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eHealth, telehealth, and telemedicine in the management of the COVID-19 pandemic and beyond: Lessons learned and future perspectives

Andrea Giacalone, Luca Marin, Massimiliano Febbi, Thomas Franchi, Marcos Roberto Tovani-Palone

Abstract

In this article, we discuss evidence supporting the effective implementation of eHealth, telehealth, and telemedicine during the coronavirus disease 2019 pandemic, with a view towards its permanent future integration in healthcare. We performed a literature search for articles describing the use of telehealth/telemedicine in the pandemic context using five databases. The articles selected describe the use of telemedicine as its advantages in terms of practicality and cost-effectiveness. This synthesis of articles is applicable to high-, middle- and low-income countries. Some of the notable benefits include breaking down geographical and time barriers, reducing waiting lists and crowding in healthcare facilities, and saving on national healthcare expenditure. However, there are a number of difficulties with the widespread implementation of telemedicine services that mainly relate to bureaucratic and regulatory concerns. Moreover, it is also important to make healthcare professionals and providers aware of the limits of this tool to avoid potential cases of negligence. Patients in turn will have to be made aware of and be educated on the use of this new healthcare modality before it is accepted by them. In the current socio-economic climate, it is therefore essential to implement a telehealth model aimed at efficiency and continuity of healthcare, as well as leading to an improvement in the quality of life of patients,
whilst optimising existing resources and reducing costs. In that regard, the adoption of eHealth, telehealth, and telemedicine services should be considered highly timely, despite current existing limitations.

**Key Words:** eHealth; Telehealth; Telemedicine; Coronavirus disease 2019; Pandemics; Delivery of healthcare

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**Core Tip:** In an attempt to contain the spread of coronavirus disease 2019, increasing pressure was placed on the healthcare sector to adapt to challenge of delivering care, thereby necessitating the adoption of innovative telehealth solutions to both ensure and optimize patient care. This has resulted in the accelerated development, utilisation and acceptability of telemedicine in several fields. In this sense, the current pandemic presents a once-in-a-generation opportunity for countries to implement appropriate telemedicine services. As healthcare continues to evolve and innovate, one of the main shifts in practice that we are likely to experience will be the growing use of digital healthcare technologies.

**INTRODUCTION**

The coronavirus disease 2019 (COVID-19) pandemic represents the most serious public health threat in modern times, with long-lasting negative sequelae being seen in several sectors of the normal lives of those in affected countries around the world. In an attempt to contain the spread of the disease, increasing pressure was placed on the healthcare sector to adapt to challenge of delivering care, thereby necessitating the adoption of innovative telehealth solutions to both ensure and optimize patient care [1]. This has resulted in the accelerated development, utilisation and acceptability of telemedicine [2-3]. Prior to the pandemic, the use of telehealth was limited, with the main use cases of telehealth interventions being the care of patients with noncommunicable diseases, such as diabetes; however, the pandemic has propelled the widespread adoption of eHealth across numerous settings [4-6].

Telemedicine brings with it a host of benefits to patients, healthcare providers and the wider society, including reductions in the need for hospitalizations or readmissions, as well as on overall costs of healthcare and length of inpatient stay. In addition, it has been suggested that its use may provide psychological benefits to patients, including greater rates of satisfaction and medication adherence [7]. eHealth, telehealth and telemedicine solutions can be used interchangeably, providing convenient, low cost, and accessible health-related information and communication remotely, using internet-based technologies [8].

Several areas of healthcare have seen the successful adoption of telemedicine during the COVID-19 pandemic, ranging from mental health services to physical therapy and many others [4-6]. This article highlights the evidence for and opportunities presented by the use of telehealth/telemedicine during a pandemic scenario, as well as in periods of normality.

**METHODS**

A thorough literature search for articles was performed using five academic literature databases: CINAHL, MEDLINE/PubMed, Web of Science, Scopus, and Google Scholar. The search was done by combining keywords related to COVID-19, eHealth, telehealth and telemedicine, using the Boolean operators AND, OR, or NOT. The most recent, relevant and reliable scientific articles were considered and included in the review.
TELEHEALTH FOR PHYSICAL AND MENTAL WELLBEING

The incidence of mental health conditions saw a steep incline during the pandemic, likely due to measures of social isolation and fear of social interaction. Although mental health services began experimenting with the use of telemedicine as a means of providing mental health care in the period prior to the pandemic, this practice had only been implemented in less than 1% of consultations[9]. Peri-pandemic, these numbers have increased exponentially, with data revealing that 41% of mental health care and/or substance abuse services were facilitated by telemedicine interventions[10]. Indeed, Zhou *et al*[11] have recommended the implementation of ‘telemental health’ services as a viable and appropriate approach to supporting patients, their families, and healthcare providers during these challenging times.

Another important aspect of consideration is that during the periods of confinement due to COVID-19, many people experienced a change in their eating habits and a reduction in physical activity levels. An illustrative example of the use of telemedicine can also be seen here. Increases in body weight in patients with non-alcoholic fatty liver disease (NAFLD) may lead to disease progression, whilst weight gain in patients with human immunodeficiency virus (HIV) has been associated with the onset of cardiovascular disease. Policarpo *et al*[12] monitored the eating habits of these patients through a telemedicine dietary intervention, which successfully limited weight gain in NAFLD-HIV patients, serving to reinforce the effectiveness of using such tools in the management of patients’ conditions.

TELEHEALTH AND ITS WIDER APPLICATIONS

A recent study by Kichloo *et al*[13] highlights various advantages of telemedicine, including its cost-effectiveness, increased access to speciality services, and key potential to help mitigate the growing worries of physician shortage. Miller *et al*[14] validated these advantages in their study that assessed the implementation of telehealth physical therapy services in the context of the COVID-19 pandemic, in which the authors identified several strategies to aid its implementation. Over the three-month period from March to May 2020, the authors conducted 4548 physical therapy sessions remotely via a telehealth platform. A survey completed by each patient to assess the effectiveness of this intervention, revealed that 94% of participants felt satisfied with the outcome they received from the sessions and that 92% would attend another telehealth session. These novel findings provide important patient-focused evidence to support the implementation of telehealth physical therapy as a feasible alternative to in-person visits during, and indeed after, the pandemic.

Stanhope *et al*[15] have additionally substantiated these findings and recommended the continuation of telephysiotherapy as a form of primary care post-COVID-19, prior to face-to-face sessions where needed, due to its particularly successful implementation during the pandemic. In this context, it is also worth noting that the telemanagement of patients with home-based bilevel positive airway pressure ventilation has been found to reduce the need for endotracheal intubation in the early stages of COVID-19 pneumonia, whilst decreasing contact time with healthcare staff and the possibility of transmission of COVID-19. Thus, the practice of such telehealth intervention could prevent disease progression and hospitalization in some cases[16].

Furthermore, Thatcher *et al*[17] highlighted in their work several opportunity costs of attending orthopedic clinic consultations in person. Their survey found that patients often miss work (46%), lose income (34%) and drop out of their usual recreational activities (27%) in order to attend consultations. Patients became aware that through telemedicine it is possible to avoid the need for travel or time spent waiting in the clinic, resulting in time saved to dedicate to their usual activities. However, most patients (61%), preferred for their first consultation to be in-person, with telemedicine used for orthopedic follow-up care. Telemedicine can reduce both overcrowding in outpatient clinics and waiting lists. This would be an advantage for severe acute respiratory syndrome coronavirus 2 infection prevention as well as ensuring timely access to treatment for all those in need[18].

TELEHEALTH-BASED MODELS OF CARE

A model of care based on the use of telemedicine from the first contact between healthcare professionals and patient (in a primary care setting), has been shown to be of fundamental importance. Gudi *et al*[19] outlined how telehealth interventions have the potential to address persistent challenges in primary care worldwide, while strengthening the public health response to COVID-19. Further, Monaghan *et al*[20] corroborated this notion in their systematic review of eight studies, which concluded that telehealth interventions are able to improve the overall delivery of care whilst maintaining the safety of patients and healthcare providers during the pandemic.

Looking forwards, Doraiswamy *et al*[21] provided compelling evidence for the ongoing application of telehealth interventions in the future landscape of healthcare. However, this review highlights discrepancies in the application of telemedicine in resource-limited settings, which may serve to widen the economic and societal divide already seen in healthcare. This concern is of course valid, given that many
countries do not have any form of telemedicine integrated into their national healthcare systems. Although there is a strong focus on the growth of telemedicine in high-income countries, the telemedicine revolution could have an even greater benefit in low- and middle-income countries, where it has the potential to improve healthcare access to the most vulnerable and geographically remote patients[22]. In this sense, the COVID-19 pandemic could be viewed as a once-in-a-generation opportunity for countries to implement telemedicine services through an appropriate regulatory framework[23]. For this to become a reality, aspects such as privacy and data protection should also be addressed by governments and health authorities in order to ensure the safety of users[24].

RISKS AND LIMITATIONS OF TELEHEALTH

As with face-to-face medical consultation, telehealth and telemedicine practices similarly carry liability risks. The three main areas for telecare pitfalls relate to: Documentation issues, poor triage decisions, and a dysfunctional office system. This can lead, in some cases, to superficial use of defined care pathway that can put the patient at risk[25]. In addition to the risks to patient, healthcare professionals must take responsibility for their actions within the scope of their competence. This means being aware of the legal aspects relevant to the delivery of telehealth and telemedicine services. Thus, telemedicine service providers are encouraged to determine in advance what each local region’s policies and requirements are for informed consent, malpractice insurance coverage and maintaining privacy and security in this type of setting[26].

It is noteworthy that not all medical consultations can be performed through telemedicine, so healthcare professionals must be able to assess whether or not the situation is suitable for remote consultations. Moreover, patients should always be informed about the functionalities and limitations of this type of health care delivery[27]. This is especially pertinent given the relatively low levels of patient awareness regarding telemedicine and that many patients have never used it before[28].

In the current healthcare service environment, there remains a concern that system security can be targeted by a cyberattack. In order to guarantee the security of patients and their data, it is important to ensure adequate and effective security measures are in place[29].

CONCLUSION

As healthcare continues to evolve and innovate, one of the main shifts in practice that we are likely to experience will undoubtedly be the growing use of digital healthcare technologies, such as the Internet of Things, the Internet of Medical Things, big data analytics, artificial intelligence, machine learning, 5G and beyond telecommunications, and blockchain technology[30,31]. Whilst not discounting the high initial costs when adopting telehealth approaches to care[32], we conclude that there is currently sufficient evidence in the literature to validate telehealth and telemedicine interventions as viable alternative to providing optimal patient management in many areas of healthcare[33].

FOOTNOTES

Author contributions: Giacalone A conceptualized the study and wrote the original draft; Franchi T and Tovani-Palone MR helped with literature acquisition and data validation; Marin L, Febbi M, Franchi T and Tovani-Palone MR helped in writing the original draft; Giacalone A, Franchi T and Tovani-Palone MR wrote the review; Franchi T and Tovani-Palone MR edited the manuscript; Tovani-Palone MR supervised the study.

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Developing natural marine products for treating liver diseases

Qian Wei, Jin-Sheng Guo

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Abstract

In recent years, marine-derived bioactive compounds have gained increasing attention because of their higher biodiversity vs land-derived compounds. A number of marine-derived compounds are proven to improve lipid metabolism, modulate the gut microbiota, and possess anti-inflammatory, antioxidant, antibacterial, antiviral, and antitumor activities. With the increasing understanding of the molecular landscape underlying the pathogenesis of chronic liver diseases, interest has spiked in developing new therapeutic drugs and medicine food homology from marine sources for the prevention and treatment of liver diseases.

Key Words: Natural marine products; Liver disease; Treatment; Liver

Core Tip: The prevalence of liver diseases has been rising worldwide, especially non-alcoholic fatty liver disease that is associated with increasingly urbanized lifestyles and dietary changes. Effective and cost-efficient drugs and medicine food homology are needed in concert with improving liver health. Marine sources are rich and play an important role in the generation of unique drugs. A number of marine-derived compounds are proven to improve lipid metabolism, modulate the gut microbiota, prevent reactive oxygen species formation, and possess anti-inflammatory and anticancer activities, which means that they can be an invaluable source for the discovery of new compounds for the prevention and treatment of liver diseases.

