the potential threat of antibiotic resistance dramatically enhanced the need for alternative therapies.

Li *et al*[18] found 1222 cases of *Staphylococcus aureus* (82.5%) in 1481 cases of breast abscess in lactation by bacterial culture of abscess puncture fluid. Among them, 962 cases (65.0%) were methicillin-susceptible *Staphylococcus aureus*, 260 cases (17.6%) were methicillin-resistant *Staphylococcus aureus*, and 20 cases (1.4%) were *Staphylococcus epidermidis*. Drug sensitivity and resistance were analyzed in 260 strains of MRSA. It was found that 100% of MRSA was resistant to penicillin, amoxicillin clavulanate and cephalosporins, 45.0% of MRSA was resistant to tetracycline, 85.0% of MRSA was resistant to clindamycin, and 82.9% of MRSA was resistant to erythromycin. In most instances, when bacterial milk culture and drug sensitivity tests were performed for patients with breastfeeding mastitis and breast abscess, it was found that these bacteria were resistant to penicillin and cephalosporin antibiotics. Therefore, the actual therapeutic effect of antibiotics was poor.

Percutaneous aspiration, surgical incision and drainage are all surgical procedures. They have the following side effects: Influence of anesthesia on milk; separation of mother and baby; high cost; trauma

Table 1 The results of bacteria culture in the milk before/after administration and the resistance of penicillin and cephalosporin

Date	Before/after administration	Bacteria cultured in milk	Penicillin resistance	Cephalosporin resistance
August 31, 2022	Before	*Staphylococcus epidermidis*	Yes	Yes
September 2, 2022	After (Gualou Xiaoyong decoction)	*Staphylococcus epidermidis*	Yes	Yes
September 9, 2022	After (Gualou Xiaoyong decoction)	*Staphylococcus aureus*	Yes	Yes
September 16, 2022	After (Gualou Xiaoyong decoction)	*Staphylococcus aureus*	Yes	Yes
September 23, 2022	After (Gualou Xiaoyong decoction)	*Staphylococcus epidermidis*	Yes	Yes
September 30, 2022 (combined with cold)	After (Gualou Xiaoyong decoction)	*Staphylococcus aureus*	Yes	Yes
October 7, 2022 (add 2 boxes of azithromycin tablets)	Before (azithromycin tablets)	*Staphylococcus aureus*	Yes	Yes
October 17, 2022	After (azithromycin tablets)	*Staphylococcus epidermidis*	Yes	Yes

and pain of patients; cessation of breastfeeding; and leaving local scars on the breast, *etc*[19]. Therefore, the development of traditional Chinese medicine and traditional Chinese medicine therapy is recommended. In this instance, the combination of Gualou Xiaoyong decoction and painless breast opening manipulation resulted in favorable clinical outcomes for the treatment of breast abscess in lactation.

The Program Committee of the International Society of Nursing Medicine advises moms with breast abscesses to continue breastfeeding because there is no evidence that healthy breastfed infants are at risk when their mothers are infected (Amir and the Program Committee of the Society of Breastfeeding Medicine, 2014). In this case, we recommended temporary cessation of breastfeeding from one breast for 1 d when the patient discovered pus in the milk. We recommended that the patient continue breastfeeding in the subsequent treatment process. We believe that continued breastfeeding can reduce breast milk stasis, which is conducive to disease recovery, and infants have received sufficient breast milk nutrition during this practice as we have not found adverse effects in previous cases. In this case, there was also no adverse reaction of the infant, such as nausea, vomiting, abdominal pain, abdominal distension, diarrhea, fever, *etc.*

Postpartum breast abscess is a common and intractable disease in clinical practice. In this case, the patient received a non-invasive treatment. On the 2nd d of treatment, the breast mass of the patient was significantly reduced, the pain was significantly reduced, and the general asthenia was improved. All conscious symptoms disappeared after 3 d, the breast abscess disappeared after 12 d of treatment, and the inflammation imaging disappeared after 27 d of treatment. It was a relatively short treatment cycle for the treatment of breast abscess, and our treatment method was not traumatic. We only needed outpatient oral drug treatment, the patient did not need hospitalization and surgery, and she had no pain.

Pileri *et al*[19] and others reported that fine needle puncture was effective in the treatment of breast abscess. However, it often required multiple puncture treatments, and patients felt pain and trauma and often needed antibiotic treatment. However, through milk culture, we found that most of the bacteria in the milk were *Staphylococcus* and *Streptococcus*. These bacteria are often resistant to antibiotics (penicillin and cephalosporins) that could be used during lactation, so it is ineffective to use these two types of antibiotics. Aminoglycoside or quinolone antibiotics are often sensitive to this kind of bacteria, but these two kinds of drugs are not suitable for lactating women.

Through our clinical observation, we found that traditional Chinese medicine has a definite effect on the treatment of lactating mastitis and breast abscess. First, the patients with breast abscesses are still in lactation, and the milk continuously secreted by the breast will aggravate the breast abscess. Therefore, good lactation techniques are needed to solve the problem of milk stasis. Secondly, the traditional Chinese medicine Gualou Xiaoyong decoction has a good clinical effect through our clinical observation. After our clinical observation of more than 100 cases of lactation mastitis and 4 cases of breast abscess, we found that after the use of Gualou Xiaoyong decoction and painless lactation manipulation, the breast lump and pain of the patients disappeared quickly, the skin redness disappeared, the body temperature returned to normal, the WBC and the percentage of neutrophils returned to normal, and the changes of mastitis and breast abscess disappeared under B-ultrasound.

Table 2 Characteristics of similar cases

Ref.	Interventions	Population characteristics	Breastfeeding cessation rate	Outcome
Pileri *et al*[19], 2022	B-ultrasound guided fine needle puncture	13 of the 64 patients needed hospitalization, 4 cases of bilateral abscesses, 16 cases with the largest abscess diameter greater than 5 cm	The average breastfeeding time was 5 mo, and 40.6% of females with breast abscesses continued to breastfeed for more than 6 mo. 21 mothers stopped breastfeeding	All abscesses > 5 cm in diameter were positive for *Staphylococcus aureus*, 56% of which were antibiotic resistant. All patients received antibiotic treatment, 71.9% (46/64) of them underwent fine needle aspiration
Colin *et al*[29], 2019	The same as above, if necessary, VAB shall be used	92 lactating women, 105 abscesses in total, 82 of 92 patients (89%) had 1 abscess, 10 patients (11%) had 2 or more abscesses (range, 2-4 cm). 4 patients had bilateral abscesses	18% of women stop breastfeeding	A total of 202 ultrasound-guided fine-needle puncture operations were performed. The number of percutaneous punctures/aspirates per abscess ranged from 1% to 6.4% of patients failed puncture and received incision and drainage surgery
Elagili *et al*[30], 2007	The same as above, if necessary, abscessotomy shall be used	16 (53.3%) non-lactating women and 14 (46.7%) lactating women had abscess diameters ranging from 1 cm to 15 cm (median: 4 cm). The volume of pus was between 1 mL and 200 mL (median: 14 mL)	Breastfeeding was encouraged, but rates of continuing or stopping breastfeeding were not recorded	15 patients (50%) only needed one aspiration, 10 patients needed multiple aspiration, and 5 patients needed incision and drainage. Mean symptom duration was 11.63 d (range: 3-28 d)
Hagiya *et al*[31], 2014	Operative incision and drainage	A 27-year-old Japanese female presented with high fever, tender breast, red and swollen left breast 17 d after delivery	Stopped breastfeeding	Ceftriaxone, daptomycin, vancomycin and other antibiotics were used for intravenous drip successively. Surgical incision was performed to drain about 15 mL of purulent secretion. The patient was discharged on the 10th d and took clindamycin orally
Wang *et al*[32], 2013	VAB	40 cases of lactation and 30 cases of non-lactation breast abscess who failed to use antibiotics and/or needle aspiration	Stopped breastfeeding during drainage	The skin inflammation disappeared within 6 d in all patients (median: 3.02 ± 6.65 d)
Kang and Kim [15], 2016	Fine needle aspiration *vs* VAB	Fine needle aspiration in 25 patients with breast abscess and VAB in 19 patients with breast abscess	No information about breastfeeding	Compared with the VAB group, the cure rate of the needle aspiration group had no significant difference
Lou *et al* [13], 2022	Arthroscopic system	19 cases of breast abscess in lactation	1 patient with breast fistula stopped breastfeeding, the other 18 patients resumed breastfeeding within 2 wk, of which 13 patients resumed breastfeeding within 1 wk	All patients were cured and did not recur during the 6-mo follow-up period. 1 patient stopped breastfeeding due to milk fistula, and the rest were cured

VAB: Vacuum-assisted biopsy.

In the treatment of this case, after the patient's clinical symptoms subsided and the routine blood routine work, CRP, PCT and ultrasound returned to normal, the bacteria in the milk were still cultured (*Staphylococcus aureus* and *Staphylococcus epidermidis* were alternately cultured), leading us to hypothesize that there may be a disparity between the types and numbers of bacteria infecting the breast and the severity of the disease.

Carmichael and Dixon[20] and Fetherston[21] also reported that there was an inconsistency between the bacterial load and the severity of lactation mastitis and breast abscess. Compared to the infection itself, the immune system response to injury appeared to correlate more strongly with the severity of the sickness, and the bacteria were not sufficient to cause the disease on their own. In addition, mastitis is frequently characterized by an absence of dangerous bacteria, prompting some clinical researchers to suggest the terms "infectious" and "non-infectious" mastitis[22,23]. Many women with potentially harmful bacteria on their skin or breast milk will not develop mastitis. However, many mastitis-afflicted mothers do not have pathogenic bacteria in their milk[3]. It was expected that the recent Cochrane systematic review emphasized the uncertainty around the use of antimicrobial medicines in the treatment of mastitis in light of these findings. Therefore, the prophylactic use of antibiotics to prevent mastitis is ineffective[24], and there is not enough evidence to support the use of antibiotics to treat mastitis and breast abscesses[24]. According to some researchers, the host's inflammatory mediators are the primary cause of mastitis, and these same inflammatory mediators may contribute to inadequate breastfeeding in clinical and subclinical mastitis[25].

Gualou Xiaoyong decoction is an often-prescribed treatment regimen in our department. It has a highly effective clinical effect in the treatment of lactation mastitis and lactation breast abscesses. It is composed of the following drugs: Bupleurum chinense, pericarpium trichosanthis, fructus arctii, luffa, lobelia, dandelion, red peony root, herb, peach kernel, coix seed, red bean, angelica, fried atractylodes

macrocephala, honeysuckle and forsythia suspensa. In the prescription, bupleurum and trichosanthes peel are used to soothe the liver and regulate qi. Stir fried atractylodes macrocephala with bran strengthens the spleen and stomach. Arctium lappa L, scutellaria barbata L, dandelion, honeysuckle, forsythia suspensa L, angelica, paeonia lactiflora and peach kernel cool the blood, nourish the blood, promote blood circulation and remove blood stasis. Coix seed and adzuki bean detoxify and discharge pus. The entire prescription has the effects of soothing the liver and stomach, dispersing phlegm, softening the body, eliminating heat, detoxification and pus and dredging the breast.

Wu *et al*[26] studied the Trichosanthes and Arctium decoction (containing 12 Chinese medicines, including trichosanthes kirilowii, arctium fruit, trichosanthes root, scutellaria baicalensis, cape jasmine, forsythia, honeysuckle, licorice, dried tangerine peel, green tangerine orange peel, radix bupleuri, which are similar to the Gualou Xiaoyong decoction in this study), and found that quercetin, luteolin, fisetin, kaempferol and urushiflavin are the main active ingredients. Quercetin has anti-inflammatory, antioxidant and antifungal properties and can inhibit nuclear factor-kappa B (NF-κB) signaling pathway to enhance the transcriptional activity of NRF2-ARE, thus playing a role in controlling bovine mastitis. It can reduce the expression of inducible nitric oxide synthase and regulate the production of inflammatory precursor nitric oxide.

Luteolin has a significant systemic anti-inflammatory effect. It can regulate the toll-like receptor 2 and toll-like receptor 4 signal pathways induced by *Staphylococcus aureus* and inhibit IκBα and NF-κB. The phosphorylation of BP65 regulates the expression of matrix metallopeptidase 2 and matrix metallopeptidase 9 and prevents mastitis. Fisetin is widely used to regulate the long-term immune imbalance of human inflammation, which can activate SIRT1 and inhibit NF-κB activation of inflammatory pathways, thereby reducing tumor necrosis factor α and interleukin 6 expression levels to control the occurrence of inflammation.

Kaempferol can reduce interleukin 6, tumor necrosis factor and the expression of ANGPTL2 in cells to prevent the occurrence of mastitis in mice. It can inhibit NF-κB phosphorylation and the BP65 subunit IκBα, thus playing a therapeutic role in mastitis. Urushiflavin has a good anti-inflammatory effect on nephritis, endometritis and airway inflammation *in vivo* and inflammatory skin disease *in vitro*. Ye *et al*[27] found that the extract from scutellaria baicalensis georgi-safflower-dandelion-honeysuckle had a dose-dependent antibacterial effect on *Staphylococcus aureus*, *Escherichia coli* and *Streptococcus agalactis*.

Milk buildup is a significant factor in the incidence of mastitis during breastfeeding. The collected milk not only causes breast pain and discomfort and a decrease in milk volume but is also an excellent medium for bacterial growth, exacerbating and recurring breast inflammation[28]. Therefore, it is essential to empty the breast entirely. The non-painful breast opening method has a speedy impact, and the patient experiences no discomfort or negative effects. This technique combines the massage of distant acupoints along the meridians with local breast massage, which has a positive effect on breast opening. With the help of the Gualou Xiaoyong decoction, it can soothe the liver and stomach, expel phlegm, soften and firm the body, clear away heat, detoxify and expel pus and promote lactation. The patients' clinical symptoms greatly decrease and diminish within a short time. The total amount of leukocytes, neutrophils, CRP, PCT and other inflammatory markers rapidly return to normal, and the flaky, low-echo region of the breast dissipates rapidly with ultrasound. Therefore, we consider this method to be a superior means of treating the disease and deserving of further clinical investigation.

CONCLUSION

The combination of Gualou Xiaoyong decoction and painless breast opening manipulation has a positive clinical effect on breast abscess during lactation and has the advantages of a short treatment course, no effect on milk secretion, no effect on breastfeeding, no toxic side effects and no pain for patients. This method is worthy of further investigation.

FOOTNOTES

Author contributions: Jin LH, Ye HJ and Zheng HL conducted the studies, participated in collecting data and drafted the manuscript; Lin YX, Yang Y, Liu JL and Li RL drafted the manuscript; All authors read and approved the final manuscript.

Supported by Zhejiang Traditional Chinese Medicine Science and Technology Plan, No. 2023ZL449.

Informed consent statement: The patient provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors report having no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Li-Hua Jin 0000-0002-6595-2737; Hui-Ling Zheng 0000-0001-6978-9597; Hui-Jun Ye 0000-0002-9401-6796.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