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INTRODUCTION

Liver diseases are rapidly emerging as global health priorities. With increasingly urbanized lifestyles and dietary changes involving high caloric contents, the overall prevalence of non-alcoholic fatty liver disease (NAFLD) has increased dramatically. Non-alcoholic steatohepatitis (NASH) has become one of the leading causes of liver transplantation in the United States[1]. NAFLD is associated with metabolic syndrome and the development of cardiovascular and kidney diseases. Alcoholic liver disease (ALD) is caused by heavy alcohol intake. Almost 50% of cirrhosis-related deaths are due to excessive alcohol consumption[2]. Hepatitis B virus (HBV) infection is the most common cause of chronic hepatitis worldwide and remains the primary cause of cirrhosis and hepatocellular carcinoma (HCC) in most Asian nations. Hepatitis C virus (HCV) has infected 71 million people worldwide[3]. HCC is one of the most common malignant tumors worldwide. HBV, HCV, NAFLD, and ALD are significant risk factors for HCC. Drug-induced liver injury (DILI) is an important cause of acute liver failure. All chronic liver diseases can lead to liver cirrhosis and decompensation, thus requiring effective and cost-efficient treatments.

The ocean accounts for 70% of the Earth’s surface area[4]. Marine organisms are known for their ability to produce large amounts of bioactive compounds, whose biological activities could interfere with the pathogenesis of many diseases. Interest in marine organisms as a source of health-promoting agents has increased in recent decades. Marine organisms are classified as marine plants (e.g., seaweeds and mangroves), marine animals (e.g., sponges, corals, shellfish, krill, and ascidians), and marine microorganisms, according to their biological characteristics. They have been found to be rich sources of bioactive compounds with anti-inflammatory, antioxidant, antibacterial, antiviral, anti-tumor, and lipid-lowering activities. This review discusses current applications of bioactive marine compounds in studying liver diseases (briefly summarized in Table 1).

NAFLD

NAFLD is a spectrum of common liver diseases and currently is responsible for a global disease epidemic with an estimated worldwide prevalence of 25%[5]. The highest rates are reported in South America and the Middle East, followed by Asia, the USA, and Europe. NAFLD includes a range of diseases ranging from fatty liver to NASH, liver fibrosis, cirrhosis, and liver cancer. Insulin resistance, lipotoxicity, mitochondrial dysfunction, oxidative stress, intestinal microbiome disorders, and genetic and epigenetic factors are related to NAFLD pathogenesis[6]. Data from several studies have shown improvements in patients with NASH after treatment with vitamin E, liraglutide, statins, glitazones, and pioglitazone[7]. However, no special therapeutic medications have been approved by the Federal Drug Administration (FDA). In the absence of effective pharmacological agents for NAFLD, lifestyle interventions such as increased exercise and energy restriction, lowering hepatic lipid levels, and increasing insulin sensitivity are important measures. Several studies of bioactive marine substances have provided new therapeutic prospects for NAFLD.

Fish oil contains a variety of n-3 long-chain polyunsaturated fatty acids (PUFAs), including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which can activate the peroxisome proliferator receptor (PPAR) and downregulate the expression of sterol regulatory element binding protein 1c (SREBP-1c) and carbohydrate response element-binding protein (ChREBP). N-3 PUFA can not only protect against dyslipidemia, insulin resistance, and obesity, but also has anti-inflammatory and antioxidant properties. Previous findings have shown that n-3 PUFA supplementation can prevent NAFLD[8]. Functional lipids from the starfish Asterias amurensis oil, such as n-3 PUFA and carotenoids (which have antioxidant activities and can preserve insulin sensitivity), dose-dependently decreased liver lipid accumulation and improved liver steatosis in CS7BL/6N mice fed a high-fat diet (HFD)[9]. Krill represent a rich source of protein with essential amino acids and minerals. In fish oils, EPA and DHA are present in the form of triacylglycerol (TAG), whereas they are present as phospholipids (PLs) in krill, which has stronger anti-inflammatory and insulin hypersensitivity properties. A krill phospholipid-protein complex (PPC) from Euphausia superba can reduce hepatic lipogenesis in rats, which is associated with an increased total antioxidant capacity.

Sea cucumber sulfated polysaccharide (SCSP) inhibits the expression of the main regulatory mediator of liver lipid genesis, SREBP-1c, which leads to inhibited hepatic triglyceride synthesis. SCSP also significantly increases PPARγ expression, thus promoting the β oxidation of fatty acids. SCSP is barely absorbed in the gut, which leads to modulation of the gut microbiota. Therefore, SCSP may have unique effects on NAFLD and other pathological liver diseases[10,11].

Carotenoids are natural pigments with strong antioxidant activities. Their benefits in treating liver diseases and related complications have been widely reported. Astaxanthin (AST) is an important xanthophyll carotenoid, which is mainly derived from marine organisms and algae. Its antioxidant effect is 10 times that of β-carotene and 100 times that of vitamin E. In addition to its strong antioxidant properties, AST can also regulate various signaling pathways, such as reducing the activities of JNK and ERK-1 to lower liver insulin resistance, inhibiting PPAR-γ expression to reduce liver fat synthesis,
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<td>Krill</td>
<td>Antarctic krill (Euphausia superba)</td>
<td>PPC, peptides</td>
<td>Increased total antioxidant capacity in plasma, increased liver gene expression of mitochondrial SOD2, and reduced plasma level of the inflammatory mediator IL-2</td>
<td>NAFLD/rat model, HFD-induced</td>
<td>[11]</td>
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<td>Upregulated SOD, CAT, and GPx in liver tissues, downregulated TNF-α and IL-6 mRNA expression, increased Nrf2 and HO-1 expression, and suppressed ethanol-induced apoptotic proteins in the liver</td>
<td>ALD/mouse model, ethanol-induced</td>
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<td>Shellfish</td>
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<td>Oligopeptides</td>
<td>Regulating NF-κB-dependent anti-inflammation signaling pathways to inhibit inflammation; regulating AMPK-α, PPAR-α, and SREBP-1c to improve lipid-metabolism disorders; regulating Bcl-2/Bax anti-apoptosis signaling pathways to prevent liver cell apoptosis</td>
<td>NAFLD/mouse model, HFD-induced</td>
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<tr>
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<td>Starfish/algae</td>
<td>Harmatecoccus pluvialis</td>
<td>Astaxanthin</td>
<td>Exerted antioxidant and anti-inflammatory activities by increasing SOD, CAT, and GPx activity and GSH, and reducing lipid peroxidation in the liver, inhibited the expression of inflammatory factors such as TNF-α and ROS production; inhibited MAPK and NF-κB pathways</td>
<td>NAFLD/mouse model, HFD-induced; ALD/mouse model, alcohol-induced; DILI/mouse model, APAP, ConA, LPS-induced liver IR, ischemia-induced</td>
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<td>Algae</td>
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<td>Fucoxanthin</td>
<td>Activating the Nrf2-mediated signaling pathway and downregulating the expression of the TLR4-mediated NF-κB signaling pathway</td>
<td>ALD/mouse model, alcohol-induced</td>
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<td>Algae</td>
<td>Laminaria japonica</td>
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<td>Algae</td>
<td>Red alga (Laurencia tristicha)</td>
<td>Aplysin (a marine bromosesquiterpene)</td>
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<td>Anti-inflammatory activity against MGO-induced inflammation in human hepatocytes by preventing increased expression of pro-inflammatory genes and AGE formation</td>
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<tr>
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<td>Algae</td>
<td><em>Hypnea muciformis</em></td>
<td>Ethanolic extract</td>
<td>Regulated activities/levels of lipid-peroxidation byproducts, antioxidant enzymes, and</td>
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<td><em>Akkermansia</em> and reduced endotoxin-bearing Proteobacteria, improved SCFA and endotoxin</td>
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<td>(LPS) levels, and improved gut tissue index</td>
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<tr>
<td>Algae</td>
<td><em>Spirulina platensis</em></td>
<td>95% ethanol extracts (SPL95, major fatty acids)</td>
<td>AMPK-signalling pathway; downregulated mRNA and protein levels of SREBP-1c, 3-hydroxy-3-methyl glutaryl coenzyme A reductase, and acetyl-CoA carboxylase pathway members; upregulated levels of adenosine 3,5-monophosphate-activated protein kinase-α in the liver; enrichment of beneficial bacteria including Prevotella, Alloprevotella, Porphyromonadaceae, Barnesiella, and Paraprevotella; decreasing microbes such as Turicibacter, Romboutsia, Phascolarctobacterium, Olsenella, and Clostridium XVIII</td>
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<td>Fungus</td>
<td><em>Aspergillus versicolor</em></td>
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<td>NAFLD and obesity/mouse model, HFD-induced</td>
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<td>Lipid metabolism improvement</td>
<td>Fish</td>
<td>Fish</td>
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<td>Fish oil, omega-3-PUFA</td>
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<td>Starfish</td>
<td><em>Asterias amurensis</em></td>
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<td>Shrimp shell</td>
<td>Chitosan oligosaccharide</td>
<td>COS23 (Chitosan oligosaccharide)</td>
<td>Regulated lipid-related pathways, especially inhibition of the expression of FFA synthesis-related and inflammation-related genes, altered plasma lipid profiles, decreased abundance of Mucispirillum and increased abundance of Coprococcus in gut microbiota, and protected the intestinal barrier by up-regulating the expression of tight junction-related genes</td>
<td>NAFLD and obesity/mouse model, HFD-induced</td>
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<td>Algae</td>
<td>Red seaweed</td>
<td><em>Palmaria mollis</em> (bacon-like taste)</td>
<td>Upregulated the expression of genes involved in PPAR pathways, and downregulated the PPAR pathways</td>
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<td>Algae</td>
<td>Green algae</td>
<td>SPX (a carotenoid)</td>
<td>Suppression of LXRα activity, and downregulation of nuclear transcription factor SREBP-1c and a set of related genes</td>
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<td><em>Spirulina platensis</em></td>
<td>95% ethanol extract (SPL95)</td>
<td>Downregulating the expression of SREBP-1c, 3-hydroxy-3-methyl</td>
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**Note:** The effects and models mentioned are based on the referenced studies provided in the context.
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<td>Sponge</td>
<td>Dactylompongeia metachromia</td>
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<td>Ascidian</td>
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<td>Cladosiphon okamuranus</td>
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<td>Anti-cholestatic</td>
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<td>Theonella swinhoei</td>
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<td>Anti-fibrotic</td>
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<td>Facoidan, Reduced TGF-β1 expression</td>
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<td>Starfish/algae</td>
<td>Haeumactococcus pluvialis</td>
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<td>Source</td>
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<td>Action</td>
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<tr>
<td>Algae</td>
<td><em>Arthospira platensis</em></td>
<td>Interfering with the TGF-β pathway, reducing inflammation and oxidative stress, and reversing the hepatotoxic bile acid profile</td>
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<td>Sponge</td>
<td><em>Pseudoceratina spp.</em></td>
<td>Disruption of microtubule dynamics, antimitotic agents</td>
<td>HCC/in vitro, rat liver microsomes [58]</td>
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<td>Sponge</td>
<td><em>Crambe crambe</em></td>
<td>Inhibition of cell-cell adhesion; interference with tight junction formation, cell-matrix adhesion, and focal adhesions; altered cytoskeleton dynamics; inhibited cell migration</td>
<td>HCC/cell model [60]</td>
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<td><em>Erylus spp.</em></td>
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<td>Soft coral</td>
<td><em>Spongodes spp.</em></td>
<td>Inhibition of STAT3 phosphorylation</td>
<td>HCC/cell model -</td>
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<td>Soft coral</td>
<td><em>Sinularia flexibilis</em></td>
<td>Suppressed phosphorylation of members in the ERK, JNK, MAPK, FAK/PI3K/PI3K/PI/Ktor pathways; reduced MMP-2, MMP-9, and uPA expression; inhibited HCC migration, invasion, and cell metastasis; increased G2/M cell-cycle arrest; induced apoptosis; activated DNA-damage responses</td>
<td>HCC/cell model -</td>
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<tr>
<td>Shellfish</td>
<td><em>Arca subcrenata Lischke</em></td>
<td>Reduced VEGF2 phosphorylation, and altered the downstream components of the VEGF signaling pathways</td>
<td>HCC/cell model; HCC/transgenic zebrafish model -</td>
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<tr>
<td>Shrimp, crab</td>
<td>Chitin from shells</td>
<td>Cytotoxicity</td>
<td>HCC/cell model -</td>
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<td>Jellyfish</td>
<td><em>Nemopilema nomurai</em></td>
<td>Dual inhibition of the Akt and mTOR signaling pathways</td>
<td>HCC/tumor xenograft animal model -</td>
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<td>Sea urchin</td>
<td><em>Paracentrotus lividus Oocytes</em></td>
<td>Antioxidant capacity, hydrogen peroxide generation</td>
<td>HCC/cell model -</td>
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<tr>
<td>Starfish/algae</td>
<td><em>Haematococcus pluvialis</em></td>
<td>Regulating [AK1/STAT3, NF-kB, Wnt/β catenin; inhibiting the binding of AFB1 to liver DNA and plasma albumin; reducing reactive oxygen metabolites/biological antioxidant potential ratio; regulating nucleoside diphosphate kinase (NPK) nm-23</td>
<td>Hepatoma/rat model, AFB1-induced; HCC/mouse model, DEN-induced; HCC/cell model [14]</td>
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<tr>
<td>Algae</td>
<td><em>Undaria pinnatifida</em></td>
<td>Induced apoptosis via the ROS-mediated mitochondrial pathway</td>
<td>HCC/cell model -</td>
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<td>Microorganisms</td>
<td>Mangrove endophytic fungus</td>
<td>Induced apoptosis through the Akt/FOXO pathway</td>
<td>HCC/cell model; HCC/xenografted tumor model -</td>
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<td>Fungus</td>
<td><em>Aspergillus terreus</em> strain PF-26, associated with marine sponges (+)Terrein</td>
<td>Induced cell-cycle arrest in G2/M phase; decreased expression of proteins related to cell morphology (fibronectin, N-cadherin, and vimentin); altered expression of genes related to cell-cycle progression</td>
<td>HCC/cell model [59]</td>
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<tr>
<td>Bacteria</td>
<td><em>Bacillus spp.</em> II (EPS11)</td>
<td>Blocking cell adhesion and attenuating filiform structure formation</td>
<td>HCC/cell model -</td>
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</table>
downregulating TGF-β1/Smad3 expression to inhibit hepatic stellate cell (HSC) activation and liver fibrosis, and inhibiting the JAK/signal transducer and activator of transcription 3 (STAT3) and Wnt/β-catenin signaling pathways to exert antitumor effects. Therefore, AST plays significant roles in preventing and treating NAFLD, liver fibrosis, HCC, DILI, and ALD[12]. Siphonaxanthin (SPX) is a carotenoid derived from green marine algae that can significantly inhibit liver X receptor α (LXRα) activity and downregulate the expression of SREBP-1c and several related genes to inhibit liver adipogenesis[13].

Data from several studies showed that various bioactive components from brown algae can alleviate liver steatosis to a certain extent, especially fucoidan. Fucoidan is a sulfated polysaccharide extracted from brown marine algae that can regulate the ROS/JNK/Akt signaling pathways, reduce insulin resistance, inhibit sugar transport, regulate lipid metabolism and the gut microbiota, and reduce liver steatosis[14]. Some other bioactive compounds from brown algae, such as indole-4-carboxaldehyde, unsaturated alginate oligosaccharides (UAOS), and diphlorethohydroxycarmalol (DPhC), can inhibit inflammation and lipid metabolism, but further clinical trials are needed to confirm their efficacies against NAFLD. An in vivo animal study showed that the red algae *Palmaria mollis* can upregulate PPAR α expression, thereby activating fatty acid β oxidation and inhibiting lipid synthesis to improve liver steatosis[15].

*Spirulina* is a cyanobacteria capable of photosynthesis, which implies that they are rich in antioxidants. PUFAs in a 95% ethanol extract of the microalgae *Spirulina platensis* (SPL95) can regulate the gut microbiota, and reduce lipid synthesis and liver fat in rats fed an HFD by upregulating AMPK-α and downregulating members of the SREBP-1c-signaling pathway[16].

Asperlin is a natural fungal product isolated from the marine-derived fungus *Aspergillus versicolor* LZD-44-03. Asperlin improved lipid metabolism, ameliorated liver steatosis, and modulated the gut microbiota in mice fed an HFD[17].

Chitosan oligosaccharide (COS), a natural polysaccharide hydrolyzed from shrimp shell chitosan, has attracted extensive attention because of its potential use in various promising biomedical applications, including those related to anti-oxidation, anti-inflammation, immune stimulation, and anti-hypertension. An enzymatically digested product of COS, known as COS23, can reduce hepatotoxic lipid levels, inhibit the expression of FFA synthesis-related genes and inflammatory-related genes, regulate the gut microbiota, and up-regulate the expression of tight junction-related genes to improve intestinal barrier dysfunction, thereby improving diet-induced NAFLD.[18]

**ALD**

Alcohol abuse is the seventh leading risk factor for death globally, and the liver is the main organ involved in alcohol metabolism. Excessive alcohol intake can damage liver cells and cause ALD[19]. The risk is increased in people who have heavy alcohol use (> 3 drinks per day in men and > 2 drinks in women) for > 5 years. Heavy drinking increases intestinal permeability and the influx of lipopolysaccharide (LPS) to the liver, activates Kupffer cells, and leads to high Toll-like receptor 4 (TLR4) expression, which in turn releases large amounts of ROS and tumor necrosis factor (TNF-α) or other inflammatory factors, leading to liver toxicity. Drinking can also reduce the PL levels in liver cell membranes. Environmental factors and *PNPLA3* and *TM6SF2* gene mutations can also induce ALD progression[20]. Current treatments for ALD depend on ensuring lasting alcohol abstinence, and the treatment strategies beyond alcohol abstinence are largely those used for complications of cirrhosis, such as controlling ascites, treating and preventing hepatic encephalopathy recurrence and variceal bleeding, and monitoring for hepatocellular cancer[21].
Recent data have shown the effects of natural extracts on preventing and/or lessening alcoholic liver injury. AST may prevent ALD progression through pathways related to chemokine signaling, NOD-like receptor signaling, and TLR signaling[22].

Aplysin was extracted from the red alga Laurencia tristicha and exerts a potent hepatoprotective effect against ALD by enhancing the antioxidant defense system, alleviating oxidative damage, and regulating apoptosis-related gene expression[23].

Fucoxanthin (Fx) is a red-orange carotenoid extracted from marine seaweed that has strong anti-obesity, anti-inflammatory, and anti-cancer activities. In vivo data indicated that Fx attenuated alcohol-induced oxidative lesions and inflammatory responses by activating the nuclear factor erythroidocyte-2-related factor 2 (Nrf2)-mediated signaling pathway and downregulating the expression of members of the TLR4-mediated nuclear factor-kappa B (NF-κB) signaling pathway, respectively.

Fucoidan from Fucus vesiculosus was found to protect against alcohol-induced liver damage in mice. The associated mechanism potentially involved suppressing hepatic production of inflammatory cytokines, such as TGF-β1, COX-2, and NO, and enhancing antioxidant defense systems by activating the HO-1 pathway.

Marine collagen peptides (MCPs) are derived from the skin of chum salmon (Oncorhynchus keta) by enzymatic hydrolysis; MCPs can protect against early alcoholic liver injury in rats, based on their antioxidative activities and improvements in terms of lipid metabolism[24].

Krill (Euphausia superba)-derived peptides are renowned for their antioxidant activities, and peptide fractions from krill protein hydrolysates protect against alcohol-induced oxidative damage in BALB/c mice. This hepatoprotective effect might be attributed to activation of the Nrf2/HO-1 pathway.

HCV INFECTION

HCV results in an infectious liver disease, with multiple genotypes. HCV infection can lead to steatosis, liver cirrhosis, and HCC. Approximately 3% of the world’s population are infected with HCV[25]. The most effective HCV treatment regimen depends on the genotype of the predominant viral strain in infected patients. Overall, there are 11 HCV genotypes, with genotypes 1–6 being the most common [26]. Traditional therapy involves treatment with a combination of pegylated interferon alpha and ribavirin. The current FDA-approved direct acting antivirals are commonly used in combinations as pan-genotypic to effectively inhibit HCV replication with minimal side effects. However, the occurrence of resistance (either natural or after failure) and drug-drug interactions can limit treatment effectiveness. Natural HCV inhibitors still need to be investigated.

Harzianic acids A and B, isolated from the sponge-related Trichoderma harzianum fungus, inhibit viral activity by reducing RNA levels[27]. Total extract and derived fractions from red sea Amphimedon spp. sponges exhibited inhibitory potential against HCV NS3 helicase and protease. Among Amphimedon spp.-derived phytochemicals, nakinadine B and 3,4-dihydro-6-hydroxymanzamine A were noted as promising anti-HCV drug candidates, warranting future clinical investigation[28]. Fucoidan extracted from the marine alga Cladosiphon okamuranus (C. okamuranus) Tokida dose-dependently inhibited an HCV replicon system, suggesting that fucoidan may be a useful food additive with antiviral activity for treating chronic liver diseases[29].

Lobohedleoidle isolated from the formosan soft coral Lobophytum crassum, significantly reduced HCV replication by suppressing cyclooxygenase-2 (COX-2) expression[30].

DILI

The main elimination mechanisms of exogenous drugs involve the liver, kidney, and bile. Sixty percent of drugs are metabolized by the liver. DILI is a type of liver disease caused by drugs and their metabolites. Severe cases are life-threatening. The incidence of clinically significant DILI varies from country to country. Despite its rarity (< 1%, as determined with most patient series), it has been found to be the most common cause of acute liver failure in both Europe and the United States[31]. The most important initial step in terms of managing suspected DILI is to discontinue the implicated agent, as ongoing or even worsening injury can occur despite withdrawal of the causative agent. Drugs presently used to treat DILI are mainly those that protect liver cells, scavenge free radicals, inhibit oxidation, stabilize cell membranes, promote detoxification, lower enzymes, and promote immune regulation, including ursodeoxycholic acid, N-acetylcysteine, various steroids, and glutathione, among others. However, there is still a lack of drugs that treat DILI specifically.

Fucoidan displayed a hepatoprotective effect on acetaminophen overdose-induced liver toxicity, based on the suppression of CYP2E1, one of the enzymes that metabolizes acetaminophen. Fucoidan also exerts anti-oxidant, anti-apoptotic, and anti-inflammatory activities by increasing the production and expression of glutathione, superoxide dismutase, glutathione peroxidase, and Bcl-2, but decreasing the expression of Bax, cleaved caspase-3, and inflammatory mediators, including TNF-α, IL-1β, and iNOS[32]. An ethanolic extract of Hyphena muciformis (red algae) was found to possess antioxidant,
antitumor, and antimicrobial activities and to exhibit hepatoprotective activity against CCl4-induced toxicity in rats[33].

Fish oil can reduce liver damage caused by lipopolysaccharides, cisplatin, and acetaminophen by inhibiting TLR4 and nucleotide-binding oligomerization domain protein signaling pathways, and their antioxidant properties[34,35].

**OTHER LIVER DISEASES**

*Styela plicata* is a marine animal that synthesizes bioactive components with anti-tumor, antibacterial, and antiviral effects. Previous data showed that the bioactive compounds of ascidians can inhibit HBV DNA replication and have potential therapeutic value against chronic HBV infection[36]. Yamashita et al [37] also showed that metachromin A, a merosesquiterpene isolated from the marine sponge *Dactylospongia metachromia*, can inhibit HBV production by impairing viral promoter activity.

The farnesoid X receptor (FXR) can mediate bile acid secretion, and theonellasterol (isolated from the marine sponge *Theonella swinhoei*) is a highly selective FXR antagonist that can protect against liver injury in cholestasis[38].

**LIVER FIBROSIS**

Liver fibrosis is a scar-repair process that occurs after liver injury caused by various factors. It is characterized by liver myofibroblast (MFC) activation and excessive accumulation of extracellular matrix (ECM) proteins, and is pathologically characterized by the formation of regenerative nodules of hepatocytes, which can lead to cirrhosis and liver failure. Chronic HBV and HCV infections, alcoholic steatohepatitis, and NASH are the main causes of chronic progressive liver disease, leading to the onset of liver cirrhosis and decompensation. During chronic liver injury, silent HSCs are activated to become highly proliferative MFCs at the cellular level, resulting in α-smooth muscle actin (α-SMA) expression and excessive production of type I and type III collagen, as well as other scar tissue components. At the molecular level, pro-fibrotic factors, including transforming growth factor-β (TGF-β1), platelet-derived growth factor, and connective tissue growth factor; multiple signaling pathways such as the TLR4, and damage due to reactive oxygen species (ROS) play key roles in this process[39].

Owing to the unique chemical properties of sulfur atoms, sulfur-containing compounds are powerful antioxidants that exhibit promising activities for treating liver fibrosis. For example, ovothiol A (a sulfur-containing molecule) isolated from sea urchin eggs was found to have an anti-fibrotic effect on mice with carbon tetrachloride (CCL4)-induced liver fibrosis. This anti-fibrotic effect may be related to reduced expression of mediators involved in the progression of liver fibrosis, such as TGF-β1, α-SMA, and tissue inhibitor of metalloproteinase (TIMP-1)[40].