REFERENCES

1 **World Health Organization (WHO)**. Global strategy for infant and young child feeding. Geneva: WHO, 2003. Available from: https://www.who.int/
2 **NHMRC**. Infant Feeding Guidelines. Canberra: National Health and Medical Research Council; 2012
3 **World Health Organization (WHO)**. Mastitis: Causes and management. Geneva, Switzerland: WHO, 2000. Available from: https://www.who.int/
4 **Ingman WV**, Glynn DJ, Hutchinson MR. Inflammatory mediators in mastitis and lactation insufficiency. *J Mammary Gland Biol Neoplasia* 2014; **19**: 161-167 [PMID: 24961655 DOI: 10.1007/s10911-014-9325-9]
5 **Foxman B**, D'Arcy H, Gillespie B, Bobo JK, Schwartz K. Lactation mastitis: occurrence and medical management among 946 breastfeeding women in the United States. *Am J Epidemiol* 2002; **155**: 103-114 [PMID: 11790672 DOI: 10.1093/aje/155.2.103]
6 **Patel SH**, Vaidya YH, Patel RJ, Pandit RJ, Joshi CG, Kunjadiya AP. Culture independent assessment of human milk microbial community in lactational mastitis. *Sci Rep* 2017; **7**: 7804 [PMID: 28798374 DOI: 10.1038/s41598-017-08451-7]
7 **Li D**, Li J, Yuan Y, Zhou J, Xiao Q, Yang T, Li Y, Jiang L, Gao H. Risk factors and prognosis of acute lactation mastitis developing into a breast abscess: A retrospective longitudinal study in China. *PLoS One* 2022; **17**: e0273967 [PMID: 36048839 DOI: 10.1371/journal.pone.0273967]
8 **Haifeng G**, Yi Z, Ying C, Xin L, Yan L, Songtao D, Yajun G, Xiangping H, Si C, Xingxing L. Exploring the Efficacy of Comprehensive Management of Breast Abscesses in Restoring Milk Volume. *J Hum Lact* 2022; **38**: 171-176 [PMID: 33818190 DOI: 10.1177/08903344211005400]
9 **Jackson VP**. The role of US in breast imaging. *Radiology* 1990; **177**: 305-311 [PMID: 2217759 DOI: 10.1148/radiology.177.2.2217759]
10 **Spencer JP**. Management of mastitis in breastfeeding women. *Am Fam Physician* 2008; **78**: 727-731 [PMID: 18819238]
11 **Lawrence RA**, Lawrence RM. Breastfeeding: a guide for the medical profession. 6th ed. St. Louis: Elsevier Mosby, 2005
12 **Branch-Elliman W**, Lee GM, Golen TH, Gold HS, Baldini LM, Wright SB. Health and economic burden of post-partum Staphylococcus aureus breast abscess. *PLoS One* 2013; **8**: e73155 [PMID: 24039877 DOI: 10.1371/journal.pone.0073155]
13 **Lou L**, Ma W, Liu X, Shen H, Wang H, Lv H. Application of arthroscopic system in the treatment of lactational breast abscess. *BMC Surg* 2022; **22**: 397 [PMID: 36401263 DOI: 10.1186/s12893-022-01845-z]
14 **Dixon JM**. Breast infection. *BMJ* 2013; **347**: f3291
15 **Kang YD**, Kim YM. Comparison of needle aspiration and vacuum-assisted biopsy in the ultrasound-guided drainage of lactational breast abscesses. *Ultrasonography* 2016; **35**: 148-152 [PMID: 26753603 DOI: 10.14366/usg.15041]
16 **Lam E**, Chan T, Wiseman SM. Breast abscess: evidence based management recommendations. *Expert Rev Anti Infect Ther* 2014; **12**: 753-762 [PMID: 24791941 DOI: 10.1586/14787210.2014.913982]
17 **Chuwa EW**, Wong CM, Tan YY, Hong GS. MRSA breast abscesses in postpartum women. *Asian J Surg* 2009; **32**: 55-58 [PMID: 19321404 DOI: 10.1016/S1015-9584(09)60010-5]
18 **Li Y**, Ma XJ, He XP. Clinical characteristics of lactational breast abscess caused by methicillin-resistant Staphylococcus aureus: hospital-based study in China. *Int Breastfeed J* 2021; **16**: 80 [PMID: 34641942 DOI: 10.1186/s13006-021-00429-6]
19 **Pileri P**, Sartani A, Mazzocco MI, Giani S, Rimoldi S, Pietropaolo G, Pertusati A, Vella A, Bazzi L, Cetin I. Management of Breast Abscess during Breastfeeding. *Int J Environ Res Public Health* 2022; **19** [PMID: 35565158 DOI: 10.3390/ijerph19095762]
20 **Carmichael AR**, Dixon JM. Is lactation mastitis and shooting breast pain experienced by women during lactation caused by Candida albicans? *Breast* 2002; **11**: 88-90 [PMID: 14965651 DOI: 10.1054/brst.2001.0313]
21 **Fetherston C**. Mastitis in lactating women: physiology or pathology? *Breastfeed Rev* 2001; **9**: 5-12 [PMID: 11424519]
22 **Thomsen AC**, Espersen T, Maigaard S. Course and treatment of milk stasis, noninfectious inflammation of the breast, and infectious mastitis in nursing women. *Am J Obstet Gynecol* 1984; **149**: 492-495 [PMID: 6742017 DOI: 10.1016/0002-9378(84)90022-x]
23 **Thomsen AC**, Hansen KB, Møller BR. Leukocyte counts and microbiologic cultivation in the diagnosis of puerperal mastitis. *Am J Obstet Gynecol* 1983; **146**: 938-941 [PMID: 6688325 DOI: 10.1016/0002-9378(83)90969-9]
24 **Crepinsek MA**, Taylor EA, Michener K, Stewart F. Interventions for preventing mastitis after childbirth. *Cochrane Database Syst Rev* 2020; **9**: CD007239 [PMID: 32987448 DOI: 10.1002/14651858.CD007239.pub4]
25 **Jahanfar S**, Ng CJ, Teng CL. Antibiotics for mastitis in breastfeeding women. *Cochrane Database Syst Rev* 2013;

CD005458 [PMID: 23450563 DOI: 10.1002/14651858.CD005458.pub3]
26 **Wu Z**, Yang Q, Ma H. Study the Mechanism of Gualou Niubang Decoction in Treating Plasma Cell Mastitis Based on Network Pharmacology and Molecular Docking. *Biomed Res Int* 2022; **2022**: 5780936 [PMID: 35757473 DOI: 10.1155/2022/5780936]
27 **Ye D**, Sun J, Li Y. Evaluation of Toxicity, Bacteriostatic, Analgesic, Anti-Inflammatory, and Antipyretic Activities of Huangqin-Honghua-Pugongying-Jinyinhua Extract. *Vet Sci* 2021; **8** [PMID: 34941857 DOI: 10.3390/vetsci8120330]
28 **Omranipour R**, Vasigh M. Mastitis, Breast Abscess, and Granulomatous Mastitis. *Adv Exp Med Biol* 2020; **1252**: 53-61 [PMID: 32816262 DOI: 10.1007/978-3-030-41596-9_7]
29 **Colin C**, Delov AG, Peyron-Faure N, Rabilloud M, Charlot M. Breast abscesses in lactating women: evidences for ultrasound-guided percutaneous drainage to avoid surgery. *Emerg Radiol* 2019; **26**: 507-514 [PMID: 31154537 DOI: 10.1007/s10140-019-01694-z]
30 **Elagili F**, Abdullah N, Fong L, Pei T. Aspiration of breast abscess under ultrasound guidance: outcome obtained and factors affecting success. *Asian J Surg* 2007; **30**: 40-44 [PMID: 17337370 DOI: 10.1016/S1015-9584(09)60126-3]
31 **Hagiya H**, Shiota S, Sugiyama W, Otsuka F. Postpartum breast abscess caused by community-acquired methicillin-resistant Staphylococcus aureus in Japan. *Breastfeed Med* 2014; **9**: 45-46 [PMID: 24050119 DOI: 10.1089/bfm.2013.0057]
32 **Wang K**, Ye Y, Sun G, Xu Z. The Mammotome biopsy system is an effective treatment strategy for breast abscess. *Am J Surg* 2013; **205**: 35-38 [PMID: 23036601 DOI: 10.1016/j.amjsurg.2012.05.012]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1857-1861

DOI: 10.12998/wjcc.v11.i8.1857

ISSN 2307-8960 (online)

CASE REPORT

Treatment of a large area perioral viral herpes infection following noninvasive ventilation: A case report

A-Mao Tang, Jia-Ying Xu, Rong Wang, Yi-Min Li

Specialty type: Health care sciences and services

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: Amlak BT, Ethiopia; Chiu H, Taiwan

Received: December 11, 2022
Peer-review started: December 11, 2022
First decision: January 9, 2023
Revised: January 14, 2023
Accepted: February 22, 2023
Article in press: February 22, 2023
Published online: March 16, 2023

A-Mao Tang, Jia-Ying Xu, Rong Wang, Department of Digestion, The Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou 310000, Zhejiang Province, China

Yi-Min Li, Department of Nursing, The Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou 310006, Zhejiang Province, China

Corresponding author: Yi-Min Li, MBBS, Chief Nurse, Department of Nursing, The Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, No. 261 Huansha Road, Shangcheng District, Hangzhou 310006, Zhejiang Province, China. hlb54316@163.com

Abstract

BACKGROUND

Alphaherpesvirus belongs to the Herpesviridae family and has large, monopartite double-stranded linear DNA. It mainly infects the skin, mucosa, and nerves, and can affect various hosts, including humans and other animals. Here, we present a case of a patient seen by the gastroenterology department at our hospital who experienced an oral and perioral herpes infection following treatment with a ventilator. The patient was treated with oral and topical antiviral drugs, furacilin, oral and topical antibiotics, local epinephrine injection, topical thrombin powder, and nutritional and supportive care. A wet wound healing approach was also implemented with good response.

CASE SUMMARY

A 73-year-old woman presented to the hospital with a chief complaint of "abdominal pain for 3 d with dizziness for 2 d." She was admitted to the intensive care unit for septic shock and spontaneous peritonitis secondary to cirrhosis and was given antiinflammatory and symptomatic supportive treatment. A ventilator was used to assist breathing for acute respiratory distress syndrome, which developed during her admission. A large area of herpes infection appeared in the perioral region 2 d following noninvasive ventilation. The patient was transferred to the gastroenterology department, at which time she had a body temperature of 37.8 C and a respiratory rate of 18/min. The patient's con-sciousness was intact, and she no longer had abdominal pain or distension, chest tightness, or asthma. At this point, the infected perioral region changed in appearance and was now accompanied by local bleeding with crusting of blood at the wounds. The surface area of the wounds measured approximately 10 cm × 10 cm. A cluster blisters appeared on the patient's right neck, and ulcers developed in her mouth. On a

subjective numerical pain scale, the patient reported a pain level of 2. Overall, her diagnoses other than the oral and perioral herpes infection included: (1) Septic shock; (2) spontaneous peritonitis; (3) abdominal infection; (4) decompensated cirrhosis; and (5) hypoproteinemia. Dermatology was consulted regarding the treatment of the patient's wounds; they suggested treatment with oral antiviral drugs, an intramuscular injection of nutritious nerve drugs, and the application of topical penciclovir and mupirocin around the lips. Stomatology was also consulted and suggested the use of nitrocilin in a local wet application around the lips.

CONCLUSION
Through multidisciplinary consultation, the patient's oral and perioral herpes infection was successfully treated with the following combined approach: (1) Application of topical antviral and antibiotic treatments; (2) keeping the wound moist with a wet wound healing strategy; (3) systemic use of oral antiviral drugs; and (4) symptomatic and nutritional supportive care. The patient was discharged from the hospital after successful wound healing.

Key Words: Ventilator; Viral herpes; Nursing care; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Herpes simplex virus can be latent in the sensory ganglia of the host and reactivate periodically, resulting in recurrent herpes infection. The patient presented in this case report achieved good recovery after multidisciplinary consultation, treatment of the viral infection with oral and topical administration of antiviral drugs, the anti-inflammatory effect of furacilin, hemostasis with local epinephrine injection and application of thrombin lyophilized powder, and the use of a wet wound healing approach.

Citation: Tang AM, Xu JY, Wang R, Li YM. Treatment of a large area perioral viral herpes infection following noninvasive ventilation: A case report. *World J Clin Cases* 2023; 11(8): 1857-1861
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1857.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1857

INTRODUCTION

Alphaherpesvirus belongs to the Herpesviridae family, and has a relatively large, monopartite, double-stranded linear deoxyribonucleic acid (DNA). It mainly infects the skin, mucosa, and nerves, and can affect various hosts including humans and other animals. Here, we present the case of a patient seen by the gastroenterology department at our hospital who experienced an oral and perioral herpes infection following noninvasive ventilation during admission to the intensive care unit (ICU)[1]. The patient was treated with topical and oral antiviral and antibacterial drugs, uracil, hemostatic measures, and nutritional and supportive care[2,3]. A wet wound healing approach was also implemented with good results.

CASE PRESENTATION

Chief complaints

Following noninvasive ventilation in the ICU, a 73-year-old female patient developed an oral and perioral herpes infection.

History of present illness

A large wound developed around the patient's lips and in her mouth 2 d after noninvasive ventilation during admission to the ICU for management of decompensated cirrhosis complicated by abdominal infection, spontaneous peritonitis, hypoproteinemia, acute respiratory distress syndrome (ARDS) and septic shock.

History of past illness

The patient initially presented to the hospital with a 3-d history of abdominal pain accompanied by 2 d of dizziness. She was admitted to the ICU, where she was found to have decompensated cirrhosis complicated by abdominal infection, spontaneous peritonitis, hypoproteinemia, ARDS, and septic

shock. She was treated with noninvasive ventilation for management of ARDS.

Personal and family history

The patient did not have any pertinent personal or family medical history.

Physical examination

The patient was transferred to the gastroenterology department for further management. At this point, her consciousness was intact and she had no ongoing abdominal pain or distension, no chest tightness, and no asthma. The perioral wound progressed to exhibit local bleeding with crusting of blood, and measured approximately 10 cm × 10 cm.

Laboratory examinations

The following laboratory values were observed in the patient at the time of transfer to gastroenterology: Prothrombin time 15.9 sec; partial thromboplastin time 34.5 sec; albumin 27.9 g/L; alanine aminotransferase 56 U/L; total bilirubin 129.4 μmol/L; neutrophils 79.2%; hemoglobin 87 g/L; platelet count 48 × 10^9/L; and high sensitivity C-reactive protein 77 mg/L.

MULTIDISCIPLINARY EXPERT CONSULTATION

Dermatology was consulted regarding treatment of the patient's perioral wounds; they suggested treatment with oral antiviral drugs, intramuscular injection of nutritious nerve drugs, and application of topical penciclovir and mupirocin around the lips. Stomatology was also consulted, and they suggested wet application of topical nitrocilin around the lips.

FINAL DIAGNOSIS

Perioral herpes infection secondary to noninvasive ventilation.

TREATMENT

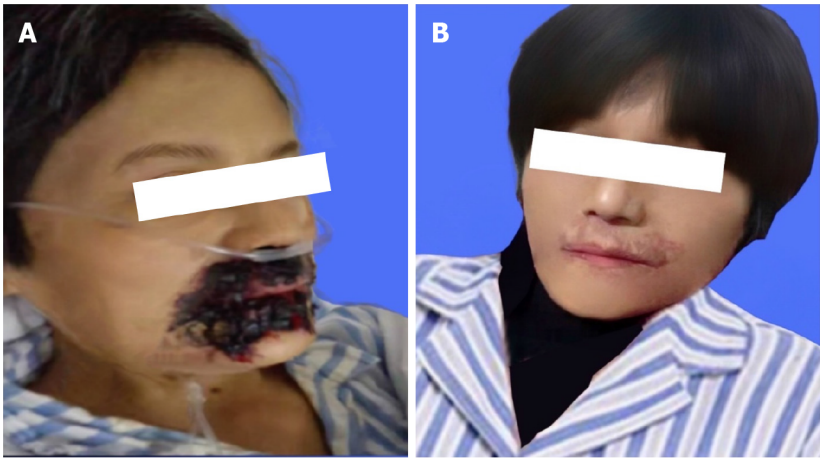
The patient achieved good recovery after multidisciplinary consultation and treatment including oral and topical antiviral and antibiotic administration, nutritional and symptomatic supportive care, the anti-inflammatory effect of furacilin, hemostasis with local epinephrine injection and application of topical thrombin lyophilized powder, and the use of a wet wound healing approach.

OUTCOME AND FOLLOW-UP

Following treatment, the patient's wound fully healed and she was discharged from the hospital. The perioral wound before and after treatment is depicted in Figure 1.

DISCUSSION

Herpes simplex virus (HSV) can be latent in the sensory ganglia of the host and reactivate periodically, resulting in recurrent infection. Herpes infection is characterized histologically by epidermal blistering and necrosis and the presence of multinucleated epithelial giant cells, eosinophilic intranuclear inclusions, and significant neutrophilic and lymphocytic inflammatory infiltrate[4]. An immune response can be stimulated immediately by HSV infection, and, if so, lesions are typically limited to the skin surface and mucous membranes. However, when HSV infection occurs in newborns with immature immune function or people with immune deficiency (*i.e.* in the settings of organ transplantation, immunosuppressant use, or anti-tumor treatment), herpes can spread throughout body to infect the brain, liver, lung, eye, adrenal gland, skin and mucous membranes, and other various sites. Herpes infection in an immunocompromised setting is serious and carries a high mortality rate[5-7]. When the skin has extensive damage, such with eczema or burns, HSV often manifests as generalized infection of skin the and mucous membranes and can cause disseminated lesions. The patient in the present report had a large perioral wound measuring 10 cm × 10 cm accompanied by bleeding, difficulty opening the mouth, pain, and changes in self-image. After consultation, the cause of the patient's wound was identified as herpes infection. The wound was effectively managed with antiviral



DOI: 10.12998/wjcc.v11.i8.1857 **Copyright** ©The Author(s) 2023.

Figure 1 Perioral wound due to herpes infection, before and after treatment. A-B: Herpes infection causing large wound around the lips before (A) and after (B) medical treatment and wet wound care.

treatment, the anti-inflammatory effect of furacilin, and local hemostatic therapy. Additionally, a wet wound healing approach was implemented, and, through keeping the wound moist, healing was achieved.

One of the antiviral medications used in the management of the patient's perioral herpes infection was topical penciclovir. Penciclovir is a nucleoside antiviral drug that inhibits HSV types I and II and can be administered topically with a cream. The antibacterial medication mupirocin is suitable for skin infection caused by Gram-positive cocci, and is used to treat primary skin infections, pustulosis, furuncle, folliculitis, and infections secondary to eczema[8,9]. Furacilin can interfere with bacterial glucose metabolism and the oxidase function to cause bacteriostasis or sterilization[10]. This drug has a broad spectrum of antibacterial activity, and is effective against various Gram-positive and anaerobic pathogenic bacteria; however, it not as effective in the treatment of infections caused by *Pseudomonas aeruginosa, Proteus* spp., or *Pneumococcus* spp.[11,12]. It is also ineffective against fungi and molds, but it is still effective against bacterial infections secondary to mold[13].

Epinephrine injection can cause constriction of small arteries with a less potent effect on veins, and is especially effective on the small vessels of the skin and mucosae. Lyophilized thrombin powder is also used for hemostasis of small blood vessels, gastrointestinal bleeding, and traumatic bleeding that is not amenable to surgical ligation. Epinephrine and lyophilized thrombin powder can function well in achieving local hemostasis, and according to the wet healing theory, this combination is more likely to reduce the potential cost associated with the use of advanced wound dressings. This is accomplished *via* the promotion of wound healing by keeping the wound wet and has been associated with faster healing rates[14]. In the present case, we used a nitrofurazone dressing with regular dressing change. Also, a gentle dressing change technique was used to prevent injury to the healing skin.

Finally, with respect to the psychology of the patient and her family, we used a gradual communication strategy. This strategy facilitated cooperation between the patient and her family and medical staff, which we believe improved the treatment outcome and promoted her ongoing rehabilitation.

CONCLUSION

This case report shares valuable experience in the clinical management of perioral herpes infection following noninvasive ventilation. There are few reports in the literature describing an effective treatment plan with respect to such a case. In the present case, the patient's wound healed after administration of oral and topical antiviral medications, furacilin, local epinephrine and topical thrombin powder, and a wet wound healing approach with no observed adverse reactions or toxic side effects. In patients managed with noninvasive ventilation, nursing and supportive staff should be aware of the signs of perioral herpes infection, including unusual pain with or without associated wounds of the skin around the mouth. The treatment regimen described in this case report was effective in accelerating the wound healing process and eradicating local herpes infection. Therefore, in patients who develop HSV infection following noninvasive ventilation, the authors suggest that the pharmacological and wound care measures applied here should be pursued.