In addition, Nakazato et al[41] found that fucoidan from *C. okamuranus* Tokida reduced N-nitrosodi-ethylamine-induced liver fibrosis. It exerted an anti-fibrotic effect by downregulating TGF-β1 and CXCL12 expression and reducing lipid peroxidation.

*Spirulina* liquid extract (SLE), a patented water extract of *Arthrospira platensis*, protects against hepatic fibrosis by inhibiting inflammation, oxidative stress, and whole-body insulin resistance in a mouse model of Western diet-induced NASH[42]. Astaxanthin (AST) from starfish and algae exerts anti-fibrotic effects through the TGF-β1/Smad3 signaling pathway in hepatic stellate cells[43].

**HCC**

HCC is the most common primary liver cancer, accounting for approximately 75%-85% of such cases [44], and the third leading cause of cancer-related mortality worldwide. HCC has a high fatality rate, with a 5-year survival rate of only 30%-40%[45]. An estimated 70%-90% of HCC cases arise in the setting of cirrhosis[46]. HCC treatment mainly includes liver resection, liver transplantation, radiofrequency or microwave ablation, radiotherapy, and chemotherapy. Sorafenib, a multi-kinase VEGF inhibitor, is the most widely used systemic chemotherapeutic drug approved as a first-line agent for unresectable or advanced HCC. Other small-molecule inhibitors such as sunitinib, brivanib, and erlotinib have been studied for their efficacy in treating advanced HCC[47]. However, these anti-tumor drugs still have disadvantages related to drug resistance, poor efficacy, and large side effects. In recent decades, investigators have become committed to researching natural products as new anti-tumor drugs.

Sponges host diverse microbial communities, such as fungi, bacteria, and microalgae, and are rich in bioactive peptides that are important candidates for drug development. Data from many studies have shown that various sponge metabolites have anti-tumor activities in liver cancer cells in vitro. Ceratamine A and B isolates from *Pseudoceratina* spp. sponges can behave as antimitotic agents by disrupting microtubule dynamics[48]. Similarly, (+)-terrein, isolated from the marine sponge *Aspergilllas*
Wei Q et al. Marine products for liver diseases

Various active components isolated from the soft coral *Sinularia flexibilis*, such as 11-epi-sinulariolide acetate and sinulariolide, could inhibit HCC cell migration and invasion by reducing matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), and urokinase-type plasminogen activator (uPA) expression[53]. Sinularin induced DNA damage, G2/M phase arrest, and apoptosis[54].

In recent years, increasing attention has been paid to the anti-tumor activities of cockles. Some data have shown that polypeptides derived from cockles can exert anti-tumor activity by inhibiting the MAPK signaling pathway[55]. Guo et al[56] found that the ASP-3 protein isolated from *Arca subcrenata* inhibited HepG2 cell proliferation.

Marine microorganisms can produce various metabolites with unique structures and pharmacological activities, such as SZ-685C[57], which is a naturally biological active substance isolated from secondary metabolites of marine mangrove endophytic fungus number 1403 and could induce apoptosis through the Akt/FOXO pathway. EPS11, a bacterial polysaccharide extracted from *Bacillus spp.* 11, can inhibit the growth and metastasis of HCV-related liver cancer cells (HuH7.5 cells) by blocking their adhesion and destroying the formation of filamentous structures.

*Nemopilema nomurai* is one of the largest jellyfish species. The venom *Nemopilema nomurai* (NnV) contains highly selective dual inhibitors of the Akt and mTOR signaling pathways, which induce cytotoxicity and apoptosis in HepG2 cells, but not normal cells[58]. Yet, NnV can inhibit the metastasis and invasion of HepG2 cells by inhibiting the epithelial–mesenchymal transition[59].

Fucoidan extracted from the brown seaweed *Undaria pinnatifida* induces apoptosis in human HCC SMMC-7721 cells by increasing ROS production and inducing mitochondrial oxidative damage, mitochondrial membrane potential depolarization, and caspase activation. Fucoidan can also reduce lymphangiogenesis and tumor lymphatic (by suppressing HIF-1α/VEGF-C signaling), and then attenuate the PI3K/Akt/mTOR signaling pathways. Phycobiliproteins are components of red algae that include phycocerythrin, phycocerycyanin, phycocyanin, and allophycocyanin, which can have anti-oxidative, anti-viral, anti-tumor, immunity-enhancing, and anti-inflammatory effects[60]. Park et al[61] demonstrated that dietary RPE could modulate the gut microbiota of H22 HCC cell-bearing mice. In *vitro* experiments have revealed that COS showed significant antitumor activity against HepG2 tumor cells.

Ovothiol A, isolated from *Paracentrotus lividus* oocytes, can inhibit HepG2 cell proliferation by activating an autophagic process.

CONCLUSION

Treatments for chronic liver diseases, i.e., etiological treatment, protective treatment for liver injury, antifibrotic treatment, and treatment of decompensated complications of liver cirrhosis, are all effective and of great significance in preventing the progression of liver disease, maintaining liver function, reducing complications of portal hypertension, and preventing liver cancer. In recent years, intense research of marine resources has brought to light new prospects for developing marine-based drugs. Marine-derived bioactive compounds show great potential in health products and medicine. With the discovery of bioactive marine compounds and in-depth discussions of their therapeutic mechanism, their applications will continue to expand, and ultimately benefit more patients and humans. However, most of the information discussed above has only been demonstrated in *vitro* or in animal studies. The effects of these compounds in humans have yet to be fully characterized. Further research, including clinical trials, must be carried out before such marine compounds can be applied therapeutically.

FOOTNOTES

Author contributions: Qian W drafted the manuscript; Guo JS conceptualized and revised the manuscript; all authors have read and approved the final manuscript.

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Case Control Study

Analysis of bacterial spectrum, activin A, and CD64 in chronic obstructive pulmonary disease patients complicated with pulmonary infections

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Abstract

BACKGROUND
Pulmonary infections often lead to poor prognoses in patients with chronic obstructive pulmonary disease (COPD). Activin A and CD64 play crucial pathological roles in the development of COPD.

AIM
To explore the bacterial spectrum via analysis of activin A levels, CD64 index, and related mechanisms in COPD patients complicated with pulmonary infection.

METHODS
Between March 2015 and January 2018, a total of 85 patients with COPD, who also suffered from pulmonary infections, were enrolled in this study as the pulmonary infection group. In addition, a total of 96 COPD patients, without pulmonary infection, were selected as the control group. Sputum samples of patients in the pulmonary infection group were cultivated for bacterial identification prior to administration of antibiotics. The neutrophil CD64 index was measured using flow cytometry, serum activin A levels were detected via an enzyme-linked immunosorbent assay, and activin A, Smad3, TLR4, MyD88, and NFκB protein expression was analyzed by Western blotting.

RESULTS
Gram-negative bacteria were identified in 57.65% of the sputum samples in the pulmonary infection group. The most prevalent Gram-negative species were Pseudomonas aeruginosa and Klebsiella pneumoniae. Conversely, Gram-positive bacteria were identified in 41.18% of the sputum samples in the pulmonary
infection group. The most common Gram-positive species was *Streptococcus pneumoniae*. Fungi were identified in 1.17% of the sputum samples in the pulmonary infection group. The CD64 index was significantly higher in the pulmonary infection group (0.91 ± 0.38) than in the control group (0.23 ± 0.14, P < 0.001). The serum activin A levels were significantly higher in the pulmonary infection group (43.50 ± 5.22 ng/mL), compared to the control group (34.82 ± 4.16 ng/mL, P < 0.001). The relative expression levels of activin A, Smad3, TLR4, MyD88, and NFKB were all significantly higher in the pulmonary infection group, compared to the control group (all P < 0.001).

**CONCLUSION**

Pulmonary infections in COPD patients are mainly caused by *Streptococcus pneumoniae, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. Pulmonary infections can significantly increase neutrophil CD64 index and serum levels of activin A, thereby activating the activin A/Smad3 signaling pathway, which may positively regulate the TLR4/MyD88/NFκB signaling pathway.

**Key Words:** Chronic obstructive pulmonary disease; Infection; Activin A; CD64 index

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**Core Tip:** This study explores the bacterial spectrum via analysis of activin A levels, CD64 index, and related mechanisms in chronic obstructive pulmonary disease (COPD) patients complicated with pulmonary infection. Based on our analyses, pulmonary infections in COPD patients are mainly caused by *Streptococcus pneumoniae, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. Pulmonary infections can significantly increase neutrophil CD64 index and serum activin A levels, thereby activating the activin A/Smad3 signaling pathway, which may positively regulate the TLR4/MyD88/NFκB signaling pathway.

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**INTRODUCTION**

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease, characterized by progressive and persistent airflow obstruction, along with high morbidity and mortality. COPD is often complicated by a collection of underlying diseases. This disease, coupled with poor nutrition and immunologic function, can often lead to a high incidence in pulmonary infections[1,2]. In turn, pulmonary infections can worsen COPD and promote acute exacerbations of COPD (AECOPD), which further aggravates patient prognosis. This is the main cause of death in COPD patients[3-5].

Under normal conditions, CD64 is scarcely expressed. Following infection, however, CD64 Levels rise due to the direct stimulation of pathogenic microorganisms or the indirect stimulation of inflammatory cytokines. Therefore, the neutrophil CD64 index can act as an early diagnostic marker for infection[4-6]. Moreover, multiple reports correlated the CD64 index with the severity associated with COPD and bacterial infections. Qian and Huang[7], for instance, observed that the CD64 index is higher in patients with AECOPD than those with stable COPD and healthy volunteers, and that the CD64 index is higher in AECOPD patients with positive bacterial sputum cultures than in those with negative cultures. This suggests that the CD64 index can be a guiding marker that offers better therapeutic implications, compared to conventional diagnosis, for the use of antibiotic treatments in AECOPD patients. Similarly, Titova et al[8] also demonstrated that the neutrophil CD64 index possesses approximately the same level of diagnostic accuracy as CRP in diagnosing pneumonia in patients hospitalized with AECOPD.

Activin A is a glycoprotein that promotes follicle-stimulating hormone secretion from pituitary gland. It is a member of the transforming growth factor beta superfamily and participates in the regulation of proliferation, chemotaxis, and apoptosis of neutrophils, macrophages, fibroblasts and other cells. Activin A also plays pathological roles in a series of respiratory diseases like COPD, asthma, and pulmonary fibrosis[9-11]. In 2014, Verhamme et al[12] first reported that activin A plays a key role in regulating inflammation in COPD patients and that the expression of activin A is significantly increased in the airway smooth muscle cells, bronchial epithelial cells, and alveolar macrophages of COPD patients. These conclusions were further confirmed in animal models whereby cigarette smoke exposure...
induced a significant increase in activin A levels in the lungs and bronchoalveolar lavage fluid of mice. Moreover, the cigarette smoke-exposed bronchial epithelial cells exhibited higher levels of activin A and lower levels of its endogenous inhibitor follistatin \textit{in vitro}. Nevertheless, there are few reports on the effects of pulmonary infections on the CD64 index and activin A in patients with COPD, and the underlying mechanism remains unclear. Therefore, this study analyzed the bacterial spectrum and expressions of the CD64 index and activin A in COPD patients with pulmonary infection, and discussed the relevant mechanisms.

**MATERIALS AND METHODS**

**General information**

Between March 2015 and January 2018, a total of 85 patients with COPD, who also suffered from pulmonary infections, and a total of 96 COPD patients, without pulmonary infection, were enrolled from the First Affiliated Hospital of Chongqing Medical University, and were assigned to either the pulmonary infection or control group. Baseline characteristics, such as, age, gender, forced expiratory volume in the first second (FEV1), and FEV1/forced vital capacity (FVC) ratio were collected for comparisons. All participants signed informed consent before entry into the study, and all clinical practices were consistent with our institution’s code of ethics. This study conformed with the 2013 revised Helsinki Declaration and was approved by the Medical Ethics Committee of The First Affiliated Hospital of Chongqing Medical University.

**Inclusion and exclusion criteria**

**Inclusion criteria:** (1) COPD: Diagnostic criteria consistent with the Global Strategy for the Diagnosis, Management, and Prevention of COPD (2016 revised edition): Patients who had dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors, such as, smoking. The diagnosis was further confirmed via post-bronchodilator spirometry (FEV1/FVC ratio < 0.7)\cite{13}; (2) AECOPD: Patients with COPD, who experienced a sustained increase in cough, shortness of breath, sputum production or purulence of sputum, and/or dyspnea; and (3) Pulmonary infections: COPD patients who experienced fever, produced abnormal sounds like crackles or ronchi in lungs, and exhibited pulmonary infiltrates on chest X-ray. Pathogenic bacteria were isolated from the cultures of their sputum samples.

**Exclusion criteria:** (1) COPD patients who received antibiotics, hormones, or immunosuppressive drugs within 1 mo prior to admission; (2) COPD patients who suffered from other infections, such as abdominal, skin, soft tissue, bone, and cartilage infections; (3) COPD patients with pulmonary infection, but pathogenic bacteria could not be isolated from sputum culture; (4) COPD patients who also suffered from other respiratory diseases like asthma, bronchiectasis, pneumothorax, hemotherox, or comorbidities; (5) COPD patients who also suffered from tumors, autoimmune diseases, cardiovascular and cerebrovascular diseases, or renal and hepatic dysfunction; (6) COPD patients with other diseases that could lead to acute exacerbations, such as, heart failure, spontaneous pneumothorax, pulmonary embolism, or pleural effusion; and (7) COPD patients who died or suffered worsening of condition due to un-related diseases during hospitalization.

**Identification of pathogenic bacteria**

The sputum samples were collected from the lower airways of patients in the pulmonary infection group and were cultivated for bacterial identification before these patients were given antibiotics. Patients rinsed their mouths with normal saline before sputum collection to avoid contamination by oral flora. In case of difficulty in sputum collection, due to coughing, samples were taken \textit{via} fiberoptic bronchoscopy. Gram staining was initially performed on the sputum samples. Sputum samples containing < 10 squamous epithelial cells and > 25 Leukocytes per low-power field (squamous epithelial cells/leukocytes < 1:2.5) were considered qualified, otherwise the sputum sample was re-collected. The qualified samples were then inoculated on blood agar and MacConkey agar plates, and cultured at 37 °C for 24 h before the fully automated VITEK 2 Compact bacterial identification system (BioMérieux) was applied for the identification of pathogenic bacteria. All samples were processed according to the National Guide to Clinical Laboratory Procedures\cite{14}.

**Assessment of CD64 index**

Upon hospital admission, we collected 2 mL venous blood from the median cubital vein in the antecubital fossa of all patients and treated each sample with the anticoagulant agent, ethylenediaminetetraacetic acid. Subsequently, to each 50 μL of anti-coagulated blood, 5 μL of anti-CD64-PE (Invitrogen, MA5-16436) and 5 μL of anti-CD45-PerCP (Invitrogen, MHCD4531) were added, mixed thoroughly, and the mixture was incubated at room temperature in the dark for 30 min. This was followed by red cell lysis with 500 μL of hemolytic agent (Beijing Tongsheng Shidai Biotech Co., Ltd., Z6910001S) incubated at room temperature in the dark for an additional 15 min. The test samples were then centrifuged at 3000 r/min for 5 min. Subsequently, the supernatants were removed and the cell pellets were resuspended in

\[\text{...}\text{additional text...}\]
300 μL PBS for flow cytometry analysis using instrument from Becton-Dickinson, FACS Calibur. Monocytes, lymphocytes, and neutrophils were identified by an established gate, based on the forward and side scatters, as well as CD45-PerCP. For each test sample, the fluorescence signals of 10000 cells were collected, and the average fluorescence intensities of sub-populations were measured. The lymphocyte CD64 levels were used as the internal negative control (≤1.0), whereas the monocyte CD64 levels were set as the internal positive control (>8.0). The CD64 index was calculated as follows: CD64 index = (CD64 average fluorescence intensity on the neutrophil/CD64 average fluorescence intensity on the lymphocyte)/(CD64 average fluorescence intensity on the monocyte/CD64 average fluorescence intensity on the neutrophil).

**Enzyme-linked immunosorbent assay**

Upon hospital admission, we collected 2 mL of venous blood from all patients. Following a 20 min incubation at room temperature, the blood samples were centrifuged at 6000 r/min for 15 min. Subsequently, the supernatants were collected and analyzed for serum activin A levels using the Elisa kit (Shanghai Renjie Biological Technology Co., Ltd. RJI2742), following manufacturer’s instructions.

**Western blot**

Upon hospital admission, we collected 2 mL of heparinized venous blood from all patients. The blood samples were then centrifuged at 2000 r/min for 10 min to separate the blood components into three layers: Blood plasma, a buffy coat containing platelet cells, and red blood cells. The blood plasma was collected in sterile centrifuge tubes containing 1 mL of 1.090 g/mL Percoll solution (Solarbio, P8370) and an additional 1mL of 1.077 g/mL Percoll solution were successively added to the tubes. The buffy coat layer of centrifuged samples was next pipetted into a Percoll density gradient solution, and was followed by another centrifugation at 2000 r/min for 15 min, which separated the components into four layers: Blood plasma, Percoll solution, neutrophils, and Percoll solution. The neutrophils were then pipetted into a new centrifuge tube, mixed with blood plasma and centrifuged again at 1000 r/min for 10 min. Following this, the cells were rinsed three times, and re-suspended in an appropriate amount of plasma. After the cell count, 10^9 cells were collected, completely lysed by adding 100 μL of lysis buffer (Beyotime Biotech, China, P0013), and centrifuged at 12000 r/min for 5 min. The supernatants were then collected for BCA protein quantification (Beyotime Biotech, China, P0012). For each test sample, 20 μg of total protein was obtained for polyacrylamide gel electrophoresis. The proteins were then transferred onto PVDF membranes, and blocked in 5% non-fat dry milk at room temperature for 2 h. After the blocking process, the membranes were incubated with primary antibodies for either anti-activator A (1:500, Abcam, ab89307), anti-Smad3 (1:500, Abcam, ab40854), anti-MyD88 (1:500, Abcam, ab2064), anti-NFκB (1:1000, Abcam, ab32360), or anti-GAPDH (1:1000, Abcam, ab8245) at 4 °C overnight. The membranes were then rinsed three times and incubated with HRP-conjugated goat anti-rabbit IgG (Boster, BA1056, 1:2000) at room temperature, the blood samples were centrifuged at 6000 r/min for 15 min. The supernatants were then collected for BCA protein quantification (Beyotime Biotech, China, P0012). For each test sample, 20 μg of total protein was obtained for polyacrylamide gel electrophoresis. The proteins were then transferred onto PVDF membranes, and blocked in 5% non-fat dry milk at room temperature for 2 h. After the blocking process, the membranes were incubated with primary antibodies for either anti-activator A (1:500, Abcam, ab89307), anti-Smad3 (1:500, Abcam, ab40854), anti-MyD88 (1:500, Abcam, ab2064), anti-NFκB (1:1000, Abcam, ab32360), or anti-GAPDH (1:1000, Abcam, ab8245) at 4 °C overnight. The membranes were then rinsed three times and incubated with HRP-conjugated goat anti-rabbit IgG (Boster, BA1056, 1:2000) at room temperature for 1 h. The membranes were then rinsed three times, followed by incubation with the ECL substrate solution (Beyotime Biotech, China, P0018), and exposure and imaging using gel doc (Bio-Rad, GelDoc XR’). The protein band gray values were determined with the Image Pro Plus 6.0 software, and the intensity of the target protein band divided by the intensity of GAPDH in the control group was adjusted as 1[15].

**Statistical analysis**

All data were statistically processed using the SPSS 20.0 software. Data are expressed as mean ± SD. Inter-group comparisons were made with the independent-sample t-test. Enumeration data are expressed as cases/percentage (n/%). Inter-group comparisons were performed using the chi-squared test. P < 0.05 was considered statistically significant.

## RESULTS

### Comparison of baseline characteristics

Baseline patient characteristics are summarized in **Table 1**, including gender, age, course of disease, smoking history, FEV1, and FEV1/FVC. A total of 181 cases met our inclusion criteria. Among these cases, 46 patients had pulmonary infection, and 96 patients were included in the control group. The gender, patient age, disease, and smoking history between the two groups were comparable (all P > 0.05). Patients in the pulmonary infection group presented with a lower level of FEV1 (%), compared to the control group (41.30 ± 9.91 vs 47.65 ± 10.07, P < 0.001). Similarly, the level of FEV1/FVC (%) was lower in the pulmonary infection group, compared to the control group (50.48 ± 9.13 vs 58.24 ± 8.62, P < 0.001).

**Bacterial spectrum of patients with COPD, complicated with pulmonary infection**

The bacterial spectrum of patients in the pulmonary infection group is shown in **Table 2**. Among the 85 strains, 49 (57.65%) were gram-negative bacteria and 35 (41.18%) were gram-positive bacteria. The most...
Table 1 Comparison of baseline characteristics between the chronic obstructive pulmonary disease patients with pulmonary infections and those without

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>The control group</th>
<th>The pulmonary infection group</th>
<th>$\chi^2$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases, n</td>
<td>96</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>59/37</td>
<td>50/35</td>
<td>0.131</td>
<td>0.718</td>
</tr>
<tr>
<td>Age range (yr)</td>
<td>67.44 ± 8.51</td>
<td>68.83 ± 8.90</td>
<td>1.073</td>
<td>0.285</td>
</tr>
<tr>
<td>Course of disease (yr)</td>
<td>16.35 ± 7.68</td>
<td>17.13 ± 8.06</td>
<td>0.666</td>
<td>0.506</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>68 (70.83)</td>
<td>65 (76.47)</td>
<td>0.735</td>
<td>0.391</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>47.65 ± 10.07</td>
<td>41.30 ± 9.91</td>
<td>4.266</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>58.24 ± 8.62</td>
<td>50.48 ± 9.13</td>
<td>5.879</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

FEV1: Forced expiratory volume in the first second; FVC: Forced vital capacity.

Table 2 The bacterial spectrum of patients in the pulmonary infection group

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Strains</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative bacteria</td>
<td>49</td>
<td>57.65</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>16</td>
<td>18.82</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>14</td>
<td>16.47</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>7</td>
<td>8.24</td>
</tr>
<tr>
<td>Haemophilus parainfluenza</td>
<td>7</td>
<td>8.24</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
<td>5.88</td>
</tr>
<tr>
<td>Gram-positive bacteria</td>
<td>35</td>
<td>41.18</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>24</td>
<td>28.24</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>11</td>
<td>12.94</td>
</tr>
<tr>
<td>Fungus</td>
<td>1</td>
<td>1.17</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>100.00</td>
</tr>
</tbody>
</table>

The prevalent gram-negative species were *Pseudomonas aeruginosa* (16, 18.82%), followed by *Klebsiella pneumoniae* (14, 16.47%), *Haemophilus influenzae* (7, 8.24%), and *Haemophilus parainfluenzae* (7, 8.24%). Among the gram-positive bacteria, 24 (28.24%) were *streptococcus pneumoniae*, and 11 (12.94%) were staphylococcus epidermidis. Apart from these, fungi were identified in 1.17% sputum samples.

Comparison of CD64 index

The CD64 index was 0.91 ± 0.38 in the pulmonary infection group and 0.23 ± 0.14 in the control group. Based on our statistical analyses, the pulmonary infection group had significantly lower CD64 index than the control group ($P < 0.001$) (Figure 1A).

Comparison of serum levels of activin A

Figure 1B illustrates the activin A levels in the pulmonary infection and control groups. The activin A levels were 43.50 ± 5.22 ng/mL in the pulmonary infection group, and 34.82 ± 4.16 ng/mL in the control group ($P < 0.001$). Hence, the pulmonary infection group had significantly higher activin A levels than the control group ($P < 0.001$).

Pulmonary infection promotes activation of neutrophil activin A/Smad3 signaling pathway

The activin A and neutrophil Smad3 protein expressions and their corresponding statistical analyses are shown in Figure 2. The activin A expression was 3.22 ± 0.67 in the pulmonary infection group, and 1.00 ± 0.28 in the control group. The expressions of neutrophil Smad3 in the pulmonary infection group was 2.35 ± 0.49, and in the control group was 1.00 ± 0.19. Hence, patients in the pulmonary infection group presented with higher levels of activin A and neutrophil Smad3, compared to the control group ($P < 0.001$).
Figure 1 Comparison of CD64 index and serum activin A levels between chronic obstructive pulmonary disease patients with pulmonary infections and those without. A: CD64 index; B: Serum activin A. \(^{\text{d}} P < 0.001\).

**Comparisons of TLR4, MyD88, and NFκB expressions in neutrophils**

The relative expressions of neutrophil TLR4, MyD88, and NFκB were confirmed, using western blot, and are presented in Figure 3. The TLR4 expression was 2.96 ± 0.55 in the pulmonary infection group, and 1.00 ± 0.28 in the control group. The MyD88 expression was 1.98 ± 0.37 in the pulmonary infection group, and 1.00 ± 0.21 in the control group. Lastly, the NFκB expression was 2.02 ± 0.37 in the pulmonary infection group, and 1.00 ± 0.25 in the control group. Based on our statistical analyses, the levels of neutrophil TLR4, MyD88, and NFκB were significantly higher in the pulmonary infection group than the control group (all \( P < 0.001 \)).