FOOTNOTES

Author contributions: Tang AM designed the research study; Xu JY and Wang R performed the research; Li YM analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

Supported by the Construction Fund of Key Medical Disciplines of Hangzhou, No. OO20200265; the Basic Public Welfare Research Project of Zhejiang Province, No. LGF22H250005; General project of Hangzhou Health Science and Technology Plan, No. A20200320; and Zhejiang Provincial Medical and Health Technology Project, No. 2020PY016.

Informed consent statement: The patient provided informed written consent for the publication of this case report.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Jia-Ying Xu 0000-0001-9550-0857; Rong Wang 0000-0003-2806-0382; Yi-Min Li 0000-0002-2777-4458.

S-Editor: Liu JH
L-Editor: Filipodia
P-Editor: Liu JH

REFERENCES

1 **Ahlström MG**, Omland LH, Ronit A, Obel N. Immortal time bias: a possible explanation for "Impact of acyclovir use on survival of patients with ventilator-associated pneumonia and high load herpes simplex virus replication". *Crit Care* 2020; **24**: 355 [PMID: 32552904 DOI: 10.1186/s13054-020-03073-4]
2 **Schuierer L**, Gebhard M, Ruf HG, Jaschinski U, Berghaus TM, Wittmann M, Braun G, Busch DH, Hoffmann R. Impact of acyclovir use on survival of patients with ventilator-associated pneumonia and high load herpes simplex virus replication. *Crit Care* 2020; **24**: 12 [PMID: 31924246 DOI: 10.1186/s13054-019-2701-5]
3 **Coisel Y**, Bousbia S, Forel JM, Hraiech S, Lascola B, Roch A, Zandotti C, Million M, Jaber S, Raoult D, Papazian L. Cytomegalovirus and herpes simplex virus effect on the prognosis of mechanically ventilated patients suspected to have ventilator-associated pneumonia. *PLoS One* 2012; **7**: e51340 [PMID: 23236477 DOI: 10.1371/journal.pone.0051340]
4 **Bouza E**, Giannella M, Torres MV, Catalán P, Sánchez-Carrillo C, Hernandez RI, Muñoz P; Gregorio Marañón Task Force for Pneumonia. Herpes simplex virus: a marker of severity in bacterial ventilator-associated pneumonia. *J Crit Care* 2011; **26**: 432.e1-432.e6 [PMID: 21129912 DOI: 10.1016/j.jcrc.2010.10.008]
5 **Cunha BA**, Chak A, Durie N. Herpes simplex virus-1 Late-onset ventilator-associated pneumonia: the importance of cytopathologic diagnosis. *Am J Infect Control* 2010; **38**: 249-250 [PMID: 20347638 DOI: 10.1016/j.ajic.2009.08.013]
6 **Aldrak N**, Alsaab S, Algethami A, Bhere D, Wakimoto H, Shah K, Alomary MN, Zaidan N. Oncolytic Herpes Simplex Virus-Based Therapies for Cancer. *Cells* 2021; **10** [PMID: 34207386 DOI: 10.3390/cells10061541]
7 **Uche IK**, Kousoulas KG, Rider PJF. The Effect of Herpes Simplex Virus-Type-1 (HSV-1) Oncolytic Immunotherapy on the Tumor Microenvironment. *Viruses* 2021; **13** [PMID: 34206677 DOI: 10.3390/v13071200]
8 **Nath P**, Kabir MA, Doust SK, Ray A. Diagnosis of Herpes Simplex Virus: Laboratory and Point-of-Care Techniques. *Infect Dis Rep* 2021; **13**: 518-539 [PMID: 34199547 DOI: 10.3390/idr13020049]
9 **Enescu CD**, Utz Petry S, Nartker N, Moossavi M. Treatment of acyclovir-resistant herpes simplex virus with intralesional cidofovir. *JAAD Case Rep* 2021; **13**: 86-89 [PMID: 34189219 DOI: 10.1016/j.jdcr.2021.05.001]
10 **Cherenko TM**, Turchyna NS, Heletiuk YL, Andriushkova NG, Kuzminska OV. Seasonal factor and frequency of detection of herpes viruses and influenza virus in patients with ischemic stroke. *Wiad Lek* 2021; **74**: 923-928 [PMID: 34156005]
11 **Wong A**, Rawson RV, Templeton DJ. Herpes simplex virus-2 (HSV-2) pseudotumour as the initial presentation of human immunodeficiency virus infection. *Intern Med J* 2021; **51**: 1001-1002 [PMID: 34155762 DOI: 10.1111/imj.15364]
12 **Eisenstein LE**, Cunha BA. Herpes simplex virus pneumonia presenting as failure to wean from a ventilator. *Heart Lung* 2003; **32**: 65-66 [PMID: 12571550 DOI: 10.1067/mhl.2003.4]
13 **Paul A**, Ghose A. Herpes simplex virus-1 oesophagitis presenting with persistent hiccough in an immunocompetent host: A case report. *Trop Doct* 2021; **51**: 601-602 [PMID: 34152226 DOI: 10.1177/00494755211022519]
14 **de Laat EH**, van den Boogaard MH, Spauwen PH, van Kuppevelt DH, van Goor H, Schoonhoven L. Faster wound healing with topical negative pressure therapy in difficult-to-heal wounds: a prospective randomized controlled trial. *Ann Plast Surg* 2011; **67**: 626-631 [PMID: 21629111 DOI: 10.1097/SAP.0b013e31820b3ac1]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1862-1868

DOI: 10.12998/wjcc.v11.i8.1862

ISSN 2307-8960 (online)

CASE REPORT

Gastroparesis after video-assisted thoracic surgery: A case report

Hang An, Yu-Cun Liu

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

P-Reviewer: Al-Ani RM, Iraq; Rosboch GL, Italy

Received: January 7, 2023
Peer-review started: January 7, 2023
First decision: January 17, 2023
Revised: January 19, 2023
Accepted: February 21, 2023
Article in press: February 21, 2023
Published online: March 16, 2023

Hang An, Yu-Cun Liu, Department of General Surgery, Peking University First Hospital, Beijing 100034, China

Corresponding author: Yu-Cun Liu, MD, Professor, Department of General Surgery, Peking University First Hospital, No. 8 Xishiku Street, Beijing 100034, China.
2011110327@bjmu.edu.cn

Abstract

BACKGROUND

Video-assisted thoracic surgery (VATS) lobectomy is a common treatment for patients with early-stage lung cancer. Some patients can experience slight gastrointestinal discomfort after lobectomy for a moment. Gastroparesis is a gastrointestinal disorder that can be severe; it is associated with an increased risk of aspiration pneumonia and impaired postoperative recovery. Here, we report a rare case of gastroparesis after VATS lobectomy.

CASE SUMMARY

A 61-year-old man underwent VATS right lower lobectomy uneventfully but had an obstruction of the upper digestive tract 2 d after surgery. Acute gastroparesis was diagnosed after emergency computed tomography and oral iohexol X-ray imaging. After gastrointestinal decompression and administration of prokinetic drugs, the patient's gastrointestinal symptoms improved. Since perioperative medication was applied according to the recommended dose and there was no evidence of electrolyte imbalance, intraoperative periesophageal vagal nerve injury was the most likely underlying cause of gastroparesis.

CONCLUSION

Although gastroparesis is a rare perioperative complication following VATS, clinicians should be on the alert when patients complain about gastrointestinal discomfort. When surgeons resect paraesophageal lymph nodes with electrocautery, excessive ambient heat and compression of paraesophageal hematoma might induce vagal nerve dysfunction.

Key Words: Gastroparesis; Delayed gastrointestinal emptying; Video-assisted thoracic surgery; Lobectomy; Thoracic surgery; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: While postoperative gastroparesis is quite common in patients undergoing vagotomy for peptic ulcers and pylorus-sparing pancreatoduodenectomy, there are few reports following lobectomy. We report a rare case of gastroparesis after video-assisted thoracoscopic surgery. Since there was no evidence of drug-induced or electrocyte disorder-related gastrointestinal dysfunction, intraoperative periesophageal vagal nerve injury was most likely to account for gastroparesis. Clinicians should keep in mind that there is a potential possibility of vagal nerve injury after thoracic surgery even without direct nerve operation. For patients suffering gastroparesis after video-assisted thoracic surgery, conservative treatment, including gastrointestinal decompression and prokinetic medicines, can help relieve symptoms.

Citation: An H, Liu YC. Gastroparesis after video-assisted thoracic surgery: A case report. *World J Clin Cases* 2023; 11(8): 1862-1868
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1862.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1862

INTRODUCTION

According to the Global Cancer Statistics 2020 report, lung cancer is one of most common cancers worldwide, with an estimated 2.2 million new cases in 2020 and making up 11.4% of all cancer cases[1]. Curative surgery is the preferred treatment approach for patients with early-stage lung cancer. Over the past two decades, video-assisted thoracic surgery (VATS) has become an alternative to open thoracotomy with the advantage of being minimally invasive[2]. Compared with open thoracotomy, patients receiving VATS tend to experience less postoperative pain and fewer complications, and VATS has been indicated to have comparable or superior oncologic outcomes to thoracotomy[2,3]. A retrospective study carried out in China showed that the VATS rate for lung cancer was 47.6% nationwide, and in some hospitals, the rate even reached 89.7%[4]. The most common complications following VATS are prolonged air leakage, bleeding, infection and postoperative pain[5]; few patients experience gastrointestinal disorders after surgery[6,7].

Gastroparesis is an annoying gastrointestinal disorder associated with symptoms such as epigastric discomfort, abdominal pain, nausea, vomiting, and bloating. While postoperative gastroparesis is quite common in patients undergoing vagotomy for peptic ulcers and pylorus-sparing pancreatoduodenectomy, there are few case reports demonstrating delayed gastrointestinal emptying following pulmonary lobectomy. Here, we report a case of gastroparesis after VATS lobectomy.

CASE PRESENTATION

Chief complaints

A 61-year-old man complained about early satiety and postprandial fullness 2 d after VATS right lower lobectomy.

History of present illness

The patient drank clear fluid 2 h after VATS and had his first meal the next morning after surgery, which was in line with routine care in our hospital. At first, he complained about early satiety and postprandial fullness after eating food. Two days after surgery, gastrointestinal symptoms were aggravated, as the patient appeared to have upper abdominal pain and vomited a large amount of yellow-green fluid. During the process of the disease, exhaust and defecation were not impeded.

History of past illness

He presented to our hospital with coughing for the past three months. He had a chest computed tomography (CT) one month before, which showed a 6.0 cm × 4.4 cm mass in the right lower lobe of the lung with hilar and mediastinal lymphadenopathy. The subsequent bronchoscopic pulmonary biopsy failed to confirm the pathological nature of this mass.

Since the onset of symptoms, he lost 6 kg of weight even though there was no significant change in his diet and appetite.

VATS right lower lobectomy was carried out under general anesthesia combined with a paravertebral block. We exposed the thoracic cavity using a horizontal incision through the muscle between the fourth and fifth intercostal spaces, and no malignant pleural nodules or pleural effusions were found during thoracoscopic exploration. As the tumor was closely adhered to the pleura, electrocautery was used for dissection, and the right lower lobe was sealed smoothly with an endoscope linear stapler (PSE60-GIA, Johnson & Johnson, New Brunswick, NJ, United States). Subcarinal, paraesophageal and bronchial

lymph node stations were dissected using monopolar electrocautery. The surgery was performed with caution, and there was no direct evidence of iatrogenic nerve injury. During the surgery, an accumulated dose of 25 μg sufentanil was intermittently administered, and the target concentration of remifentanil at the effect site was maintained at 3 ng/mL. The total duration of this surgery was 3 h and 52 min, and the total blood loss was 300 mL. The patient used patient-control analgesia with sufentanil (1 μg/mL), which was programmed to deliver 2-mL boluses with a lockout interval of 8 min and a background infusion of 1 mL/h. According to paraffin pathological sections, the tumor was invasive adenocarcinoma with a maximum diameter of 4 cm, and no metastasis was observed in any of the examined lymph nodes (T2aN0M0 according to the eighth edition of TNM classification of lung cancer) [8].

Personal and family history

The patient had no symptom-related medical history but had smoked for many years. He denied any family history of gastrointestinal dysfunction.

Physical examination

On physical examination, the vital signs were as follows: Body temperature, 36.8 ℃; blood pressure, 127/68 mmHg; heart rate, 79 beats per min; and respiratory rate, 19 breaths per min. Furthermore, abdominal examination revealed a distended abdomen, and the bowel sounds were diminished on auscultation. When we rocked him back and forth from the hip, a succussion splash was elicited.

Laboratory examinations

The electrolyte levels were within the normal limits (Table 1). No abnormalities were found in routine blood and urine analyses.

Imaging examinations

Emergency abdominal CT showed multiple effusions in the esophagus, while the massively dilated stomach and proximal duodenum contained a mass of fluid. The inferior edge of the distended stomach reached the pelvic cavity (Figure 1). Oral iohexol X-ray imaging was carried out after gastrointestinal decompression and demonstrated delayed gastric emptying (10 min after ingestion of iohexol, the first sign of passage into the duodenum was observed, and some contrast agent was retained in the stomach 4 h after administration) (Figure 2).

FINAL DIAGNOSIS

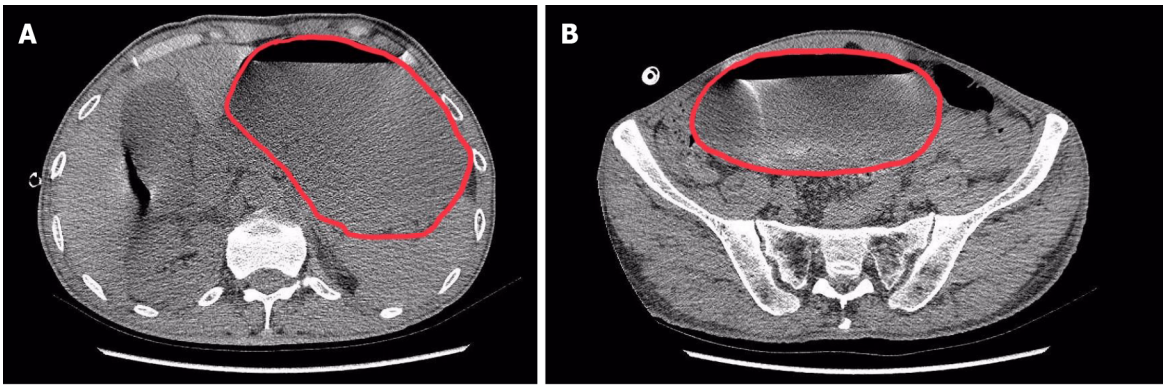
The patient's presentation, physical examination, and laboratory and radiographic investigations narrowed the working diagnosis to digestive tract obstruction or acute gastroparesis. Since CT showed no obstructing mass or stenosis in the gastrointestinal tract, the diagnosis of acute gastroparesis was more likely. The only postoperative medication interfering with gastrointestinal function was sufentanil, which was infused at a low dose for analgesia, and we ceased the opioid immediately after the onset of gastrointestinal dysfunction. Drug-related gastrointestinal motility disorder was less likely to explain the marked nausea and vomiting, and the symptoms did not improve after drug withdrawal. Since there was no evidence of electrolyte imbalance, the most likely underlying cause of gastroparesis was vagal nerve injury during surgery.

TREATMENT

Gastrointestinal decompression was implemented immediately to relieve gastrointestinal symptoms. After draining out 2600 mL of gastric contents, the patient's symptoms improved significantly. Meanwhile, medication interfering with gastrointestinal function, such as sufentanil, was ceased immediately. We provided parecoxib at a dose of 40 mg twice daily as an alternative for analgesia since the patients had no contraindication. Prokinetic drugs such as metoclopramide and cisapride were administered according to medication instructions to enhance the patient's recovery of gastrointestinal function. Gastroenterologists and nutritionists were consulted to formulate a specific therapy plan. As the patient could not tolerate enteral nutrition, parenteral support (structolipid and compound amino acid injection) was given to compensate for the need for nutritional supplementation. Antiemetics were used to relieve nausea and vomiting, and a proton-pump inhibitor was used to protect the mucosa from gastric acids.

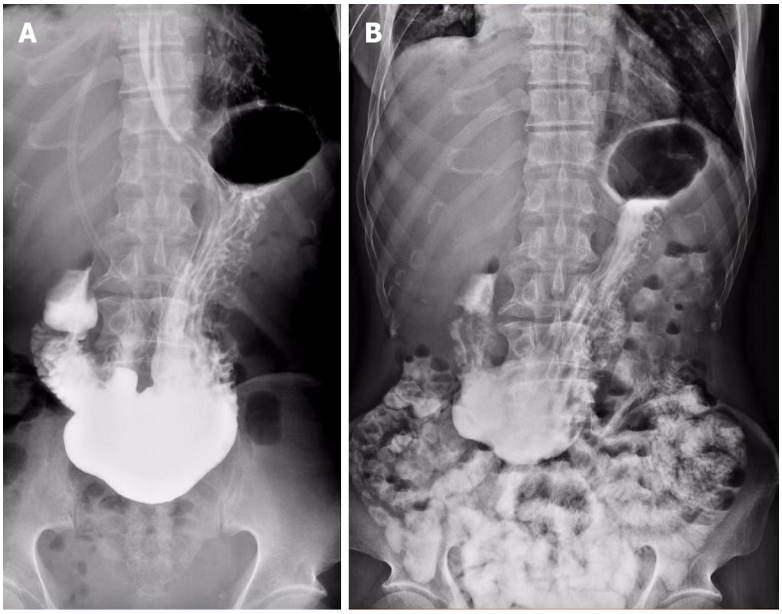
Table 1 Perioperative biochemical examination

	Before surgery	First day after surgery	Third day after surgery	At discharge from hospital
Albumin (g/L)	31.9	29.2	32.1	29.8
Creatinine (μmol/L)	60.1	65.08	82.38	50.85
Natrium (mmol/L)	132.46	137.61	137.42	136.54
Potassium (mmol/L)	4.06	4.78	4.29	4.43
Magnesium (mmol/L)	0.86	0.86	1.03	0.92



DOI: 10.12998/wjcc.v11.i8.1862 **Copyright** ©The Author(s) 2023.

Figure 1 Computed tomography axial views of the abdominopelvic cavity 2 d after video-assisted thoracic surgery. A: The red circle represents the scope of the stomach. In the abdominal cavity section, we can see severe distention in the stomach; B: The red circle represents the scope of the stomach. In the pelvic cavity section, we can see that the inferior edge of the stomach reached the pelvic cavity.



DOI: 10.12998/wjcc.v11.i8.1862 **Copyright** ©The Author(s) 2023.

Figure 2 Oral iohexol X-ray imaging at 10 min (left) and 4 h (right) after administration of contrast agent. A: 10 min after ingestion of iohexol, the first sign of passage to the duodenum was observed; B: Some contrast agent was retained in the stomach 4 h after administration.

OUTCOME AND FOLLOW-UP

Six days later, the patient was symptom-free and developed progressive feeding tolerance. He was discharged from the hospital 10 d after surgery and was able to tolerate a normal diet at the 30-d postoperative follow-up.

DISCUSSION

Surgery is the standard treatment for curable patients (clinical stage I and II non-small cell lung cancer) in whom there is no evidence of mediastinal involvement prior to surgical resection. VATS is a minimally invasive approach to the treatment of early-stage non-small cell lung cancer and has been reported to decrease postoperative complications, especially for those with significant medical comorbidities[2,3,9]. While the most common complication following thoracic surgery is pneumonia, there are few case reports on gastrointestinal disorders secondary to VATS lobectomy[5-7].

Gastroparesis is an annoying gastrointestinal disorder defined by delayed gastric emptying in the absence of a mechanical obstruction, with symptoms of nausea, vomiting, bloating, and abdominal pain. Diabetes with poor glycemic control is the most common etiology of gastroparesis[10]. The normal motor function of the gastrointestinal tract is a complex sequence of events mediated by an extrinsic nerve supply from the brain and spinal cord, complex neuronal plexus and other intrinsic or enteric pathways within the wall of the stomach and intestine (the enteric brain). They work together and alter the excitability of gastrointestinal smooth muscle. Abnormalities in any part of the sequence can result in delayed gastric emptying[11]. Previous studies have reported that some patients developed gastroparesis after surgery; among these patients suffering from gastroparesis, two-thirds had undergone therapeutic vagotomy for peptic ulcers[12]. Opioids used for postoperative analgesia can also aggravate gastrointestinal dysfunction[13]. However, the most common opioid-related gastrointestinal complication was constipation after long-term treatment with high-dose opioids[14,15]. In this case report, the patient received opioids at a low dose for a short duration and had no evidence of electrolyte imbalance, restricting the most likely underlying etiology to thoracic autonomic nervous system injury during the surgery. The sympathetic fibers innervating the stomach can cause contraction of the pylorus and reduce gastric blood flow, while the vagal nerves promote the secretion of gastrin and acid and relax the pyloric sphincter during gastric emptying[16]. Generally, they work together to coordinate gastrointestinal activity, and when the vagal nerves are injured, the activity of the sympathetic nerves will be enhanced.

The vagal nerves run behind the root of the lung and form the anterior and posterior esophageal plexuses, which are distributed along the front and back of the esophagus, respectively. Then, they merge into the anterior vagal trunk and the posterior vagal trunk, passing through the esophageal hiatus into the abdominal cavity and innervating the gastric glands and muscularis[17]. Gastroparesis has been reported as a complication after heart and lung transplantation because the vagal nerves are at high risk of injury when surgeons dissect the native lung[18]. The use of immunosuppressive medications and the progression of preexisting motility disorders aggravate gastrointestinal dysfunction in patients with end-stage lung disease as well[18]. In this case, the only medication disturbing gastrointestinal function was sufentanil, which was infused at a low dose and ceased immediately after the onset of gastrointestinal discomfort. There was no evidence of electrolyte imbalance or previous gastrointestinal disorder. The most likely underlying cause of gastroparesis was vagal nerve injury. However, no manipulation of the vagal nerve was performed during surgery, which excluded the possibility of direct neuronal damage. However, it is likely that the vagal nerve was exposed to edema caused by excessive ambient heat when we resected paraesophageal lymph nodes with electrocautery. Another possible reason accounting for the development of gastroparesis is that the thoracic vagal nerve might be compressed by a tiny paraesophageal hematoma, which would also influence the function of the vagal nerve for a while.

Although most patients suffering from gastroparesis after abdominal surgery can recover spontaneously without therapy, the alleviation of gastroparesis symptoms after thoracic surgery is still unknown. If the etiology of gastrointestinal dysfunction is reversible, conservative management (such as antacid use, raising the head of the bed, and frequent small meals) is effective for some patients with mild symptoms. Moreover, prokinetics such as metoclopramide and cisapride can be administered to improve gastric emptying and enhance the recovery of gastrointestinal function in most patients[12]. Since the most common etiology of gastroparesis after thoracic surgery is vagal nerve injury, surgical intervention can be considered if the symptoms are refractory and last for more than one year. Recently, surgical interventions, including pyloroplasty and gastrojejunostomy, have been indicated to be effective in treating refractory gastroparesis[12,19,20]. However, the proportion of patients receiving surgical treatment has yet to be studied. In this case, there was no direct damage to the patient's vagal nerve, which allowed for gastrointestinal symptom relief after decompression with a nasogastric tube and medication with metoclopramide and cisapride. We also had some limitations regarding the management of this patient. First, the etiology of gastrointestinal dysfunction is putative, and it was impractical to assess the severity of nerve injury. After excluding other causes, intraoperative autonomic nervous system injury was the most likely etiology for the patient's gastroparesis. Second, the gold standard for the diagnosis of gastroparesis is delayed gastric emptying on scintigraphy[21], but the patient refused to be examined due to financial reasons. We chose oral iohexol X-ray imaging as an alternative to evaluate gastrointestinal motility.

CONCLUSION

In this article, we report a rare case of gastroparesis after VATS lobectomy. The most likely etiology of the patient's postoperative gastroparesis was indirect vagal nerve injury during the surgery. In this procedure, no direct manipulation of the vagal nerves was performed, but neuronal edema caused by electrocautery or compression of a tiny hematoma might account for transient gastrointestinal dysfunction. For patients suffering severe nausea and vomiting after thoracic surgery, gastroparesis should be considered after exhaustive inspection. Early detection and early treatment are vital to the recovery of patient gastrointestinal function.

FOOTNOTES

Author contributions: An H contributed to manuscript writing and editing and data collection; Liu YC contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

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 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).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Hang An 0000-0002-4484-1296; Yu-Cun Liu 0000-0002-5455-2797.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

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 **Yan TD**, Cao C, D'Amico TA, Demmy TL, He J, Hansen H, Swanson SJ, Walker WS; International VATS Lobectomy Consensus Group. Video-assisted thoracoscopic surgery lobectomy at 20 years: a consensus statement. *Eur J Cardiothorac Surg* 2014; **45**: 633-639 [PMID: 24130372 DOI: 10.1093/ejcts/ezt463]
3 **Klapper J**, D'Amico TA. VATS versus open surgery for lung cancer resection: moving toward a minimally invasive approach. *J Natl Compr Canc Netw* 2015; **13**: 162-164 [PMID: 25691607 DOI: 10.6004/jnccn.2015.0023]
4 **Cai J**, Zhou J, Yang F, Wang J. Adoption Rate of Video-Assisted Thoracic Surgery for Lung Cancer Varies Widely in China. *Chest* 2018; **153**: 1073-1075 [PMID: 29626953 DOI: 10.1016/j.chest.2017.12.027]
5 **Imperatori A**, Rotolo N, Gatti M, Nardecchia E, De Monte L, Conti V, Dominioni L. Peri-operative complications of video-assisted thoracoscopic surgery (VATS). *Int J Surg* 2008; **6** Suppl 1: S78-S81 [PMID: 19186114 DOI: 10.1016/j.ijsu.2008.12.014]
6 **Burel J**, El Ayoubi M, Baste JM, Garnier M, Montagne F, Dacher JN, Demeyere M. Surgery for lung cancer: postoperative changes and complications-what the Radiologist needs to know. *Insights Imaging* 2021; **12**: 116 [PMID: 34383170 DOI: 10.1186/s13244-021-01047-w]
7 **Bédat B**, Abdelnour-Berchtold E, Perneger T, Licker MJ, Stefani A, Krull M, Perentes JY, Krueger T, Triponez F, Karenovics W, Gonzalez M. Comparison of postoperative complications between segmentectomy and lobectomy by video-assisted thoracic surgery: a multicenter study. *J Cardiothorac Surg* 2019; **14**: 189 [PMID: 31699121 DOI: 10.1186/s13019-019-1021-9]
8 **Rami-Porta R**, Asamura H, Travis WD, Rusch VW. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017; **67**: 138-155 [PMID: 28140453 DOI: 10.3322/caac.21390]
9 **Cheng AM**, Wood DE. VATS versus open surgery for lung cancer resection: moving beyond the incision. *J Natl Compr Canc Netw* 2015; **13**: 166-170 [PMID: 25691608 DOI: 10.6004/jnccn.2015.0024]

10 **Sharayah AM**, Hajjaj N, Osman R, Livornese D. Gastroparesis in a patient with diabetic ketoacidosis. *Cleve Clin J Med* 2019; **86**: 238-239 [PMID: 30951455 DOI: 10.3949/ccjm.86a.18116]

11 **Lacy BE**, Parkman HP, Camilleri M. Chronic nausea and vomiting: evaluation and treatment. *Am J Gastroenterol* 2018; **113**: 647-659 [PMID: 29545633 DOI: 10.1038/s41395-018-0039-2]

12 **Shafi MA**, Pasricha PJ. Post-surgical and obstructive gastroparesis. *Curr Gastroenterol Rep* 2007; **9**: 280-285 [PMID: 17883974 DOI: 10.1007/s11894-007-0031-2]

13 **Bianchi G**, Ferretti P, Recchia M, Rocchetti M, Tavani A, Manara L. Morphine tissue levels and reduction of gastrointestinal transit in rats. Correlation supports primary action site in the gut. *Gastroenterology* 1983; **85**: 852-858 [PMID: 6193028]

14 **Balbale SN**, Cao L, Trivedi I, Stulberg JJ, Suda KJ, Gellad WF, Evans CT, Lambert BL, Jordan N, Keefer LA. High-Dose Opioid Use Among Veterans with Unexplained Gastrointestinal Symptoms Versus Structural Gastrointestinal Diagnoses. *Dig Dis Sci* 2021; **66**: 3938-3950 [PMID: 33385263 DOI: 10.1007/s10620-020-06742-0]

15 **Bell TJ**, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). *Pain Med* 2009; **10**: 35-42 [PMID: 18721170 DOI: 10.1111/j.1526-4637.2008.00495.x]

16 **Gillespie JS**, Maxwell JD. Adrenergic innervation of sphincteric and nonsphincteric smooth muscle in the rat intestine. *J Histochem Cytochem* 1971; **19**: 676-681 [PMID: 5121868 DOI: 10.1177/19.11.676]

17 **Jackson RG**. Anatomy of the vagus nerves in the region of the lower esophagus and the stomach. *Anat Rec* 1949; **103**: 1-18 [PMID: 18108865 DOI: 10.1002/ar.1091030102]

18 **Blackett JW**, Benvenuto L, Leiva-Juarez MM, D'Ovidio F, Arcasoy S, Jodorkovsky D. Risk Factors and Outcomes for Gastroparesis After Lung Transplantation. *Dig Dis Sci* 2022; **67**: 2385-2394 [PMID: 34524597 DOI: 10.1007/s10620-021-07249-y]

19 **Akindipe OA**, Faul JL, Vierra MA, Triadafilopoulos G, Theodore J. The surgical management of severe gastroparesis in heart/lung transplant recipients. *Chest* 2000; **117**: 907-910 [PMID: 10713028 DOI: 10.1378/chest.117.3.907]

20 **Hibbard ML**, Dunst CM, Swanström LL. Laparoscopic and endoscopic pyloroplasty for gastroparesis results in sustained symptom improvement. *J Gastrointest Surg* 2011; **15**: 1513-1519 [PMID: 21720926 DOI: 10.1007/s11605-011-1607-6]

21 **Vijayvargiya P**, Jameie-Oskooei S, Camilleri M, Chedid V, Erwin PJ, Murad MH. Association between delayed gastric emptying and upper gastrointestinal symptoms: a systematic review and meta-analysis. *Gut* 2019; **68**: 804-813 [PMID: 29860241 DOI: 10.1136/gutjnl-2018-316405]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1869-1877

DOI: 10.12998/wjcc.v11.i8.1869

ISSN 2307-8960 (online)

CASE REPORT

Hyperlactemia associated with secondary hepatocellular carcinoma resection in relation to circulation stability and quality of recovery: A case report

Yu Meng, Huan-Shuang Pei, Jia-Jia Yu

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

P-Reviewer: Ji X, China; Salimi M, Iran

Received: January 7, 2023
Peer-review started: January 7, 2023
First decision: January 30, 2023
Revised: February 7, 2023
Accepted: February 21, 2023
Article in press: February 21, 2023
Published online: March 16, 2023

Yu Meng, Huan-Shuang Pei, Jia-Jia Yu, Department of Anesthesiology, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050000, Hebei Province, China

Corresponding author: Huan-Shuang Pei, MM, Associate Professor, Department of Anesthesiology, The Fourth Hospital of Hebei Medical University, No. 12 Jian-Kang Road, Chang'an District, Shijiazhuang 050000, Hebei Province, China. wxhmz99999@163.com

Abstract

BACKGROUND

Intraoperative hyperlactatemia often affects circulatory stability, vital organ function, and postoperative recovery, poses a serious prognostic risk, and requires considerable attention from anesthesiologists. Here, we describe a case of hyperlactatemia during the postoperative resection of liver metastases after chemotherapy for sigmoid colon cancer. This did not affect the patient's circulatory stability or quality of awakening, which is rarely reported in clinical practice. We present our management experience with the aim of providing a reference for future studies and clinical practice.

CASE SUMMARY

A 70-year-old female patient was diagnosed with postoperative liver metastasis following chemotherapy for sigmoid colon cancer. Laparoscopic right hemicolectomy and cholecystectomy under general anesthesia were required. Metabolic disorders, primarily hyperlactatemia, often occur intraoperatively. After treatment, other indices quickly returned to normal, lactate levels decreased slowly, and hyperlactatemia persisted during the awakening period. However, this did not affect the patient's circulatory stability or awakening quality. This condition has rarely been clinically reported. Therefore, we report our management experience in order to guide clinical practice in this regard. Hyperlactatemia did not affect circulatory stability or the quality of awakening. We considered that active intraoperative rehydration avoided serious harm to the organism caused by hyperlactatemia due to insufficient tissue perfusion, while hyperlactatemia caused by decreased lactate clearance due to impaired liver function associated with surgical resection had a mild effect on the function of important organs.

CONCLUSION

Active intraoperative rehydration avoided serious harm to the organism caused

by hyperlactatemia. Strengthening body temperature protection could improve lactate circulation.

Key Words: Circulation; Hyperlactatemia; Laparoscopy; Quality of awakening; Secondary hepatocellular carcinoma; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Intraoperative hyperlactatemia often affects circulatory stability and vital organ function, posing serious prognostic risks. Cases wherein circulatory stability and recovery quality are unaffected are rarely reported. We consider that aggressive intraoperative rehydration avoids serious harm to the organism caused by hyperlactatemia due to insufficient tissue perfusion. Enhanced thermoprotection also improved lactate circulation. There may be individual differences in metabolism and lactate may have a slow clearance profile. The impact on circulation and quality of awakening was mild. Awakening extubation can be performed to reduce the duration of mechanical ventilation and risk of delayed extubation, and to shorten the hospital stay.

Citation: Meng Y, Pei HS, Yu JJ. Hyperlactemia associated with secondary hepatocellular carcinoma resection in relation to circulation stability and quality of recovery: A case report. *World J Clin Cases* 2023; 11(8): 1869-1877
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1869.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1869

INTRODUCTION

The management of intraoperative hyperlactatemia poses a serious challenge to anesthesiologists. To date, it is well recognized that hyperlactatemia poses a serious risk to the organism, requiring a great deal of attention from anesthesiologists. The common causes of increased lactate are increased production due to inadequate tissue perfusion, decreased clearance due to decreased kidney function, and disturbed circulation of lactate due to decreased liver function.

Here, we describe a case of hyperlactatemia during postoperative resection of liver metastases following chemotherapy for sigmoid colon cancer that did not affect the patient's circulatory stability and quality of recovery, which has been rarely reported in clinical practice.

Based on our management experience, we found that this condition was not due to hyperlactatemia caused by inadequate tissue perfusion and did not cause irreversible damage to vital organs. There was minimal impact on the patient's circulation and quality of recovery. Therefore, we decided to remove the tracheal tube, reduce any unnecessary mechanical ventilation time, reduce the risk of delayed extubation, and shorten the length of hospital stay. We report our management experience with the aim of providing a reference for clinical anesthesia.

CASE PRESENTATION

Chief complaints

We report the case of a 70-year-old elderly female patient (weight, 60 kg; height, 156 cm; body mass index 24.7 kg/m^2). Laparoscopic right hemicolectomy and cholecystectomy were performed under general anesthesia. The patient's chief complaint was sigmoid colon cancer with a duration of 10 mo, as well as liver metastasis (with a duration of four months) following postoperative chemotherapy.