**DISCUSSION**

COPD often occurs in the elderly, due to multiple underlying diseases, weak cough reflex, and low immune function. This ultimately leads to high incidences of pulmonary infections[1,2]. This study found that pulmonary infections in COPD patients are mainly caused by Gram-negative bacteria like *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Our conclusion is consistent with the results of the Qu et al[16] study. In another study, Zhou et al[17] reported that COPD patients with pulmonary infections are more likely to have diabetes, elevated risk of ventilator usage, and prolonged bed rest, compared to COPD patients without pulmonary infection. Moreover, the study demonstrated that pulmonary infections are mainly caused by Gram-negative bacteria including *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*. Nevertheless, our study revealed that the pulmonary infections in COPD patients are mainly caused by Gram-negative bacteria, such as, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. This inconsistency may be related to the collection and treatment of samples and the isolation and identification of bacterial strains.

CD64 is usually expressed in low quantities in neutrophils, but a significant rise in expression occurs with the stimulation of pathological factors or inflammatory cytokines. Therefore, the neutrophil CD64 index is used as a diagnostic and prognostic biomarker in multiple diseases like systemic lupus erythematosus, neonatal sepsis, bacterial peritonitis, and inflammatory bowel diseases[4-6]. Previous studies found that CD64 is also an important diagnostic and prognostic biomarker in COPD patients[8, 18]. In fact, Qian and Huang[7] found that the level of CD64 is significantly increased in patients with AECOPD or COPD with positive bacterial sputum culture. Our study also showed that the CD64 index is significantly higher in the pulmonary infection group than in the control group, which is consistent with prior publications.

Activin A is a member of the transforming growth factor beta superfamily that participates in multiple physiological and pathological processes like embryogenesis, neuroprotection, apoptosis, and fibrosis[9,19]. Several studies reported that activin A is significantly increased during infections and inflammatory diseases, including sepsis, inflammatory bowel diseases, and rheumatoid arthritis[10,11, 20]. Moreover, activin A plays critical roles in regulating inflammation during COPD. Likewise, Verhamme et al[12] reported that the expression of activin A is significantly increased in the airway smooth muscle cells, bronchial epithelial cells, and alveolar macrophages of COPD patients. These conclusions were further confirmed in animal models. The administration of follistatin in cigarette smoke-exposed mice was shown to significantly decrease accumulation of monocytes, macrophages, neutrophils, as well as CD4+ and CD8+ T-lymphocytes. This suggests that the significant increase in
activin-A is not caused by pulmonary inflammation in COPD models, but is, in fact, a mediator of COPD development. Likewise, the results of our study demonstrated that the level of serum activin A is significantly higher in the pulmonary infection group than in the control group. This indicates that pulmonary infections are consistent with other infections or inflammatory diseases in stimulating a significant increase of activin A levels in COPD patients.

Smad3 is a downstream key effector of transforming growth factor-β1 and it plays a significant role in COPD patients, particularly, in terms of regulating inflammation, airway remodeling, and fibrosis[21, 22]. Mahmood et al[23] observed that the activation of the Smad3 signaling pathway is linked to the epithelial mesenchymal transition and loss of lung function. Furthermore, a recent study reported that the Smad3 signaling pathway is also a major effector of the activin A biological activity[24]. In our research, we employed neutrophils protein expression analysis to reveal that pulmonary infection significantly promotes expressions of activin A and Smad3 in neutrophils, which indicates that the activin A/Smad3 signaling pathway is strongly activated during this time. In another study, the TLR4/MyD88/NFκB signaling pathway activation in neutrophils was shown to be an important contributor to the significant activin A secretion during the pathophysiology of endotoxemia[25]. In our study, we also demonstrated that pulmonary infection can significantly promote expressions of TLR4, MyD88, and NFκB in neutrophils, which indicates that the elevated serum activin A levels and activation of the activin A/Smad3 signaling pathway may be strongly related to the activation of the TLR4/MyD88/NFκB signaling pathway.

This study focused on the bacterial spectrum, and expressions of the CD64 index and activin A in patients with COPD, complicated with pulmonary infections. But, there are still many scientific aspects that have not been discussed. First, this article only discussed the effects of pulmonary infections in COPD patients, however it remains unclear whether infections caused by other types of bacteria produces similar or different results. Second, previous studies reported that the activin A antagonist
follistatin effectively alleviates pathological conditions associated with pulmonary fibrosis. But, the role of follistatin in patients with COPD, complicated with pulmonary infections, remains unclear[26–28]. Third, this study explored alterations within the TLR4/MyD88/NFκB signaling pathway after separation of the patients’ neutrophils. However, the relationship between this signaling pathway and activin A expression still lacks strong evidence. Therefore, in vitro cytological experiments are warranted for verification of this correlation via targeted inhibition and/or overexpression investigations.

CONCLUSION

In conclusion, pulmonary infections in COPD patients are mainly caused by *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. Pulmonary infections can result in a significant increase in the neutrophil CD64 index and serum levels of activin A, and, in turn, activate the activin A/Smad3 signaling pathway, which may be positively regulate the TLR4/MyD88/NFκB signaling pathway.
ARTICLE HIGHLIGHTS

Research background
A sharp exacerbation of chronic obstructive pulmonary disease (COPD) is often triggered by a lung infection and often has a poor prognosis.

Research motivation
Since COPD induces complex inflammatory events, Activin A and CD64 may collectively contribute to the development and progression of this disorder.

Research objectives
To analyze the bacterial profile of COPD patients with pulmonary infections and to assess activin A levels, CD64 index, and the underlying mechanisms involved in disease development.

Research methods
The whole data set consisted of 85 COPD patients with pulmonary infection and 96 COPD patients without pulmonary infection. Sputum samples were obtained from patients with pulmonary infections for further bacterial culture. The levels of CD64 index, activin A, Smad3, TLR4, MyD88, and NFκB proteins were assessed and compared between 85 COPD patients with pulmonary infections and 96 COPD patients without pulmonary infections.

Research results
In the pulmonary infection group sputum samples, the Gram-negative bacteria, Gram-positive bacteria, and Fungi were 57.65%, 41.18%, and 1.17%, respectively. In addition, the relative CD64 index, and levels of activin A, Smad3, TLR4, MyD88, and NFκB proteins were all significantly higher in the pulmonary infection group, compared to the control group (all \( P < 0.001 \)).

Research conclusions
Pulmonary infections in COPD patients may be caused by a variety of pathogens. In COPD patients, the CD64 index and serum activin A levels were significantly increased in patients with lung infection, compared to those without. This may have a positive regulatory effect on the downstream activin A/Smad3 and TLR4/MyD88/NFκB signaling pathways.

Research perspectives
Together, our findings provide a novel mechanism underlying pulmonary infection in COPD patients, and offer a potential therapeutic target for an enhanced and effective therapy against COPD.

FOOTNOTES

Author contributions: Fei ZY and Guo M designed the study, wrote the paper and reviewed the manuscripts; Fei ZY and Guo M should be as the co-corresponding authors; Fei ZY and Wang J performed the research and collected data; Liang J and Zhou X contributed to the analysis and editing of the manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

Informed consent statement: The data were not involved in the patients’ privacy information, so the informed consent was waived by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

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

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE statement-checklist of items, and the manuscript was prepared and revised according to the STROBE statement- checklist of items.

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Comprehensively evaluate angiogenesis in patients with pancreatic adenocarcinoma

Wen Liu, Bo Yin, Zong-Hui Liang, Yang Yu, Na Lu

Wen Liu, Bo Yin, Zong-Hui Liang, Yang Yu, Na Lu

Pancreatic adenocarcinoma is one of the most common malignant tumors of the digestive system. More than 80% of patients with pancreatic adenocarcinoma are not diagnosed until late stage and have distant or local metastases.

AIM
To investigate the value of computed tomography (CT) perfusion imaging in the evaluation of angiogenesis in pancreatic adenocarcinoma patients.

METHODS
This is a retrospective cohort study. Patients with pancreatic adenocarcinoma and volunteers without pancreatic diseases underwent CT perfusion imaging from December 2014 to August 2017 in Huashan Hospital, Fudan University, Shanghai, China.

RESULTS
A total number of 35 pancreatic adenocarcinoma patients and 33 volunteers were enrolled. The relative blood flow (rBF), and relative blood volume (rBV) were significantly lower in patients with pancreatic adenocarcinoma than in the control group ($P < 0.05$). Conversely, the relative permeability in patients with pancreatic adenocarcinoma was significantly higher than that in controls ($P < 0.05$). In addition, rBF, rBV, and the vascular maturity index (VMI) were significantly lower in patients with pancreatic adenocarcinoma than in controls ($P < 0.05$).
lower in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma \( (P < 0.05) \). Vascular endothelial growth factor (VEGF), CD105-MVD, CD34-MVD, and angiogenesis rate \( (AR) \) were significantly higher in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma \( (P < 0.05) \). Significant correlations between rBF and VEGF, CD105-MVD, AR, and VMI \( (P < 0.01) \) were observed. Moreover, the levels of rBV were statistically significantly correlated with those of VEGF, CD105-MVD, CD34-MVD, and VMI \( (P < 0.01) \).

**CONCLUSION**

Perfusion CT imaging may be an appropriate approach for quantitative assessment of tumor angiogenesis in pancreatic adenocarcinoma.

**Key Words:** Pancreatic adenocarcinoma; Perfusion computed tomography; Angiogenesis; Evaluation; Imaging; Quantitative assessment

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**Core Tip:** A total of 35 pancreatic adenocarcinoma patients and 33 volunteers were enrolled in the study. The relative blood flow, relative blood volume, and relative peak enhancement were significantly lower in patients with pancreatic adenocarcinoma than in the control group \( (P < 0.05) \). Conversely, the relative permeability in patients with pancreatic adenocarcinoma was significantly higher than that in controls \( (P < 0.05) \).

**Citation:** Liu W, Yin B, Liang ZH, Yu Y, Lu N. Computed tomography perfusion imaging evaluation of angiogenesis in patients with pancreatic adenocarcinoma. *World J Clin Cases* 2022; 10(8): 2393-2403

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i8/2393.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i8.2393

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**INTRODUCTION**

Pancreatic adenocarcinoma is one of the most common malignant tumors of the digestive system. The prognosis of pancreatic adenocarcinoma is poor, with 5-year survival rates lower than 5\%[1]. Importantly, more than 80\% of patients with pancreatic adenocarcinoma are not diagnosed until late stage and have distant or local metastases[1,2]. Therefore, early detection of pancreatic adenocarcinoma is critical for improving prognosis outcomes.

Accumulating evidence indicates that vascularity is crucially involved in the tumorigenesis and drug responsiveness of pancreatic adenocarcinoma[3,4]. Thus, the evaluation of angiogenesis in pancreatic adenocarcinoma is of considerable significance for the diagnosis, treatment, and prognosis[5-8]. Computed tomography (CT) perfusion imaging provides information on tissue hemodynamics, which facilitates the more effective characterization and identification of pancreatic adenocarcinoma[9-11]. For instance, perfusion CT imaging has been widely applied in brain tumors, and the perfusion parameters have been proven to be of great significance in brain disease diagnosis[12-15]. However, relative perfusion parameters in pancreatic adenocarcinoma diagnosis have not yet been reported.

Therefore, in the present study, we performed perfusion CT imaging to explore the correlations between CT perfusion parameters and immunohistochemical angiogenesis indices, and their application for evaluating their diagnostic value in pancreatic adenocarcinoma.

**MATERIALS AND METHODS**

**Study design and subjects**

This retrospective cohort study was conducted in Fudan University from December 2014 to August 2017. Subjects with pancreatic ductal adenocarcinoma and volunteers without pancreatic diseases were enrolled. Pancreatic adenocarcinoma patients with other pancreatic diseases were excluded. This study protocol was approved by the Institutional Review Board of Fudan University, Shanghai, China (2014-04-02). Written informed consent was obtained from each participant.