History of present illness

The patient was admitted to a local hospital 10 mo prior due to abdominal pain, mucus, and bloody stools. Colonoscopy revealed sigmoid colon cancer and pathological results showed hypofractionated adenocarcinoma. After completing the relevant examinations, the patient received three cycles of neoadjuvant chemotherapy. Later, the patient developed colic abdominal pain focused in left lower abdomen that was accompanied by nausea and vomiting; intestinal obstruction was considered. Under general anesthesia, the patient underwent laparoscopic-assisted radical resection of the sigmoid colon cancer, left adnexal resection, double-lumen fistula of the terminal ileum, and chemotherapy with membrane infusion and release of intestinal adhesions.

Postoperative pathology of the sigmoid colon reported moderate-to-low differentiated adenocarcinoma with necrosis, small foci with phosphorylation, invasion of the muscular layer to the perintestinal fat, and visible nerve invasion. A pathological diagnosis of sigmoid colon cancer was made.

After four cycles of postoperative chemotherapy, the patient was treated with three cycles of intravenous targeted drug infusion (four months prior), and the lesion was reduced on review.

History of past illness

The patient had no previous history of hypertension, diabetes, or coronary heart disease. She had a history of cerebral infarction for more than six months and had not undergone any special treatment.

Personal and family history

The patient denied any relevant family history of cancer or chronic disease.

Physical examination

The patient had a temperature of 36.3 °C, a heart rate of 85 beats/min, a respiratory rate of 19 breaths/min, and a blood pressure (BP) of 139/97 mm Hg. Her height and weight were 156 cm and 60 kg, respectively. The patient showed normal development, a positive nutritional status, and clear consciousness. Difficult airway (Mallampati class II) was not detected during the preoperative evaluation. The nail-chin spacing was > 6 cm, mouth opening was > 6 cm, and head extension was > 35°. Cardiopulmonary examination findings were unremarkable, and the patient was classified as American Society of Anesthesiology (ASA) class II.

Laboratory examinations

The patient's blood counts were as follows: Erythrocyte count 3.07 × 10^{12}/L, hemoglobin 103.0 g/L; erythrocyte pressure volume, 31.7%; liver function: Alanine transferase 11.2 U/L, aspartate aminotransferase 27.9 U/L, total protein 56.2 U/L, albumin 34.7 U/L, albumin:globulin ratio 1.61, total bilirubin 6.3 μmol/L. Other laboratory tests, such as routine urine and renal function tests, were within normal limits.

Imaging examinations

Abdominal computed tomography suggested liver metastasis (Figure 1A). All other test results were unremarkable.

FINAL DIAGNOSIS

Postoperative diagnosis

Postoperative liver metastasis following chemotherapy for sigmoid colon cancer and cerebral infarction.

Pathological diagnosis

Hypofractionated adenocarcinoma (Figure 1B).

TREATMENT

The patient underwent laparoscopic resection of multiple metastatic carcinomas in the right lobe of the liver and ileostomy with a double-lumen fistula return under general anesthesia. The patients fasted and abstained from food and drink prior to surgery. The patient was admitted to the room where cuff BP, electrocardiography, partial pressure of oxygen, and the bispectral index were routinely monitored. Venous access to the left upper limb was established.

Invasive arterial BP monitoring was performed by radial artery puncture after local anesthesia, and arterial blood gas testing was performed. The patient's BP on admission was 188/75 mmHg, her heart rate was 67 beats/min, and her pulse oximetry was 92%.

After the anesthesia plan was finalized, we administered a routine induction of anesthesia, as follows: Oxygen denitrogenation by face mask for 3 min, intravenous sufentanil 50 μg, remazolam 14 mg, rocuronium 50 mg. Two minutes later, a 7.5 single-lumen tracheal tube was successfully inserted *via* the mouth. After successful tracheal intubation, a single-lumen central venous catheter was inserted through the right internal jugular vein. An ultrasonography-guided transverse abdominal muscular nerve block was performed.

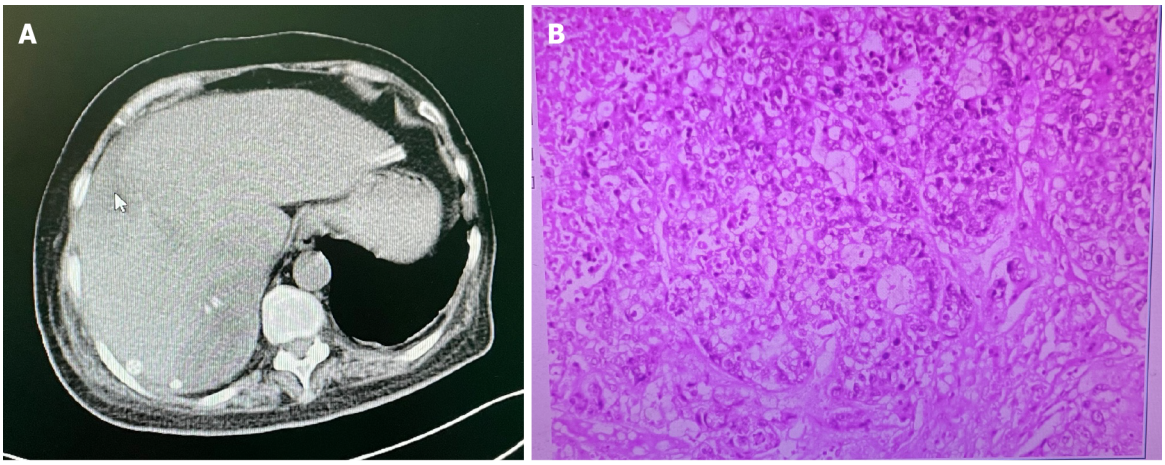
Anesthesia was maintained with continuous intravenous pumping of 0.05-0.20 μg/kg/min remifentanil, inhalation of 2%-3% sevoflurane, and intermittent sedation of cisatracurium. In this patient presenting with multiple hepatic metastases, we implemented the Pringle method as a blocking technique to reduce intraoperative bleeding. Intermittent intraoperative arterial blood gas testing was performed (Table 1).

For metabolic disturbances that appeared intraoperatively, we provided timely treatment, including rehydration, potassium supplementation, and acid correction. Laparoscopic exploration revealed a non-

Table 1 Results of blood gas analysis in a patient with metastatic liver cancer who underwent resection of multiple metastatic tumors in the right lobe of the liver

Measure	Pre-anesthesia	Intraoperative 1	Intraoperative 2	Intraoperative 3	Recovery room 1	Recovery room 2	Recovery room 3
pH	7.4199	7.2946	7.2964	7.4551	7.3541	7.2965	7.3666
Potassium (mmol/L)	3.6836	3.8524	3.9770	3.5277	3.3718	3.6577	3.0349
Glucose (mmol/L)	6.2544	10.6121	15.5280	14.4482	11.2476	10.3345	10.1226
Lactic acid (mmol/L)	3.1100	2.3355	4.7321	6.3023	8.1477	9.3126	9.8924
Base surplus (mmol/L)	-1.53	-3.53	-6.24	-0.56	-5.10	-7.82	-4.87
Hct	33.382	31.879	29.717	24.776	27.867	25.012	22.024
PaO_2 (mmHg)	72.2	207.4	253.8	185.9	226.9	86.0	101.5
FiO_2	0.21	0.60	0.60	0.60	0.60	0.21	0.21

FiO_2: Fraction of inspired oxygen; Hct: Hematocrit; PaO_2: Partial pressure of oxygen.



DOI: 10.12998/wjcc.v11.i8.1869 **Copyright** ©The Author(s) 2023.

Figure 1 Abdominal computed tomography scan and pathological diagnosis imaging. A: Abdominal computed tomography scan suggestive of liver metastases; B: Image depicting the pathological diagnosis of hypofractionated adenocarcinoma.

sclerotic liver with multiple hepatic metastatic carcinomas. The tumors were located in segment V of the liver, with a tumor size of approximately 2 cm × 3 cm, adjacent to the gallbladder, and in segment VI of the liver, with a tumor size of approximately 4 cm × 5 cm.

Due to the large number of tumors, an intraoperative portal block was performed several times using the Pringle blocking technique. A hepatobiliary surgeon performed laparoscopic resection of multiple metastatic carcinomas in the right lobe of the liver and ileal double-lumen fistula reduction under general anesthesia. The patient was administered 5 mg dizocine for analgesia 0.5 h before the end of the operation as well as intravenous self-administered analgesia after the operation. The operation lasted 320 min, anesthesia lasted 375 min, 1990 mL of crystalloid fluid was infused, intraoperative blood loss was 400 mL, and the urine volume was 1000 mL.

After surgery, the patient was transferred to a recovery room for tracheal intubation. While the patient was in the recovery room, we continued to monitor her arterial blood gas and found that metabolic disorders such as hyperlactatemia were still present (Table 1). We actively treated her with rehydration, potassium supplementation, acid correction and temperature protection. After 40 min, the patient's arterial blood gas normalized, with the exception of hyperlactatemia. At this point, we found that the patient's vital signs were stable and she did not show signs of hyperlactatemia inhibiting circulation, which is extremely rare in clinical practice.

After 0.5 h, the patient's vital signs remained stable, and we decided to wake the patient up again without referring to the lactate level. The patient was then intravenously injected with neostigmine 1.5 mg and atropine 0.4 mg for inotropic antagonism, followed by intravenous flumazenil 0.4 mg five

minutes later. After the patient became conscious, muscle tone was restored, spontaneous breathing and the cough reflex were restored, respiratory secretions were cleared, and the tracheal tube was removed. The patient was observed for 0.5 h.

After it was determined that the patient had no complaints of discomfort and had stable vital signs, the was transferred back to the ward. The patient remained in the recovery room for 120 min, during which hyperlactatemia did not affect the patient's circulatory stability and quality of awakening, which is a rarely reported phenomenon. We consider that delayed extubation can shorten the length of hospital stay.

OUTCOME AND FOLLOW-UP

The patient returned to the ward with clear consciousness and a cooperative mindset. Her BP was 135/75 mmHg, her heart rate was 67 beats/min, and her pulse oximetry reading was 100%. On the first day after surgery, comprehensive treatment, including blood transfusion and oxygen, was administered. The patient's vital signs were stable.

On the second day after surgery, the patient's vital signs were stable. Lactate was rechecked at 1.98 mmol/L, liver function was rechecked at 383.3 U/L and 531.5 U/L. On the fourth postoperative day, the patient's liver function normalized. She recovered well and was successfully discharged from the hospital. On the postoperative pathology report, multifocal hypofractionated carcinoma was observed in the liver. The patient's vital signs were stable at the two-month postoperative follow-up visit.

DISCUSSION

Approximately 57% of secondary liver cancers are caused by hematogenous metastasis of pancreatic, gastric, and colorectal cancers, whereas lung, cervical, breast, and ovarian cancers commonly metastasize to the liver *via* hematogenous metastasis. Secondary liver cancer is insensitive to radiotherapy and chemotherapy. Therefore, early surgical resection is the single most effective treatment.

Since the liver is rich in blood flow and liver tissue is fragile, the risk of intraoperative hemorrhage is high. Therefore, a key goal of surgery is to effectively control liver bleeding. To reduce bleeding, resection is often performed after hilar block. Both Pringle's method and the hemihilar block are common clinical methods for blocking hepatic blood flow. The Pringle method is advantageous in reducing bleeding. At the same time, the anesthesiologist needs to pay close attention to the bleeding volume and rate during tumor resection, the status of the operative field, and the dynamic changes of the patient's BP and pulse rate as well as other indicators. While actively administering fluids and transfusing blood, it is necessary to pay extra attention to changes in electrolytes and metabolic indices to avoid serious metabolic disorders such as hyperlactatemia, which may affect the function of vital organs.

In this case, the patient had multiple hepatic metastases after undergoing chemotherapy for sigmoid colon cancer, which was secondary to hepatocellular carcinoma. The preoperative examination showed no significant abnormalities in cardiopulmonary, liver, or kidney function, and the routine blood tests were within the acceptable range for elective surgery. The proposed surgery was laparoscopic right hemicolectomy + cholecystectomy, and the overall assessment of this case was ASA grade II. The surgery was medium risk, such that elective surgery could be performed under general anesthesia.

Considering the proposed resection of multiple hepatic metastases in this case, bleeding control was the core consideration. Therefore, surgery was performed using the Pringle method with a hepatic portal block. The main points of perioperative anesthesia management were to ensure the appropriate depth of anesthesia; to pay extra attention to the extent of liver surgical resection, bleeding volume, and bleeding rate; to strengthen invasive hemodynamic monitoring; to emphasize enhanced volume and urine volume management; to dynamically monitor changes in the internal environment; and to administer effective temperature protection and other treatments. In summary, we used remifentanil + sevoflurane inhalation compound general anesthesia combined with a transversus abdominis nerve block, invasive arterial monitoring, and strengthened volume management, while paying attention to urinary volume, closely monitoring arterial blood gas changes, providing timely adjustment, and striving to achieve individualized and refined anesthetic management.

Normal lactate blood concentrations are in the approximate range of 1.3 mmol/L. Clinically, a blood lactate concentration of > 2.25 mmol/L is usually indicative of hyperlactatemia. A lactate concentration of > 5 mmol/L indicates lactic acidosis. In this case, the patient developed severe intraoperative metabolic disorder (Table 1). After aggressive rehydration, potassium supplementation, and acid correction, all indices except hyperlactatemia quickly returned to the normal range.

It is well known that hyperlactatemia poses a serious risk to the body. Numerous studies have shown that blood lactate levels are closely related to the criticality and prognosis of serious diseases, with higher blood lactate levels leading to more serious conditions and worse prognoses. Hyperlactatemia

leads to reduced myocardial contractility and cardiac output, resulting in tissue and organ hypoperfusion, arrhythmia, and reduced cardiovascular responsiveness to catecholamines[1].

The relationship between severe hyperlactatemia and prognosis is divided into two main categories: (1) Severe hyperlactatemia is associated with the failure of various vital organs, such as the liver, kidney, heart, sepsis, as well as other diseases whose primary conditions are difficult to reverse; and (2) Severe hyperlactatemia is associated with cardiac surgery, epilepsy, and other diseases whose primary conditions can be reversed. It was found that the second condition is associated with a significantly lower mortality rate and a mild effect on the organism[2].

In the present case, hyperlactatemia occurred intraoperatively. We actively searched for the cause and administered various treatments in a timely manner to reduce the harm caused by hyperlactatemia to the organism, with a special focus on avoiding aggravating vital organ failure due to hyperlactatemia caused by insufficient tissue perfusion.

The occurrence of hyperlactatemia is due to excessive lactate production on the one hand, and to reduced lactate clearance on the other[3]. Excessive lactate production is associated with various causes such as inadequate tissue perfusion due to volume deficit caused by the intraoperative controlled hypocentral venous pressure technique, a large extent of liver resection or use of the intraoperative Pringle method block technique, long duration of hepatic portal block, traumatic injury resulting in interruption of blood flow to the injured tissue, ischemia-reperfusion injury, hypothermia, and other causes of inadequate tissue perfusion leading to lactic acidosis. In a study by Theodoraki *et al*[4], it was found that postoperative lactic acid was significantly increased in patients undergoing Pringle's method of blockade compared to those without this method. The authors concluded that blocking hepatic blood flow not only decreased the hepatic oxygen supply and increased anaerobic metabolism, but also significantly decreased the ability of the liver to remove lactic acid.

Impaired liver function associated with surgical resection, which affects the circulation and clearance of lactic acid, can also cause lactic acid accumulation and acidosis. In addition, the kidney can use lactic acid to supply energy and synthesize glycogen *via* the pyruvate pathway, and it can also secrete lactic acid for excretion[5]. The kidney's ability to remove lactic acid increases with increased blood lactate concentrations.

In this case, hyperlactatemia did not affect the patient’s circulatory stability and quality of recovery during awakening, and we did not give vasoactive drugs for supportive treatment. This suggests that hyperlactatemia in this case did not cause serious harm to the vital organs of the body, which is rarely reported.

In regard to the possible causes of the hyperlactatemia in this case, our analysis is as follows. First, in comparing the patients’ preoperative and postoperative liver functions (Table 2), we found that the patients’ preoperative liver function was normal, whereas her postoperative liver function changed significantly. Moreover, combined with the fact that this patient had multiple liver metastases, intraoperative bleeding was relatively high. To reduce bleeding, the surgeon performed multiple hepatic portal blocks using Pringle's method, showed a greater impact on the patient's liver function. Combined with the surgery, we actively carried out rehydration, potassium supplementation, acid correction and other treatments to avoid the increase of lactic acid due to insufficient tissue perfusion and ensure the stability of the patient's circulation. On comparing the patient's preoperative and postoperative renal function, we found no significant difference. Combined with the total intraoperative crystalloid infusion of 1990 mL and a urinary volume of 1000 mL, this suggests that hyperlactatemia did not affect the patient's circulation and renal function. Comprehensive analysis showed that the patient had stable circulation and good tissue perfusion, which excluded hyperlactatemia caused by insufficient tissue perfusion and also suggested that lactate clearance in the kidneys was not affected. We consider that the extent of liver resection, intraoperative hepatic portal block time, traumatic liver injury and ischemia-reperfusion injury affected the patient's liver function to some extent, resulting in a decrease in the liver's ability to metabolize lactate, while impaired liver function affecting lactate circulation and leading to lactate accumulation may be the main reason for hyperlactatemia in this case. We note that hypothermia may affect lactate circulation, and that the observed findings may also be due to individual differences in lactate metabolism. In addition, lactate is characterized by relatively slow clearance. In sum, we analyzed the hyperlactatemia in this case as arising from decreased lactate clearance due to impaired liver function associated with surgical resection, presenting a reversible hyperlactatemia with minimal impact on the patient (Table 3).

The treatment of hyperlactatemia presents a management challenge for anesthesiologists. Identification of the cause of hyperlactatemia is the key to aggressive treatment. The first priority of treatment is to improve tissue perfusion, and patients should be treated and managed individually in consideration of their condition and in accordance with treatment principles. Blood lactate levels are an important indicator for taking therapeutic measures, and treatment should be initiated when serum lactate levels are > 4.0 mmol/L[6]. Studies have shown that aggressive rehydration can improve lactate production due to insufficient tissue perfusion while reducing the serious harm caused by hyperlactatemia to the organism.

Hypothermia affects the lactate cycle. Hypothermia is often triggered in patients undergoing hepatectomy due to several factors[7]. The results of a study by Li *et al*[8] showed that hypothermia may lead to further compromise of the patient's liver function as well as long-term ischemia and hypoxia of

Table 2 Pre-operative and post-operative liver function in a patient with metastatic liver cancer who underwent resection of multiple metastatic tumors in the right lobe of the liver

Measure	Preoperative	Postoperative day 1	Postoperative day 2	Postoperative day 5	Postoperative day 6
ALT (U/L)	11.2	405.4	383.3	151.1	109.9
AST (U/L)	27.9	745.8	531.3	54.2	35.1
TP (g/L)	56.2	48.1	41.6	49.1	48.8
ALB (g/L)	34.7	30.4	27.4	35.8	36.4
A:G	1.61	1.72	1.93	2.69	2.94
TBIL (μmol/L)	6.3	6.7	12.3	11.9	15.4

A:G: Albumin:globulin ratio; ALB: Albumin; ALT: Alanine transaminase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; TP: Total protein.

Table 3 Etiology, treatment, and prognosis of hyperlactatemia associated with resection of secondary hepatic metastatic carcinoma

Causes of disease		Treatment	Prognosis
Excessive lactic acid production	Insufficient volume leading to inadequate tissue perfusion	Aggressive fluid replacement to improve tissue perfusion	Severe hyperlactatemia is associated with failure of all vital organs and is difficult to reverse with a poor prognosis
	Longer hepatic portal block, traumatic injury leading to ischemic reperfusion injury	Rehydration, potassium replacement, correction of acidosis	
	Hypothermia	Insulation therapy	
Decreased lactate clearance	Blockage of blood flow to the liver leading to a decrease in the liver's ability to remove lactic acid	Minimize hepatic portal block time, temperature protection	Severe hyperlactatemia is associated with cardiac surgery, epilepsy and other conditions where the primary condition can be reversed, and has a mild impact on patients with a good prognosis
	Impaired liver function associated with surgical resection	Hepatoprotective therapy	
	Impaired kidney function	Maintain circulatory stability and rehydration	

liver tissue, which can further affect blood lactate and cause metabolic disorders. General nursing measures cannot ensure a normal body temperature in these patients, which leads to increased hypoxia and affects lactate metabolism. It is reported in the literature that body temperature protection can improve lactate metabolic function by maintaining a normal body temperature[8,9]. The Pringle block can completely block the portal vein, which can reduce bleeding during hepatectomy; however, it can also cause visceral and inferior vena cava system stasis. Studies have shown that visceral and inferior vena cava system stasis and tissue hypoxia due to hypothermia can increase lactate concentrations. Maintaining the patient's body surface temperature can improve the degree of hypoxia and significantly reduce lactate concentrations[10].

In this patient, to avoid hyperlactatemia due to inadequate tissue perfusion that could in turn affect vital organ function, we actively treated the patient with volume expansion, acid correction, and arterial blood gas testing. The patient's severe hyperlactatemia did not affect circulatory stability and quality of awakening, and the patient's good postoperative recovery showed that our analysis of the causes of hyperlactatemia, comprehensive treatment, and timely decision to awaken and extubate were correct (Table 4).

This case suggests that anesthesiologists should pay close attention to intraoperative hyperlactatemia, strengthen their knowledge about the causes of lactic acid increase and lactic acid metabolism, and gain a deep understanding of the varying effects of different causes of hyperlactatemia on the body, so that anesthesiologists can make correct analyses, perform timely management, and enact effective decisions on follow-up treatment when intraoperative hyperlactatemia occurs. At the same time, the surgical team should also pay closer attention to patients' preoperative liver function, and evaluate and actively treat said patients.

For patients with normal preoperative liver function, clinicians should attempt to control the inflammatory response during the perioperative period, maintain stable hemodynamics during surgery, reasonably control low central venous pressure while ensuring tissue perfusion, and minimize operative and hepatic portal block times to reduce the incidence of hyperlactatemia by reducing the degree of liver function impairment associated with surgery. In elective surgery patients with preoperative hepatitis or cirrhosis resulting in hepatic insufficiency, the incidence of intraoperative hyperlactatemia is

Table 4 Case report timeline

Item		Timeline
Preoperative	1	Ten months after diagnosis of sigmoid colon cancer, 4 months after postoperative chemotherapy for liver metastasis
	2	History of "cerebral infarction" for more than six months without special treatment
	3	Abdominal CT scan suggestive of liver metastasis
	4	The operation was performed under general anesthesia
Perioperative	5	Invasive blood pressure was monitored and arterial blood gas analysis was conducted
	6	BIS was monitored
	7	Induction of conventional anesthesia with tracheal intubation
	8	CVC after general anesthesia. Ultrasound-guided transversus abdominis block was performed
	9	Maintenance of anesthesia was performed using static inhalation compound general anesthesia
	10	The operation was performed using Pringle's method to block the hepatic metastases, and arterial blood gases were monitored dynamically intraoperatively. Hyperlactatemia was detected and treated aggressively with fluid replacement and other treatments. However, the patient's vital signs were stable
	11	The surgery was successfully completed
Postoperative	12	After the operation, the patient was transferred to the PACU. There was still hyperlactatemia detected. However, the patient's vital signs were stable
	13	Treatments such as temperature protection as well as arterial blood gas testing were implemented, and although hyperlactatemia was present, vital signs were stable and awakening was satisfactory. The patient returned to the ward after surgery
	14	The patient was discharged six days after surgery
	15	The patient was followed up two months after the operation

BIS: Bispectral index; CT: Computed tomography; CVC: Central venous catheter; PACU: Post-anesthesia care unit.

greatly increased, which can seriously affect the function of important organs and increase the difficulty of anesthesia management. Therefore, preoperative hepatoprotective therapy should be actively administered, and surgical treatment should be performed when liver function is restored to that required for elective surgery. Intraoperative attention should be paid to strengthening prevention and treatment and actively maintaining fragile liver function to reduce the incidence of hyperlactatemia, improve patient prognosis, and increase postoperative survival and quality of life.

In conclusion, our patient presented with multiple hepatic metastatic carcinomas secondary to sigmoid colon cancer. Intraoperative hyperlactatemia associated with surgical resection occurred, but the patient's circulatory stability and quality of recovery were not affected by hyperlactatemia during the awakening period, which had specific and somewhat unique reasons in this case. The quality of recovery during the awakening period and the patient's good postoperative outcome suggest that the analysis of the causes of hyperlactatemia, comprehensive management, and the decision to extubate were correct.

CONCLUSION

In this case, we found that hyperlactatemia did not affect the patient's circulatory stability or the quality of awakening. We considered that active intraoperative rehydration avoided serious harm to the organism caused by hyperlactatemia due to insufficient tissue perfusion, while hyperlactatemia caused by decreased lactate clearance due to impaired liver function associated with surgical resection had a mild effect on the function of important organs. Additionally, strengthening body temperature protection could improve lactate circulation. Future clinical trials are needed for further confirmation of the preliminary findings of this case study, which is likewise intended to provide a reference for general anesthesiologists in their clinical work.

FOOTNOTES

Author contributions: Meng Y and Yu JJ participated in the anesthesia management of the present case, and both were the major contributors to this manuscript; Pei HS helped revise the manuscript; all authors have read and approved the final manuscript.

Informed consent statement: The subject profiled in this case report provided their written informed consent for the anonymized publication of their case report findings and all accompanying images.

Conflict-of-interest statement: The authors have no actual or potential conflicts of interest to declare.

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).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Yu Meng 0000-0001-5678-237X; Huan-Shuang Pei 0000-0002-9064-0233; Jia-Jia Yu 0000-0002-6865-3580.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

REFERENCES

1 **Kraut JA**, Madias NE. Lactic acidosis. *N Engl J Med* 2014; **371**: 2309-2319 [PMID: 25494270 DOI: 10.1056/NEJMra1309483]
2 **Haas SA**, Lange T, Saugel B, Petzoldt M, Fuhrmann V, Metschke M, Kluge S. Severe hyperlactatemia, lactate clearance and mortality in unselected critically ill patients. *Intensive Care Med* 2016; **42**: 202-210 [PMID: 26556617 DOI: 10.1007/s00134-015-4127-0]
3 **Bian LY**, Yu K, Long C. Hyperlactatemia in cardiac surgery. *Yixue Zongshu* 2010; **16**: 3281-3283
4 **Theodoraki K**, Arkadopoulos N, Fragulidis G, Voros D, Karapanos K, Markatou M, Kostopanagiotou G, Smyrniotis V. Transhepatic lactate gradient in relation to liver ischemia/reperfusion injury during major hepatectomies. *Liver Transpl* 2006; **12**: 1825-1831 [PMID: 17031827 DOI: 10.1002/lt.20911]
5 **Su WL**, Zhu TH. Research progress on the etiology and treatment of hyperlactatemia. *Yinanbing Zazhi* 2017; **8**: 848-851
6 **Hu BJ**, Bo LL, Deng S, Li XM, Duan HW. Advances in research related to lactic acidosis. *Zhongguo Yiyao Daobao* 2018; **15**: 22-25
7 **Liu Y**, Liu YL, Cheng W, Yin XM, Jiang B. The expression of SIRT3 in primary hepatocellular carcinoma and the mechanism of its tumor suppressing effects. *Eur Rev Med Pharmacol Sci* 2017; **21**: 978-998 [PMID: 28338198]
8 **Li CX**, Zhang JQ, Ma LB, Li L, Du XH, Meng FM. Effect of multimodal insulation on postoperative regression and fee-for-service in patients undergoing radical hepatocellular carcinoma surgery. *Zhonghua Mazuixue Zazhi* 2017; **37**: 1304-1307
9 **Zhou H**, Jia WD, Qiao XF, Liu FP, Chen L, Hu CL. [Clinical values of multimodal preventive analgesia in patients with partial hepatectomy for liver cancer]. *Zhonghua Wai Ke Za Zhi* 2017; **55**: 141-145 [PMID: 28162215 DOI: 10.3760/cma.j.issn.0529-5815.2017.02.013]
10 **Cheung TT**, Chok KS, Chan AC, Tsang SH, Dai WC, Yau TC, Kwong A, Lo CM. Survival analysis of breast cancer liver metastasis treated by hepatectomy: A propensity score analysis for Chinese women in Hong Kong. *Hepatobiliary Pancreat Dis Int* 2019; **18**: 452-457 [PMID: 31474444 DOI: 10.1016/j.hbpd.2019.08.001]

World Journal of Clinical Cases

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

World J Clin Cases 2023 March 16; 11(8): 1878-1887

DOI: 10.12998/wjcc.v11.i8.1878

ISSN 2307-8960 (online)

CASE REPORT

Sclerosing odontogenic carcinoma of maxilla: A case report

Hui Yuh Soh, Wen-Bo Zhang, Yao Yu, Ran Zhang, Yan Chen, Yan Gao, Xin Peng

Specialty type: Dentistry, oral surgery and medicine

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Arumugam EAP, India; Hasan S, India; Sekhar P, India

Received: January 8, 2023
Peer-review started: January 8, 2023
First decision: January 30, 2023
Revised: February 6, 2023
Accepted: February 22, 2023
Article in press: February 22, 2023
Published online: March 16, 2023

Hui Yuh Soh, Wen-Bo Zhang, Yao Yu, Xin Peng, Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology & National Center for Stomatology & National Clinical Research Center for Oral Diseases & National Engineering Research Center of Oral Biomaterials and Digital Medical Devices, Beijing 100081, China

Hui Yuh Soh, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University Kebangsaan Malaysia, Kuala Lumpur 50300, Malaysia

Ran Zhang, Yan Chen, Yan Gao, Department of Oral Pathology, Peking University School of Stomatology, Beijing 100081, China

Corresponding author: Xin Peng, DDS, MD, Professor, Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology & National Center for Stomatology & National Clinical Research Center for Oral Diseases & National Engineering Research Center of Oral Biomaterials and Digital Medical Devices, No. 22 Zhongguancun South Avenue, Haidian District, Beijing 100081, China. pxpengxin@263.net

Abstract

BACKGROUND

Sclerosing odontogenic carcinoma is a rare primary intraosseous neoplasm that was featured recently as a single entity in the World Health Organization classification of Head and Neck Tumors 2017, with only 14 cases published to date. The biological characteristics of sclerosing odontogenic carcinoma remain indistinct because of its rarity; however, it appears to be locally aggressive, with no regional or distant metastasis reported to date.

CASE SUMMARY

We reported a case of sclerosing odontogenic carcinoma of the maxilla in a 62-year-old woman, who presented with an indolent right palatal swelling, which progressively increased in size over 7 years. Right subtotal maxillectomy with surgical margins of approximately 1.5 cm was performed. The patient remained disease free for 4 years following the ablation surgery. Diagnostic workups, treatment, and therapeutic outcomes were discussed.

CONCLUSION

More cases are needed to further characterize this entity, understand its biological behavior, and justify the treatment protocols. Resection with wide margins of approximately 1.0 to 1.5 cm is proposed, while neck dissection, post-operative radiotherapy, or chemotherapy are deemed unnecessary.

Key Words: Odontogenic tumor; Sclerosing odontogenic carcinoma; Head and neck

neoplasms; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Sclerosing odontogenic carcinoma is a rare disease entity with only 14 cases published to date, this case report will further substantiate the understanding to this disease and the management protocols.

Citation: Soh HY, Zhang WB, Yu Y, Zhang R, Chen Y, Gao Y, Peng X. Sclerosing odontogenic carcinoma of maxilla: A case report. *World J Clin Cases* 2023; 11(8): 1878-1887
URL: https://www.wjgnet.com/2307-8960/full/v11/i8/1878.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i8.1878

INTRODUCTION

Sclerosing odontogenic carcinoma (SOC) is an unusual primary intraosseous neoplasm that was added to the 4th edition World Health Organization (WHO) classification of Head and Neck Tumors in 2017[1]. This disease entity was first described by Landwehr and Allen[2] in 1996 and subsequently reported by Koutlas *et al*[3] in 2008. Nevertheless, this distinct entity remains poorly understood, with only 14 cases published to date[2-6], despite its recent inclusion in the latest WHO classification of Head and Neck Tumors. Clinically, it is characterized by locally aggressive, non-metastasizing properties, while histopathologically, it is typically illustrated by infiltrative thin cords and small nests of epithelial cells in the diffused sclerotic stroma[3]. However, there is no specific or distinctive immunohistochemical staining for SOC. Radiologically, it mostly presents as an osteolytic lesion, with or without bony perforation[4]. The histological resemblance of SOC to other disease entities poses a challenge to the accurate diagnosis of this neoplasm, while the paucity of literature makes standardizing treatment protocols more difficult. Herein, we describe a case of SOC of the maxilla, including diagnostic workups, treatment, and therapeutic outcomes.

CASE PRESENTATION

Chief complaints

A 62-year-old woman presented to her local hospital in December 2017 with a 7-year history of right palatal swelling. The patient first noticed a small, indolent swelling at the right anterior palate 7 years previously, which gradually increased in size over the past 2 years, associated with intermittent toothache and occasional facial swelling.

History of present illness

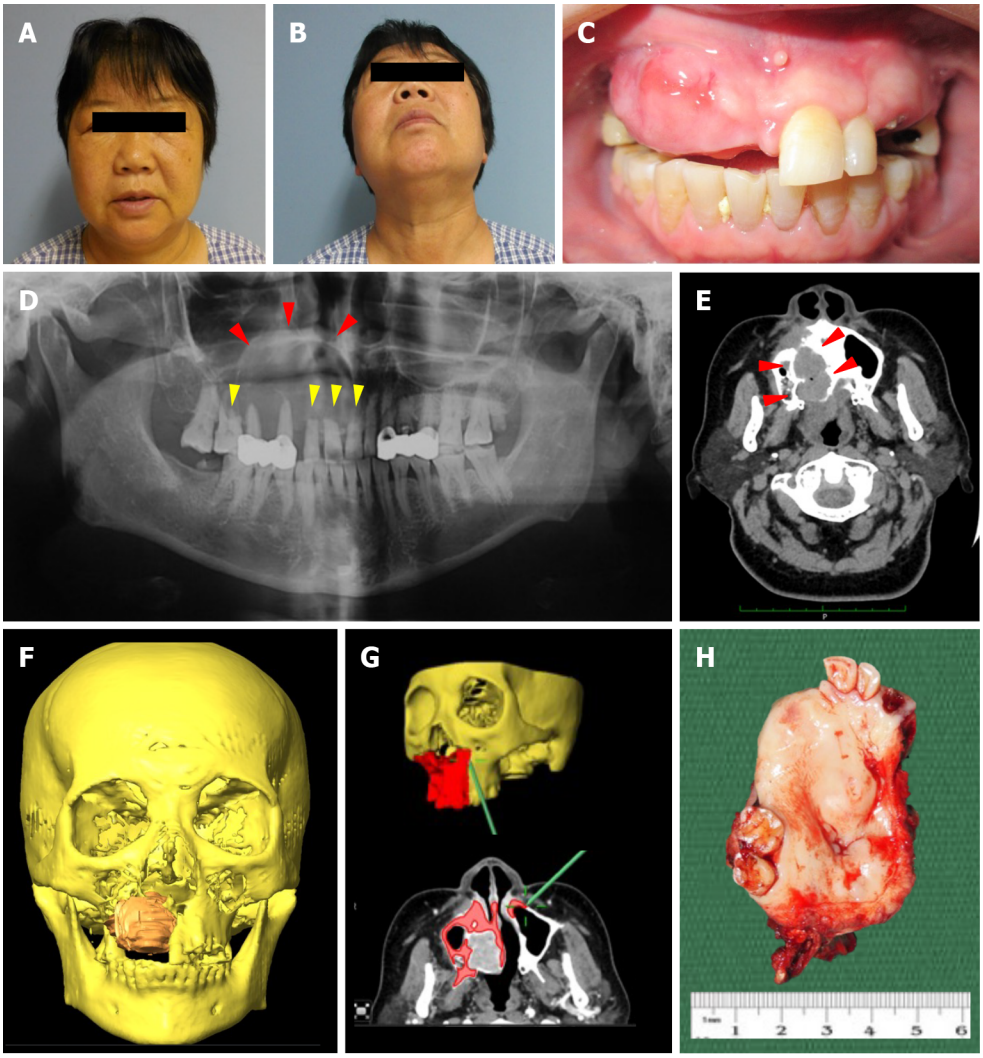
Initial clinical examination revealed a firm mass over the anterior palate, without apparent buccal and lingual expansion. The initial dental panoramic tomogram (DPT) revealed radiolucency with a welldefined sclerotic border of the right maxilla extending into the right maxillary sinus and significant root resorption of the upper central, lateral incisors, and upper right first molar. Excisional biopsy of the anterior palate was performed under local anesthesia *via* an intraoral approach, with extraction of the upper right central and lateral incisors at the local hospital. The histopathology examination showed SOC. Hematoxylin and eosin (H&E) sections showed small epithelial tumor cell cords in a densely collagenized stroma. No obvious dysplastic features were observed in the given specimen. The swelling resolved; however, the patient noticed the swelling of the palate again in April 2018, for which she was eventually referred to our institution for management of the right maxillary tumor (Supplementary material).