**Procedures**

Perfusion CT imaging was performed using a 64-slice spiral CT scanner (SOMATOM Sensation 64, Siemens Medical Solutions, Forchheim, Germany). The baseline unenhanced CT acquisition provided
wide coverage of the whole organ of interest. The field of view of perfusion CT imaging was positioned to include the maximum visible area of the tumor and a relevant arterial vessel. The abdominal aorta was used as an arterial input. An abdominal bandage was utilized to reduce the artifacts caused by respiratory motion. CT perfusion examinations were then performed in a continuous volume scan pattern using the following parameters: tube voltage 100 kV, tube current 80 mA, and a matrix of 512 × 512 pixels. The reconstructed slice thickness was 7.2 mm; the acquisition collimation was 7.2 mm, with 280 slices in each dataset. An average radiation dose of 9.3 mGy was applied. A volume of 50 mL of Omnipaque® 300 (GE Healthcare, Shanghai, China) was administered at a high flow rate (5 mL/s) using a high-pressure syringe. The contrast medium bolus was followed immediately by 15 mL of normal saline flush to increase the peak arterial enhancement. Stationary CT scans were then acquired every 1 s over a period of 70 s, with a delay of 4 s.

The obtained images were independently evaluated by two radiologists with more than 10 years’ experience. Dynamic CT perfusion data were analyzed by the pancreatic perfusion CT software package (Syngo, Siemens, Erlangen, Germany). Based on the maximum-slope method, color maps of CT perfusion parameters, including blood flow (BF), blood volume (BV), permeability, time to peak and mean transit time, maximum-density-projection and contrast-enhanced CT images were extracted. Furthermore, regions of interest (ROIs) were positioned on the highest intensity projection of tumor parenchyma to avoid selecting the vascular or the necrotic areas, and normal pancreas tissue in patients with pancreatic adenocarcinoma. For large heterogeneous tumors, the average value of three ROIs in the tumor parenchyma was used. In the control group, ROIs were located on the pancreatic head and cauda. Each CT perfusion parameter was measured three times, and the mean values were used. Relative CT perfusion parameters, including relative BF (rBF), relative BV (rBV), relative permeability (rPermeability), relative peak enhancement (rPPE), and relative time to peak (rTTP) were calculated as follows: Relative CT perfusion parameters = parameters of pancreatic adenocarcinoma tumor parenchyma/parameters of adjacent relatively normal pancreatic tissue. The relative CT perfusion parameters in the controls were calculated as parameters of the pancreatic head/parameters of the pancreatic cauda.

Tumor specimens were resected and the expression of vascular endothelial growth factor (VEGF), CD105, CD34, and alpha-smooth muscle actin (α-SMA) was detected by immunohistochemical staining. Yellow and brown yellow were used to indicate positive cells on the premise of excluding non-specific staining. Five random visual fields were selected at high magnification, and 100 cells in each visual field of each section were observed. Microvascular density (MVD) was determined by counting the total number of positive vessel walls in each tumor section. MVD was then graded using a scale of 0-5: 0 point, the proportion of chromogenic cells was less than 5%; 1 point, chromogenic cells ranged from 5% to 25%; 2 points, chromogenic cells ranged from 25% to 50%; 3 points, chromogenic cells ranged from 50% to 75%; 4 points, the proportion of chromogenic cells was more than 75%; 5 points, all cells were positive. Angiogenesis rate (AR) and vascular maturity index (VMI) are important indicators of tumor angiogenesis. AR was calculated using the following formula: AR = (CD105-MVD/CD34-MVD) × 100%. VMI was calculated according to the formula: VMI = (α-SMA-MVD/CD34-MVD) × 100%.

Demographic characteristics including age, gender, and tumor grade were collected at enrollment.

Statistical analysis
Continuous data conforming to a normal distribution are expressed as mean ± standard deviation (SD). Continuous data with non-normal distribution are presented as median (interquartile range, IQR); these data were analyzed using the independent t-test or Mann-Whitney U-test where appropriate. Categorical data are presented as count (percentage) and compared using the χ² test. Pearson correlation coefficients were employed to assess the correlations between relative CT perfusion parameters and immunohistochemical indices. Statistical analysis was performed using the SPSS 17.0 package (SPSS Inc., Chicago, IL, United States), and two-tailed \( P < 0.05 \) was considered statistically significant.

RESULTS

Baseline characteristics
A total of 68 subjects were enrolled in our analysis: 35 cases (17 males, age range 46-79 years, 25 cases with grade I-II, 10 cases with grade III-IV) in the pancreatic adenocarcinoma group and 33 cases (20 males, age range 28-68 years) in the control group. The rBV, rBF, and rPPE values of the tumor parenchyma in patients with pancreatic adenocarcinoma were significantly lower than those in the control group \( (P < 0.01) \), and the rTTP and rPermeability values of the tumor parenchyma were significantly higher than those of the controls \( (P < 0.01) \) (Table 1).

In addition, the relative CT perfusion parameters of patients with grade I-II pancreatic adenocarcinoma \( (n = 25) \) and those with grade III-IV pancreatic adenocarcinoma \( (n = 10) \) \( (P < 0.01) \) were significantly different. RBF and rBV values were significantly lower in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma \( (P < 0.01) \) (Table 2). Patients with pancreatic adenocarcinoma had a lower density on the maximum-density projection images, as well as lower
Table 1: Demographic features

<table>
<thead>
<tr>
<th></th>
<th>Pancreatic adenocarcinoma (n = 35)</th>
<th>Controls (n = 33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61.5 (46-79)</td>
<td>48 (28-68)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (48.6%)</td>
<td>20 (60.6%)</td>
<td>0.342</td>
</tr>
<tr>
<td>Female</td>
<td>18 (51.4%)</td>
<td>13 (39.4%)</td>
<td></td>
</tr>
<tr>
<td>rBF</td>
<td>0.222 ± 0.089</td>
<td>1.000 ± 0.023</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>rBV</td>
<td>0.453 ± 0.193</td>
<td>0.993 ± 0.076</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>rPE</td>
<td>0.576 ± 0.278</td>
<td>1.003 ± 0.008</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>rPermeability</td>
<td>6.000 ± 1.395</td>
<td>0.949 ± 0.165</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>rTTP</td>
<td>1.917 ± 0.208</td>
<td>1.014 ± 0.039</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

rBF: Relative blood flow; rBV: Relative blood volume; rPermeability: Relative permeability; rPE: Relative peak enhancement; rTTP: Relative time to peak.

Table 2: Relative computed tomography perfusion parameters of grade I-II pancreatic adenocarcinoma vs grade III-IV pancreatic adenocarcinoma

<table>
<thead>
<tr>
<th></th>
<th>Grade I-II pancreatic adenocarcinoma (n = 25)</th>
<th>Grade III-IV pancreatic adenocarcinoma (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rBF</td>
<td>0.266 ± 0.057</td>
<td>0.111 ± 0.042</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>rBV</td>
<td>0.546 ± 0.127</td>
<td>0.223 ± 0.123</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>rPE</td>
<td>0.586 ± 0.265</td>
<td>0.552 ± 0.321</td>
<td>0.750</td>
</tr>
<tr>
<td>rPermeability</td>
<td>5.841 ± 1.413</td>
<td>6.393 ± 1.336</td>
<td>0.297</td>
</tr>
<tr>
<td>rTTP</td>
<td>1.919 ± 0.208</td>
<td>1.911 ± 0.218</td>
<td>0.915</td>
</tr>
</tbody>
</table>

rBF: Relative blood flow; rBV: Relative blood volume; rPermeability: Relative permeability; rPE: Relative peak enhancement; rTTP: Relative time to peak.

Correlations between relative CT perfusion parameters and immunohistochemical indicators in patients with pancreatic adenocarcinoma

Additionally, VMI values were significantly lower in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma (P < 0.05). VEGF, CD105-MVD, CD34-MVD, and AR showed significantly higher values in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma (P < 0.05). However, no significant difference was observed in (α-SMA)-MVD between grade I-II pancreatic adenocarcinoma and grade III-IV pancreatic adenocarcinoma (P > 0.05) (Figure 3). Furthermore, the levels of VEGF, CD105-MVD, and CD34-MVD were significantly higher in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma. No significant difference was found in (α-SMA)-MVD between grade I-II pancreatic adenocarcinoma and grade III-IV pancreatic adenocarcinoma. A significant correlation was detected between rBF and VEGF, CD105-MVD, AR, and VMI (P < 0.01) and between rBV and VEGF, CD105-MVD, CD34-MVD, and VMI (P < 0.01). There was a moderate correlation between rBV and AR (r = -0.412, P < 0.05), and CD34-MVD (r = -0.407, P < 0.05), as depicted in Table 3 and Figure 4A and 4B. No significant correlations were observed between rPermeability, rPE, and rTTP and the immunohistochemical indices (P > 0.05) (Table 3).

DISCUSSION

In the present study, we found a correlation between the relative CT perfusion parameters and the immunohistochemical indicators. These findings indicate that CT perfusion parameters may be a useful noninvasive tool for pancreatic adenocarcinoma diagnosis.

CT perfusion imaging is performed on the basis of the central volume principle by monitoring the first pass of a bolus of iodinated contrast agent through the cerebral vasculature[16-19]. The quantitative
Table 3 Correlation between relative computed tomography perfusion parameters and immunohistochemical indicators in pancreatic adenocarcinoma patients

<table>
<thead>
<tr>
<th>Pearson correlation</th>
<th>rBF</th>
<th>rBV</th>
<th>rPE</th>
<th>rPermeability</th>
<th>rTTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>-0.670&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.557&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.182</td>
<td>0.107</td>
<td>0.071</td>
</tr>
<tr>
<td>CD105-MVD</td>
<td>-0.489&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.549&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.002</td>
<td>0.016</td>
<td>0.030</td>
</tr>
<tr>
<td>CD34-MVD</td>
<td>-0.241</td>
<td>-0.407&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.074</td>
<td>0.072</td>
<td>-0.028</td>
</tr>
<tr>
<td>AR</td>
<td>-0.497&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.412&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.049</td>
<td>-0.046</td>
<td>0.020</td>
</tr>
<tr>
<td>VMI</td>
<td>0.603&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.499&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.119</td>
<td>-0.043</td>
<td>0.150</td>
</tr>
</tbody>
</table>

<sup>a</sup>P < 0.05.  
<sup>b</sup>P < 0.01. AR: Angiogenesis rate; VMI: Vascular maturity index.

Figure 1  Representative computed tomography perfusion parameters in the pancreas of a healthy volunteer.

Maximum intensity projection  
Blood flow  
Blood volume  
Permeability

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parameters from perfusion CT can reflect the pancreatic tissue vascularity directly and can thus be utilized as a tool for detecting disturbance of the pancreatic microcirculation[20]. The relative CT perfusion parameters are beneficial for the reduction of the individual differences in pancreatic perfusion. The results of this investigation indicated that relative CT perfusion quantitative parameters may be valuable for detecting disturbances in the pancreatic microcirculation in pancreatic adenocarcinoma.

Here, we found that the rBF and rBV values in patients with pancreatic adenocarcinoma were lower than those in the controls. The rBF and rBV values in grade III-IV pancreatic adenocarcinoma were significantly lower than those in grade I-II pancreatic adenocarcinoma. Considering that the rBF and rBV values could reveal blood perfusion in pancreatic adenocarcinoma to some extent, we suggest that low rBF and rBV values may be associated with fibrosis and arteriolosclerosis in pancreatic adenocarcinoma.
The pancreatic adenocarcinoma patients had a lower density on the maximum-density projection images, as well as lower values of blood flow, blood volume, and permeability, as compared with the adjacent relatively normal pancreatic tissue.

VEGF, CD34, CD105, and AR are frequently used indicators to evaluate tumor angiogenesis. VEGF is critically involved in angiogenesis induction\cite{7,21,22}. CD34 is a total vascular endothelial cell marker, which is present in the vast majority of the blood vessels in the tumor\cite{23}. CD105 is a member of the transforming growth factor-β superfamily that participates in angiogenesis and maintaining vascularity, which is highly expressed in the endothelial cells of nascent tumor blood vessels and the vascular endothelial cells of the tumor margin. CD105 was considered an ideal target in tumor therapy for suppression of tumor angiogenesis\cite{24}. CD105-MVD was found to be an independent prognostic marker for most solid tumors\cite{25}. AR represents the percentage of CD105-MVD/CD34-MVD, reflecting the proportion of neovascularization. In the present study, we found that VEGF, CD105-MVD, CD34-MVD, and AR in grade III-IV pancreatic adenocarcinoma were significantly higher than those in grade I-II pancreatic adenocarcinoma, which is in accordance with the general characteristics of malignant
tumors, that is, tumor angiogenesis is more pronounced in pancreatic adenocarcinoma with higher malignancy. Negative correlations were found between VEGF, CD105-MVD, AR, and rBF, as well as between VEGF, CD105-MVD, CD34-MVD, and rBV. These results might have been due to the decreased amount of residual pancreatic tissue.