History of past illness

Except for long-standing diabetes mellitus and hypertension, her past medical history was unremarkable.

Personal and family history

Unremarkable.



DOI: 10.12998/wjcc.v11.i8.1878 **Copyright** ©The Author(s) 2023.

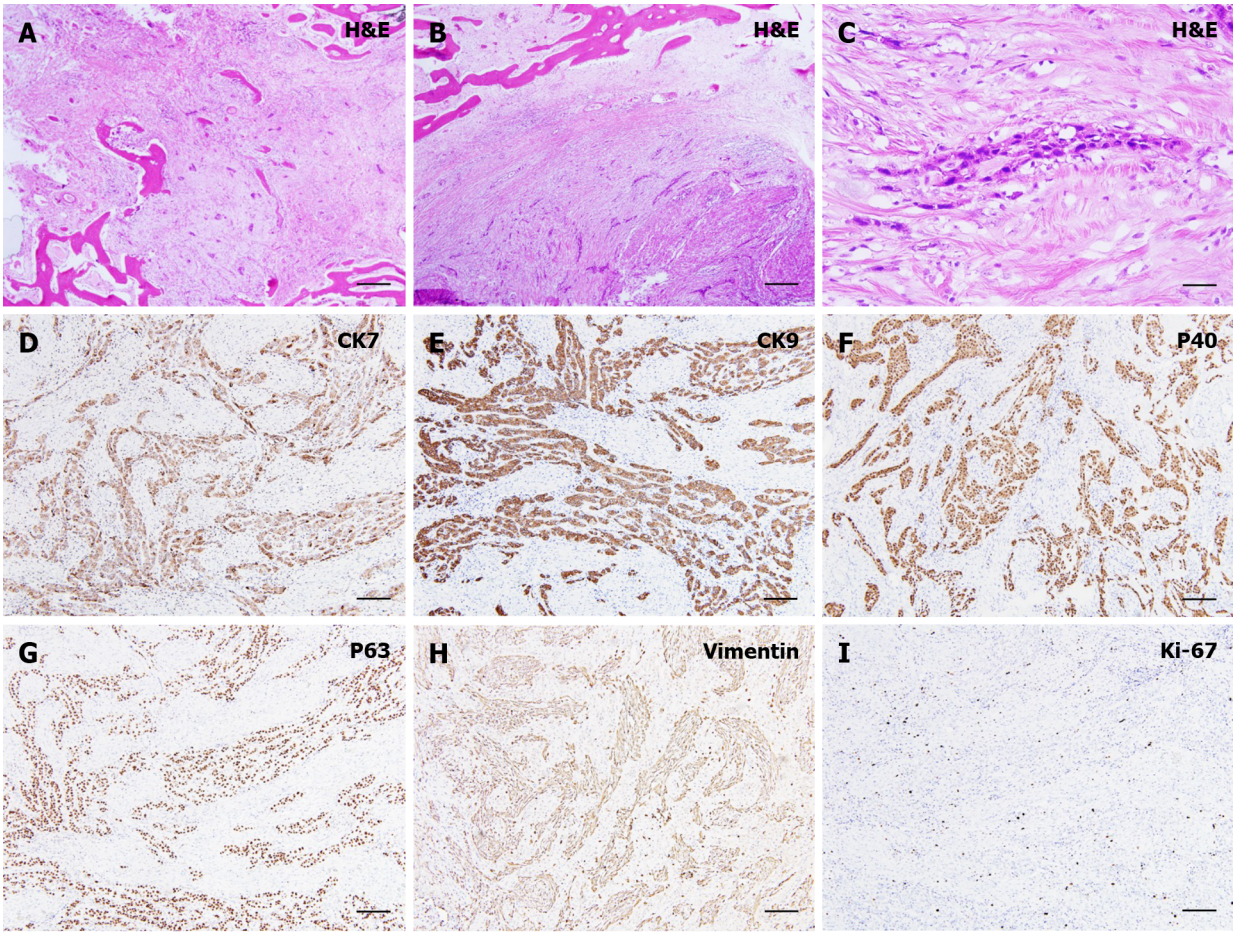
Figure 1 Clinical and radiological findings of the current case. A and B: A thorough extra-oral and intra-oral examination was performed. The patient presented with a right facial swelling without overlying skin changes. The swelling was diffuse, firm, and non-tender, causing obliteration of the right nasolabial fold. Mouth opening was not restricted and there was no palpable cervical lymphadenopathy. There were no neurosensory changes to the right infraorbital region; C: Intra-oral examination showed an irregular mass at the anterior maxilla extending from the tooth 11 to 15 region and palatally crossing the midline into the left palate. There was no obliteration of the buccal sulcus. The swelling was firm and nontender, with a non-ulcerated overlying mucosa. The adjacent teeth showed no marked increase in mobility and no fluid discharge was noted on palpation of the swelling; D: The initial dental panoramic tomogram showed a radiolucent lesion of the right maxilla extending into the right maxillary sinus (red arrows) with marked root resorption (yellow arrows); E: Computed tomography scan with contrast showed an infiltrating lesion on the right maxilla with obvious bony destruction involving the right hard palate and right inferior turbinate (red arrows); F: Tumor mapping showing an expansile mass perforating both the buccal and palatal bone; G: The osteotomy lines were planned and confirmed using the intraoperative navigation system; H: Gross specimen of the lesion.

Physical examination

Clinically, the patient presented with diffuse right facial swelling without overlying skin changes. The swelling was diffuse and firm, causing obliteration of the right nasolabial fold. Mouth opening was not restricted and there was no palpable cervical lymphadenopathy. There were no neurosensory changes to the right infraorbital region (Figure 1A and B). Intra-oral examination showed an irregular mass at the anterior maxilla, extending from the tooth 11 to 15 region, but without obliteration of the buccal sulcus. The swelling was firm and non-tender upon palpation, with non-ulcerated overlying mucosa. The adjacent teeth showed no marked increase in mobility and there was no fluid discharge noted upon palpation (Figure 1C).

Laboratory examinations

The histopathology examination of the excisional biopsy that was performed at the local hospital showed SOC. H&E sections showed small epithelial tumor cell cords in a densely collagenized stroma. No obvious dysplastic features were observed in the given specimen.



DOI: 10.12998/wjcc.v11.i8.1878 **Copyright** ©The Author(s) 2023.

Figure 2 Histological findings of the present case. A and B: Histological view focusing on small cords of epithelial cells of odontogenic origin immersed in a diffused sclerotic and collagenous stroma [hematoxylin and eosin (H&E), original magnification: × 20]; C: Evidence of vascular invasion (H&E, original magnification: × 20); D: Focal positivity in tumor cells to immunohistochemical staining for cytokeratin 7 (CK7) (original magnification: × 20); E: Immunohistochemistry for expression of CK19 demonstrating diffuse, uniform positivity in the neoplastic cells (original magnification: × 20); F: Immunohistochemistry demonstrating that the tumor cells expressed p40 (original magnification: × 20); G: Strong, diffuse positivity was seen for the expression of p63 (original magnification: × 20); H: The tumor cells were stained negative for vimentin (original magnification: × 20); I: Low proliferative activity (Ki-67) was seen (approximately 5%-10%) (original magnification: × 20). CK: Cytokeratin; H&E: Hematoxylin and eosin.

A gross pathological examination revealed a firm, expansile mass involving the right palate and right maxillary sinus. However, the overlying mucosa appeared intact and not ulcerated (Figure 1H). The resected specimens were fixed in 10% formalin, processed, and embedded in paraffin blocks for histopathological examination. H&E sections showed small nests or cords of small neoplastic epithelial cells, immersed within a sclerotic stroma, with perivascular infiltration. Under low power magnification, the tumor cells demonstrated an infiltrating nature towards mature lamellar bone fragments and generally, the tumor appeared to be non-encapsulated. The epithelial cells appeared to be faintly hyperchromatic, while focal areas of tumor islands exhibited round hyperchromatic nuclei with clear cytoplasm. Pleomorphism was uncommon and mitotic figures were scarce, with no significant cellular atypia present (Figure 2A-C). Immunohistochemically, strong positive staining was observed for cytokeratin 7 (CK7) (Figure 2D) and CK19 (Figure 2E). Tumor cell showed positive expression of p40 (Figure 2F) and p63 (Figure 2G). The tumor cells stained negative for vimentin (Figure 2H) and the proliferative activity was approximately 5%-10% according to the Ki-67 staining results, suggesting a low-grade malignancy (Figure 2I). The sections also stained negative for S-100.

Imaging examinations

The initial DPT revealed radiolucency with a welldefined sclerotic border of the right maxilla extending into the right maxillary sinus and significant root resorption of the upper central, lateral incisors, and upper right first molar. DPT was repeated and revealed an ill-defined radiolucency at the right maxilla, with a slight increase in size, as compared with the initial DPT (Figure 1D). The computed tomography (CT) scan showed an expansile enhancing osteolytic mass at the right maxilla, with marked buccal and palatal bone perforation (Figure 1E). The lesion extended into the right inferior turbinate and breached the nasal septum. No prominent radiological evidence of lymphatic spread to the cervical region was

seen.

FINAL DIAGNOSIS

A diagnosis of SOC was reached based on the clinical features and the radiological and histopathological findings.

TREATMENT

Right subtotal maxillectomy and reconstruction with a vascularized free fibula flap were performed under the guidance of an intraoperative navigation system (BrainLAB, AG, Feldkirchen, Germany). Approximately 1.5 cm surgical margins were resected, guided by the intraoperative navigation system, to ensure clear surgical margins (Figure 1F and G). The ipsilateral free vascularized fibular flap was harvested simultaneously with the tumor resection. Neck dissection was not performed because of negative clinical and radiological findings of the cervical region. Intraoperative frozen section biopsy from the surgical margins showed that all margins were tumor-free.

OUTCOME AND FOLLOW-UP

Post-operative recovery was uneventful, and the patient was subjected to standardized oral oncology follow-up. At the post-operative one and six month-reviews, the patient was pleased with her post-operative appearance and functions (Figure 3A). Upon clinical examination, the vascularized free fibula flap provided good oroantral seal and support to the facial profile. The CT scan revealed excellent bony consolidation of the graft and there was no obvious recurrence or metastasis noted radiographically or clinically (Figure 3B-D). The patient remains diseasefree 22 mo after the surgery.

DISCUSSION

SOC is a relatively rare and disputable entity that was recently featured in the 2017 WHO classification of Head and Neck Tumours[1]. Despite its recent addition to the WHO classification and its locally aggressive nature, the characteristics and treatment protocol for SOC are inadequately described because of its scarcity. The current literature review yielded 14 cases with comparable characteristics, as summarized in Table 1[2-7,9-13,15-18].

SOC seems to have peak incidence in the fourth to seventh decades of life, with a female predilection [9]. The tumor appears to have a greater propensity to affect the anterior mandible[9], with only 4 out of 11 cases involving the maxilla[2,6,7,11]. To date, including the case presented herein, there are only five reported cases involving the maxilla. Patients frequently complain of long-standing swelling[2-4,7-12], paraesthesia[3,12], pain[2,3], and tooth sensitivity[11]. Similar to our case, the patient complained of long-standing swelling, with occasional pain in the area affected. The wide spectrum of clinical presentations make determining the nature of the lesion, whether benign or malignant, difficult[14].

Radiologically, this tumor could present as well-circumscribed or poorly-defined lytic radiolucency with cortical bone perforation[2-4,9,12,13]. Our case demonstrated similar radiographical features, with both well- and ill-defined sclerotic lesions and notable cortical bone perforation. Root resorption was only described in one of the published cases[11], despite the locally aggressive nature of the tumor. The infiltrative and locally aggressive nature was demonstrated in this case, as indicated by the marked buccal and palatal bone perforation and distinct tooth root resorption on both plain radiographs and CT scans.

Histologically, the tumor is typically characterized by infiltrative thin cords or small nests of epithelial cells in the densely sclerotic stroma. Perineural, intraneural, or vascular invasion, which is another distinguishing feature, were also described in seven cases[3,8,9,11-13], similar to our case, which displayed perivascular infiltration in the H&E section. Although there is no distinctive immunohistochemical marker for SOC, consistent cytokeratin immunoreactivity was seen, with positive staining for CK5/6, p40, and p63 in most reported cases. Only one case demonstrated weak nuclear staining for p63 [7] and two cases displayed positivity for CK14[5,7]. Most cases reported negative staining for CK7, whereas our case demonstrated diffuse CK7 expression, which is similar to that reported by Tan *et al* [10], while Koutlas *et al*[3] and Irié *et al*[12] showed focal expression of CK7. Most cases reported negative results for vimentin and S-100, which is similar to the present case; only one case reported unexpected negative staining for CK19[5]. Ki-67 was used in most cases to assess the proliferative index of the tumor, which appeared to be insignificant in the reported cases, which is similar to the current

Table 1 Literature review of reported cases of sclerosing odontogenic carcinoma

Ref.	Gender, age (yr)	Site, symptoms	Duration	Radiological features	Treatment	Histopathological features			Outcome
						H&E	IMC		
							Positive staining	Negative staining	
Landwehr and Allen[2], 1996 (Koutlas *et al*[3], 2008)	F, 46	Pain in the right mandible	Not mentioned	Poorly defined osteolytic lesion with perforation of buccal plate and thinning of lingual plate	Wide resection with 1 cm margin	Islands of moderately pleomorphic neoplastic epithelial cells interspersed with dense fibrous connective tissue	CK5/6, CK19	Not mentioned	No recurrence after 12 yr
Koutlas and Warnock[8], 2005 (Koutlas *et al*[3], 2008)	M, 72	Left mandibular mass (33-35) protruding into vestibule with mental nerve paraesthesia	"Long" duration	Radiolucency affecting the lower left canine and premolar	Wide resection with ipsilateral neck dissection	Thin cords and small nests of epithelium in densely collagenized stroma with invasion of striated muscle and perineural infiltration	CK5/6, CK19, CK7 (focal), p63, E-cadherin	CK8/18, CK20, S-100, SMA, CEA, desmin	No recurrence after 5 yr
Chaisuparat *et al* [6], 2006 (Koutlas and Warnock[8], 2005; Koutlas *et al*[3], 2008)	F, 73	Enlargement of right maxilla	Not mentioned	Diffuse radiolucency involving alveolar ridge and extended into maxillary sinus	Wide resection with post-operative radiotherapy	Small nests and slender cords of epithelial cells in densely collagenized stroma with muscle and perineural infiltration	p63	Not mentioned	No recurrence after 3.5 yr
Ide *et al*[13], 2009	F, 47	2 cm mass on lower left lingual gingiva	2 yr	Unilocular radiolucency with sclerotic inferior border surrounding roots of mandibular left second premolar and first molar	Resection with neck dissection	Small islands of tumour cells reminiscing epithelial cell rests of Malassez infiltrating the cancellous bone	Not mentioned		No recurrence after 6 yr
Irié *et al*[12], 2010	M, 67	Paraesthesia in left mental region	Not mentioned	Focally expansile lesion with thinning of buccal cortical bone with admixed of radiolucent and radiopaque areas	First surgery: curettage; Second surgery: Segmental mandibulectomy with chemotherapy	Foci of thin cords and small nests of epithelial cells in fibrous stroma with epithelial cells invading into the mandibular canal	p63, CK6, CK19, CK7 (focal), AE1/AE3	S100, CEA, calretinin, CD34, vimentin, CK8, CK20, SMA, amelogenin, MIB-1 < 3%	Recurrence 8 mo after the first surgery.No recurrence after 15 mo of the second surgery
Hussain *et al* [11], 2013	M, 54	Sensitivity of upper right canine with a firm lump	Not mentioned	Well defined radiolucency associated with the upper right lateral incisor and canine teeth with loss of the lamina dura and irregular resorption of the canine root was seen	Resection with close follow-up	Small infiltrative islands in densely fibrous stroma with perineural infiltration	AE1-3, CK5/6, CK19	Not mentioned	No recurrence after 19 mo
Saxena *et al*[9], 2013	M, 42	Firm swelling at left mandibular lateral incisor to second premolars	11 mo	Well-defined unilocular lytic lesion and perforation of both buccal and lingual cortices	First surgery: excision; Second surgery: Hemimandibulectomy with radical neck dissection and radiotherapy	Cords and nests of tumour cells in dense fibrous sclerosing stroma with vascular invasion	CK5/6, P63	S100, SMA, Desmin	No recurrence after 10 mo

Tan *et al*[10], 2014	F, 31	1 cm hard swelling at lower right first molar region	Lower right first molar was extracted 10 yr ago	Well-circumscribed round radiolucent lesion with scattered specks of radiopacities with a distinct sclerotic peripheral margin	Enucleation	Small clusters neoplastic cells in diffusely sclerotic stroma	CK7, CK5/6, CK19, CK8/18, CAM 5.2, p63, p16 (weak), p53E-cadherin	Vimentin, CEA, EMA, CK20, SMA, S-100, CD1a, ER, PR, FISH EWSR 1, calretinin, CD34, desmin, Ki-67 < 2%	No recurrence after 1 yr
Wood *et al*[7], 2016 (Gordon *et al*[18], 2015)	F, 43	Asymptomatic firm lump at right anterior hard palate	Not mentioned	Enhancing soft tissue mass arising from the right hard palate with no bone destruction	Maxillectomy with wide margins and reconstruction with obturator	Small groups and prominent cords of bland hyperchromatic cells with minimal nuclear pleomorphism and eosinophilic cytoplasm	CK14, CK19, E-cadherin, weak nuclear staining to p63	S100, PR, FISH EWSR 1	Disease free after 17 mo
Hanisch *et al*[4], 2017	M, 60	Swelling at left premolar/molar region	Not mentioned	Ill-defined osteolytic changes with expansion, erosion, and perforation	Left hemimandibulectomy with ipsilateral radical neck dissectionSecondary reconstruction with CAD/CAM endoprosthesis (replacement of TMJ) and reconstruction with fibula flap	Small epithelial tumour cells and cords infiltrating lamellar bone	CK5/6, p40, p63, and MNF116	Not mentioned	Disease free after 22 mo
Todorovic *et al* [5], 2019	M, 62	Progressive left maxillary swelling with recurrent sinus infections and mobility of teeth	6 mo	Ground glass appearance with loss of trabeculations of left maxilla	Left maxillectomy and removal of skull base involving the infratemporal fossaUnderwent high-dose radiotherapy (66Gy in 33 fractions) for recurrence	Non-encapsulated tumour with mixed epithelial and mesenchymal components. Epithelial component consisted of highly infiltrative nests and cords of small polygonal and cuboidal cells with eosinophilic cytoplasm and mild-moderate nuclear atypia, usually associated with a dense background stroma. Significant intratumoral variability was observed	CK5/6, CK14, p63	CK7, CK19, CK20, EBER ISH, ER, PAX8, CDX2, FISH EWSR 1, Ki-67 10%	Recurrence at 5 mo after surgery;No recurrence 19 mo following radiotherapy
Seyiti *et al*[15], 2020	F, 54	Discomfort at left posterior mandibular region, associated with numbness of lower lip	3 mo	CBCT/SCT: irregular extensive osteolytic lesion with poorly defined borders and patchy calcifications were noted in the lesion. Slight resorption of cementum in apical region was seen. Obvious thickening of bilateral mandibular body was seen	Extensive resection and reconstruction with free fibula flap	Strands of epithelial tumor cells with clear cytoplasm infiltrating the fibrous stroma, osseous trabeculae and perineural invasion was observed	CK5/6, p63,	SMA, S-100, desmin, Ki-67 approx. 10%, EWSR1	Not mentioned
O'Connor *et al* [16], 2019	F, 43	Asymptomatic, incidental finding of radiolucency of right anterior maxilla	16 yr	Well-defined radiolucency with resorption of tooth roots and cortical thinning and erosion	First surgery: Biopsy; Second surgery: Conservative enucleation; Third surgery: Resection with a margin of 5 mm	Islands of epithelium within fibrous connective tissue that are mostly collagenous and sclerosed. Evidence of perineural invasion was seen	AE1/3, CK5, CK14, CK19	CK7, Ki-67 < 1%, FISH EWSR1	No recurrence 12 mo post-op
Kataoka *et al* [17], 2018	F, 68	Rapid, painless swelling of anterior mandibular region, with ulcerated overlying gingiva	3 mo	CT: Radiolucency around the root of central incisor, with resorption of labial cortex; no root resorption; MRI: Well-defined internal heterogenous and extraosseous mass	*En-bloc* resection of 4 incisors and alveolar bone preserving lingual periosteum	Eosinophilic polyhedral tumor cells scattered under epithelium. Dispersed tumor nests with circular patterns and pressed by sclerosing fibrous stroma. No perineural and vascular infiltration, or invasion of skeletal muscle	AE1/AE3, EMA, p63, CK19	CK5/6, Ki-67 approx. 2%, CK7	No recurrence or metastasis more than 5 yr after surgery

Present case	F, 62	Small indolent swelling at anterior palate, associated with intermittent toothache	7 yr	Well-defined sclerotic border of the right maxilla extending into the right maxillary sinus with significant root resorption was seen on upper right central and lateral incisors and upper right first molar	First surgery: Excisional biopsy; Second surgery: Right subtotal maxillectomy and reconstruction with free fibular flap	Small nests or cords of small epithelial cells, and occasionally clear cells, immersed in a diffuse sclerotic and collagenous stroma. The epithelial cells appeared to be faintly hyperchromatic and mitotic figures were uncommon. Perivascular and perineural infiltration were observed	CK7, CK19, p40, p63	Vimentin, Ki-67 5%-10%	Disease free after 22 mo

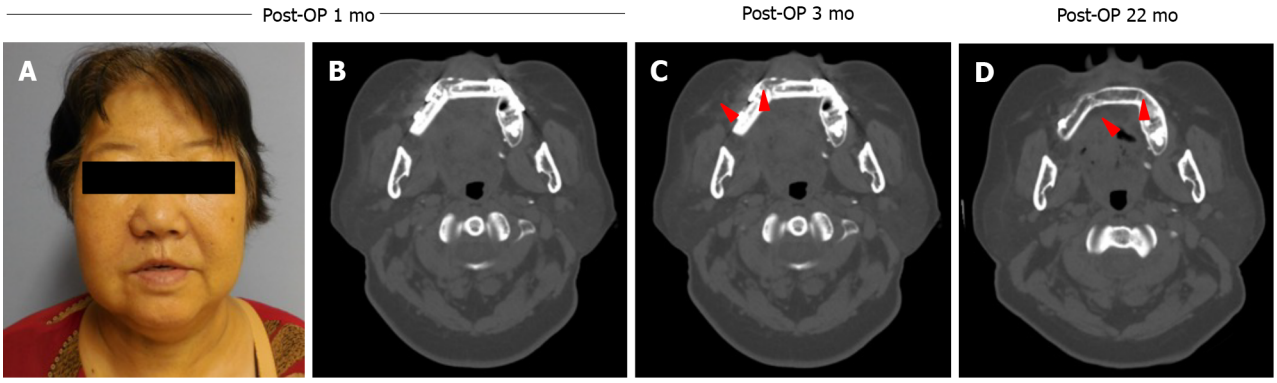
CT: Computed tomography; H&E: Hematoxylin and eosin; CK: Cytokeratin; F: Female; M: Male; IMC: Immunohistochemistry.

case.

Our case demonstrated substantial demographical, histopathological, and radiographical similarities with previous cases. In this case, the tumor was neglected, possibly because of the vague signs and symptoms. Our immunohistochemistry results were also comparable to those of other published cases, with positive staining of the tumor cells for CK19, p40, and p63. The infiltrative growth pattern with vascular invasion was also similar to the case reported by Saxena *et al*[9], while eight published cases showed evidence of perineural invasion[3,4,7,9,11,12,15,16]. In contrast, four cases reported a lack of perineural or vascular infiltration[5,10,13,17]. Although perineural invasion was often associated with poorer locoregional control and prognosis in squamous cell carcinoma, this appears to be a distinctive histopathological feature in most of the reported cases reported. However, more cases are required to further validate this specific feature as a prognostic factor or tumor grading for SOC. Distant or regional metastasis is yet to be reported in SOC, based on the available published data.

Exclusion from the differential diagnosis can be difficult because of the histopathological resemblance of SOC to other histological differential diagnoses, such as central odontogenic fibroma and desmoplastic ameloblastoma. Central odontogenic fibroma (particularly the epithelial-rich type) is clinically less aggressive than that SOC. The stroma is variably cellular, with fibroblastic connective tissue, and unlike in SOC, the stroma appears to be densely fibrous and sclerotic. Although desmoplastic ameloblastoma demonstrated dense fibrous stroma similar to SOC, it should present with focal ameloblastic columnar cells, even if the presentation is scant. A metastatic tumor was ruled out in this case, given the strong positive expression of p63, which confirmed the basal characteristics of the epithelial cells.

Currently, we lack a standardized treatment protocol because of the rarity of the tumor. SOC demonstrated permeative and locally aggressive characteristics, thus it should warrant more radical resection to prevent local recurrence. Recurrence was reported in two patients following curettage; however, there was no recurrence noted after the subsequent ablative surgery and high-dose radiotherapy, respectively[5,12]. Our case also experienced a recurrence of the tumor at one year following the excisional biopsy; therefore, conservative management of enucleation or curettage might not be adequate. Hussain *et al*[11] suggested that conservative tumor-free margins of 5 mm should be used. By contrast, Landwehr and Allen[2] reported close margins despite having 1.0 cm resection margins. The invasive properties of SOC and its close margins following 1.0 cm surgical margins, as mentioned in the previous reports, prompted us to propose that the surgical margins should be extended to 1.5 cm for both hard and soft tissues to ensure tumor-negative margins. However, more



DOI: 10.12998/wjcc.v11.i8.1878 **Copyright** ©The Author(s) 2023.

Figure 3 Post-operative clinical and radiological findings. A and B: At postoperative 1-mo review, the patient was satisfied with her appearance and functions; C: The fibular segments appeared to be in the process of osseointegration at postoperative 3mo review (red arrows); D: No sign of recurrence observed at postoperative 22-mo review. Post-OP: Post-operative.

cases are required to better appreciate the true origin, morphological features, and biological behavior to definitively ascertain the tumor resection margins.

To date, based on the currently available data, there is still no evidence of cervical lymphatic spread or distant metastasis reported. The tumor appears to have no evident metastatic capability, despite a typical long-standing history, which is again demonstrated in our case. Nevertheless, two patients were subjected to radiotherapy[5,6,9], two patients underwent neck dissection in addition to tumor resection [3,8,9], one patient underwent chemotherapy following tumor resection[12], and one patient received high-dose radiotherapy following disease recurrence[5]. However, prophylactic neck dissection or adjunct therapy, such as chemotherapy and radiotherapy, were deemed unnecessary because the tumor has yet to show metastasis potential[9,11]. As the treatment approach and its efficacy for SOC remains ambiguous, we suggest that standard oral oncology follow-up should be carried out for at least 5 years in patients diagnosed with SOC because of the locally aggressive and infiltrative nature of this tumor. More cases are required to further illustrate this entity and guide clinical diagnosis and treatment.

CONCLUSION

In summary, the biological behaviors, and characteristics of SOC remain ambiguous owing to its rarity, with limited case reports published to date. More cases are needed to further characterize this entity, understand its biological behavior, and justify the treatment protocols. To date, surgical resection with adequate surgical margins remains the mainstay treatment, with no disease recurrence in most cases, while neck dissection and postoperative radiotherapy or chemotherapy were not deemed necessary. We hope that this case report will facilitate the validation of this disease entity and contribute to the establishment of treatment protocols.

FOOTNOTES

Author contributions: All authors have made substantial contributions to the manuscript; Soh HY, Zhang WB and Yu Y collected patient's data, managed the patient, and drafted the manuscript; Zhang R and Chen Y prepared and performed microscopic examination of all the histology slides and drafted the manuscript; Chen Y and Gao Y helped interpret the histology slides and guided the diagnostic process; Peng X performed the surgery and revised the manuscript critically; All authors have read and approved the final version of the manuscript.

Informed consent statement: Written consent for publication was obtained from the patient.

Conflict-of-interest statement: The authors declare that they have 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).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-

commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Hui Yuh Soh 0000-0002-8134-0861; Wen-Bo Zhang 0000-0002-2909-3525; Xin Peng 0000-0001-8535-1771.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

REFERENCES

1 **Speight PM**, Takata T. New tumour entities in the 4th edition of the World Health Organization Classification of Head and Neck tumours: odontogenic and maxillofacial bone tumours. *Virchows Arch* 2018; **472**: 331-339 [PMID: 28674741 DOI: 10.1007/s00428-017-2182-3]
2 **Landwehr D**, Allen C. Aggressive odontogenic epithelial neoplasm mimicking metastatic brreast carcinoma:sclerosing odontogenic carcinoma? *Oral Surg Oral Med Oral Pathol Oral Radiol* 1996; **82**: 206 [DOI: 10.1016/s1079-2104(96)80235-6]
3 **Koutlas IG**, Allen CM, Warnock GR, Manivel JC. Sclerosing odontogenic carcinoma: a previously unreported variant of a locally aggressive odontogenic neoplasm without apparent metastatic potential. *Am J Surg Pathol* 2008; **32**: 1613-1619 [PMID: 18753945 DOI: 10.1097/PAS.0b013e31817a8a58]
4 **Hanisch M**, Baumhoer D, Elges S, Fröhlich LF, Kleinheinz J, Jung S. Sclerosing odontogenic carcinoma: current diagnostic and management considerations concerning a most unusual neoplasm. *Int J Oral Maxillofac Surg* 2017; **46**: 1641-1649 [PMID: 28641898 DOI: 10.1016/j.ijom.2017.05.024]
5 **Todorovic E**, Berthelet E, O'Connor R, Durham JS, Tran E, Martin M, Hayes MM, Ng TL. Sclerosing Odontogenic Carcinoma with Local Recurrence: Case Report and Review of Literature. *Head Neck Pathol* 2019; **13**: 371-377 [PMID: 30315432 DOI: 10.1007/s12105-018-0975-6]
6 **Chaisuparat R**, Coletti D, Kolokythas A, Ord RA, Nikitakis NG. Primary intraosseous odontogenic carcinoma arising in an odontogenic cyst or de novo: a clinicopathologic study of six new cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **101**: 194-200 [PMID: 16448921 DOI: 10.1016/j.tripleo.2005.03.037]
7 **Wood A**, Young F, Morrison J, Conn BI. Sclerosing odontogenic carcinoma presenting on the hard palate of a 43-year-old female: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2016; **122**: e204-e208 [PMID: 27743835 DOI: 10.1016/j.oooo.2016.07.009]
8 **Koutlas IG**, Warnock GMJ. "Intraossesous" sclerosing carcinoma of possible odontogenic origin. Report of two cases. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2005; **100**: 187 [DOI: 10.1016/j.tripleo.2005.05.013]
9 **Saxena S**, Kumar S, Rawat S, Arun Kumar KV. An indolent swelling of the parasymphyseal area. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013; **116**: 528-533 [PMID: 22835659 DOI: 10.1016/j.oooo.2012.03.031]
10 **Tan SH**, Yeo JF, Kheem Pang BN, Petersson F. An intraosseous sclerosing odontogenic tumor predominantly composed of epithelial cells: relation to (so-called) sclerosing odontogenic carcinoma and epithelial-rich central odontogenic fibroma. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014; **118**: e119-e125 [PMID: 24767700 DOI: 10.1016/j.oooo.2014.02.010]
11 **Hussain O**, Rendon AT, Orr RL, Speight PM. Sclerosing odontogenic carcinoma in the maxilla: a rare primary intraosseous carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013; **116**: e283-e286 [PMID: 23567261 DOI: 10.1016/j.oooo.2013.01.018]
12 **Irié T**, Ogawa I, Takata T, Toyosawa S, Saito N, Akiba M, Isobe T, Hokazono C, Tachikawa T, Suzuki Y. Sclerosing odontogenic carcinoma with benign fibro-osseous lesion of the mandible: an extremely rare case report. *Pathol Int* 2010; **60**: 694-700 [PMID: 20846269 DOI: 10.1111/j.1440-1827.2010.02583.x]
13 **Ide F**, Mishima K, Saito I, Kusama K. Diagnostically challenging epithelial odontogenic tumors: a selective review of 7 jawbone lesions. *Head Neck Pathol* 2009; **3**: 18-26 [PMID: 20596984 DOI: 10.1007/s12105-009-0107-4]
14 **Lim D**, Tan CC, Tilakaratne WM, Goh YC. Sclerosing odontogenic carcinoma - review of all published cases: is it a justifiable addition as a malignancy? *Braz J Otorhinolaryngol* 2022; **88**: 118-129 [PMID: 33715971 DOI: 10.1016/j.bjorl.2021.01.007]
15 **Seyiti P**, Feng Y, Gao A, Lin Z, Huang X, Sun G, Zhang L, Wang T. An extensive sclerosing odontogenic carcinoma in mandible: a case report and literature review. *Dentomaxillofac Radiol* 2020; **49**: 20190426 [PMID: 32320271 DOI: 10.1259/dmfr.20190426]
16 **O'Connor RC**, Khurram SA, Singh T, Jones K. Sclerosing odontogenic carcinoma - what we know so far. *Oral Surg* 2019; **12**: 133-138 [DOI: 10.1111/ors.12391]
17 **Kataoka T**, Fukada K, Okamoto T, Nagashima Y, Ando T. Sclerosing odontogenic carcinoma in the mandible. *J Oral Maxillofac Surg, Med Pathol* 2018; **30**: 428-433 [DOI: 10.1016/j.ajoms.2018.03.007]
18 **Gordon P**, Morrison J, Wood A, Conn B. A case report of sclerosing odontogenic carcinoma of the hard palate. *Br J Oral Maxillofac Surg* 2015; **53**: e49 [DOI: 10.1016/j.bjoms.2015.08.042]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2023 Baishideng Publishing Group Inc. All rights reserved.