Previous results demonstrated that VMI played a major role in tumor blood supply [26]. Our results showed that VMI was significantly lower in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma (P < 0.05). A positive correlation was observed between rBV, rBF, and VMI. These results could be attributed to larger quantities of mature vessels in grade I-II pancreatic adenocarcinoma than in grade III-IV pancreatic adenocarcinoma [27]. It was reported that the percentage of tumor vessels with function was less than 5% and absence of smooth muscle actin-positive pericyte coverage of tumor vessels correlated with hematogenous metastasis and prognosis of the neoplasm [28]. Accumulating evidence has shown that rBF and rBV correlate with angiogenesis markers to some extent; however, further research is required to confirm these findings.

Figure 3 Immunohistochemical indicators in patients with pancreatic adenocarcinoma. CD34-MVD, CD105-MVD, VEGF, and (α-SMA)-MVD in patients with grade III pancreatic adenocarcinoma (right) were compared with CD34-MVD, CD105-MVD, VEGF, and (α-SMA)-MVD in patients with grade I pancreatic adenocarcinoma (left). Magnification × 400.
The relative permeability of the tumor tissue in patients with pancreatic adenocarcinoma was higher than that in normal controls, which is similar to previously reported findings\cite{16,29}. Furthermore, this outcome is consistent with the influence of the increased immature neovascularization in pancreatic adenocarcinoma. The incomplete endothelium of immature tumor vessels augmented the permeability of the blood vessel walls. However, certain controversies have been reported. For example, Ho et al\cite{20} found no significant difference between the permeability of pancreatic adenocarcinoma and that of normal tissues. Additionally, Matsusaki et al\cite{30} reported that the permeability of tumor tissue in patients with pancreatic adenocarcinoma was lower than that in normal controls. Perhaps these results were associated with the existence of fibrosis and sclerosis in pancreatic adenocarcinoma.

This study is not without limitations. The sample size was relatively small, and thus a future larger study is warranted to confirm the present results. In addition, there may be selection bias due to the single center design of our investigation despite our attempts to consecutively include potential subjects for analysis.

CONCLUSION

In conclusion, the rBF and rBV values of pancreatic adenocarcinoma are correlated with the immunohistochemistry indices of angiogenesis to a certain extent. These findings suggest that perfusion CT imaging may be an appropriate technique for quantitative assessments of pancreatic adenocarcinoma microvasculature.

ARTICLE HIGHLIGHTS

Research background
Pancreatic adenocarcinoma is one of the most common malignant tumors of the digestive system. More than 80% of patients with pancreatic adenocarcinoma are not diagnosed until late stage and have distant or local metastases.

Research motivation
To investigate the value of computed tomography (CT) perfusion imaging in the evaluation of angiogenesis in pancreatic adenocarcinoma patients.

Research objectives
To investigate the value of computed tomography (CT) perfusion imaging in the evaluation of angiogenesis in pancreatic adenocarcinoma patients.
Research methods
This is a retrospective cohort study. Patients with pancreatic adenocarcinoma and volunteers without pancreatic diseases underwent CT perfusion imaging from December 2014 to August 2017 in Huashan Hospital, Fudan University Shanghai, China.

Research results
A total of 35 pancreatic adenocarcinoma patients and 33 volunteers were enrolled. The relative blood flow (rBF), and relative blood volume (rBV) were significantly lower in patients with pancreatic adenocarcinoma than in the control group (P < 0.05). Conversely, the relative permeability in patients with pancreatic adenocarcinoma was significantly higher than that in controls (P < 0.05). In addition, rBF, rBV, and the vascular maturity index (VMI) were significantly lower in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma (P < 0.05). Vascular endothelial growth factor (VEGF), CD105-MVD, CD34-MVD, and angiogenesis rate (AR) were significantly higher in grade III-IV pancreatic adenocarcinoma than in grade I-II pancreatic adenocarcinoma (P < 0.05). Significant correlations between rBF and VEGF, CD105-MVD, AR, and VMI (P < 0.01) were observed. Moreover, the levels of rBV were statistically significantly correlated with those of VEGF, CD105-MVD, CD34-MVD, and VMI (P < 0.01).

Research conclusions
Perfusion CT imaging may be an appropriate approach for the quantitative assessment of tumor angiogenesis in pancreatic adenocarcinoma.

Research perspectives
Further research on perfusion CT imaging for quantitative assessment of tumor angiogenesis in pancreatic adenocarcinoma is warranted.

FOOTNOTES

Author contributions: Liu W drafted the manuscript and assisted with data analysis; Yin B and Yu Y participated in the design and oversight of the study, and were involved in data collection; Lu N participated in the design of the study and assisted with data analysis; Liang ZH was involved in data collection and assisted with data analysis; all authors have read and approved the final manuscript.

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Retrospective Study

Epidemiological features and dynamic changes in blood biochemical indices for COVID-19 patients in Hebi

Xiao-Bo Nie, Bao-Sheng Shi, Lin Zhang, Wei-Li Niu, Ting Xue, Lan-Qing Li, Xiao-Yun Wei, Yan-Dong Wang, Wei-Dong Chen, Rui-Fang Hou

Abstract

BACKGROUND

Millions of people have died of coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and retrospective studies of the disease in local regions are necessary.

AIM

To characterize the epidemiological features and dynamic changes in blood biochemical indices for SARS-CoV-2-infected patients in Hebi, a representative city with a large floating population in North China.

METHODS

From January 25 to February 10, 2020, the clinical data of patients who tested positive for SARS-CoV-2 by quantitative real-time polymerase chain reaction in Hebi city (China) were evaluated at admission, and laboratory data for hemato logic parameters, inflammatory indices, coagulation function indices, liver
function indices, blood lipid indices, renal function indices, myocardial enzyme activities and five blood biochemical markers of immunity were evaluated at admission, upon hospitalization and before discharge.

RESULTS
Sixteen confirmed COVID-19 patients developed pneumonia but were cured after adequate treatment. Fever and fatigue were the common symptoms. The most common laboratory abnormalities of patients at admission were leukopenia, eosinopenia, decreased percentage of eosinophils, elevated high sensitivity C-reactive protein and fibrinogen levels, hypoalbuminemia, mildly increased aspartate transferase activity and levels of bilirubin, and increased levels of β2-microglobulin. Importantly, aggravated liver dysfunction was detected in most patients, which may be partially attributed to virus infection as well as medicinal treatment.

CONCLUSION
This study provides several potential diagnostic markers and dynamic biochemical indices of disease progression to better prevent, diagnose and treat COVID-19 infection.

Key Words: COVID-19; Epidemiology; Blood biochemical indices; Computed tomography imaging; Liver dysfunction

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Core Tip: Coronavirus disease 2019 (COVID-19) is still spreading across the world since the outbreak in 2020, and has caused millions of deaths. Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mass vaccination has effectively inhibited this epidemic, the emergence of new mutant strains of SARS-CoV-2 is still challenging the current prevention and treatment of COVID-19. In this retrospective study, we aimed to characterize the epidemiological features and evaluate the dynamic changes in blood biochemical indices for COVID-19 patients in Hebi, a representative city with a large floating population in North China.

INTRODUCTION
Currently, coronavirus disease 2019 (COVID-19) with an unknown source of infection has spread rapidly worldwide. According to the latest data from Johns Hopkins University (https://coronavirus.jhu.edu/map.html), as of October 20, 2021, more than 241 million people have tested positive for COVID-19, bringing the total number of deaths involving the coronavirus to more than 4.9 million, and the numbers are still increasing sharply with over two million new cases weekly. Although COVID-19 infection is self-limiting in approximately 80% of cases, male individuals, elderly individuals and those with comorbidities such as diabetes mellitus, hypertension, or underlying cardiorespiratory illness are at a higher risk of becoming severely ill[1-3]. According to previous reports, the genome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has 89% nucleotide identity with human SARS-CoV-2 and 50% identity with that of human Middle East respiratory syndrome coronavirus, and all three coronaviruses can cause severe respiratory illness[4,5]. COVID-19 infection is mainly characterized by respiratory illness with flu-like symptoms such as fever, cough and shortness of breath, whereas severe infection can cause death due to diffuse alveolar damage and progressive respiratory failure[6]. Angiotensin-converting enzyme 2 (ACE2), the human cell receptor of SARS-CoV-2, whose expression is dominant in alveolar type 2 cells, is also expressed in organs such as the liver, kidney, heart and brain; thus, SARS-CoV-2-infected patients are often observed to have systemic damage with widespread inflammation[7-10]. Preventive measures and vaccination are the best ways to protect people from this infectious disease until effective medicines are developed.

Hebi is one of the agricultural and developing cities in North China, with more than 20% of its population (1.63 million) working outside year round and returning to their home villages on holidays. Therefore, the imported case of COVID-19 infection quickly emerged the day after the Chinese Lunar New Year holiday started on January 24. Next, the number of newly confirmed cases had undergone
two rapid growth periods and soon disappeared after mandatory social isolation had been issued by the local government. Although several studies have demonstrated the epidemic, clinical, pathological features and prognosis of COVID-19 infection[6,11-13], data on epidemic areas such as Hebi are still lacking. Notably, we identified several valuable diagnostic markers and obtained dynamic indicators of disease progression by comparing the data on blood biochemical indices and computed tomography (CT) imaging of SARS-CoV-2-infected patients at admission, upon hospitalization and before discharge. We hope our study will still guide the subsequent prevention, diagnosis and personalized treatment of this disease.

MATERIALS AND METHODS

Patients
We conducted a retrospective study of the clinical characteristics of 16 patients who were enrolled in People's Hospital of Hebi, China between January 25 and February 10, 2020. All patients were diagnosed with viral pneumonia and were confirmed to be infected with SARS-CoV-2 according to the guidelines from the World Health Organization (interim) and National Health Commission of the People’s Republic of China (Trial Version 5)[14]. To confirm COVID-19 infection, nasopharyngeal swab and oropharyngeal swab samples were collected from each patient and tested to detect virus titers using quantitative real-time polymerase chain reaction (RT-PCR) to identify the ORF1ab and N genes of SARS-CoV-2. A positive PCR test was defined if the cycle threshold (Ct) value was less than 37. Virus detection was first performed by a local infectious hospital and further confirmed by Hebi’s Centers for Disease Control and Prevention (CDC). Specimens were considered negative if the Ct value from repeated tests was undetectable.

The study was approved by the Ethics Committee of People’s Hospital of Hebi at Henan University, written informed consent was obtained from all patients, and their private information was strictly confidential.

Data collection
All available medical information, including epidemic characteristics, exposure history, time of onset, medical visit, symptoms and signs, treatment strategies and clinical outcomes, was collected from the 16 confirmed patients infected with SARS-CoV-2 at admission, upon hospitalization and before discharge. Data on CT imaging and laboratory tests at three time periods were also collected, including routine blood examination, blood lipid levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, coagulation function, myocardial enzymes, liver function, renal function and immune function. However, not all patients had complete data for the three time periods, and the number of cases in some figures was less than 16.

Patient and public involvement
No patient or public involvement occurred in the development of the research design or in conducting the study.

Statistical analysis
Unpaired two-sided Student’s t-test was conducted to evaluate the statistical significance of the difference between groups of data on patients at admission and before discharge (normal distribution), and unpaired two-sided Student’s t-test with Welch’s correction was used for data with abnormal distribution. The error bar for the experiments represents the standard deviation of the mean value (mean ± SD). The data on age and time are presented as medians and interquartile ranges (IQRs). P values less than 0.1 were all presented, and those less than 0.05 were considered statistically significant. All statistical analyses and figures were assessed using SPSS 25.0 and GraphPad Prism 8.0.

RESULTS

Clinical characteristics of patients at admission
Sixteen patients with COVID-19 infection who were discharged from our hospital were enrolled. The basic clinical records are shown in Table 1. The median age was 34 (IQR: 25-53) years, 3 patients (18.7%) were aged older than 60 years, 9 patients (56.3%) were aged younger than 40 years, and 9 patients (56.3%) were female. Regarding potential exposure history, 7 patients (43.8%) were living outside of Hebi and returned to Hebi after the Chinese Lunar New Year holiday started on January 24. Next, the confirmed cases (n = 6, 37.5%) with COVID-19 infection in Hebi had undergone a rapid growth period from January 25 to January 31, 2020, and these cases had exposure in Hubei. The number of newly confirmed cases (n = 10; 62.5%) reached another rapid growth period (February 5 to February 10, 2020).
### Table 1 Clinical features of patients with coronavirus disease 2019 at admission (n = 16)

<table>
<thead>
<tr>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>34 (25, 53)</td>
</tr>
<tr>
<td>≥ 60</td>
</tr>
<tr>
<td>3 (18.7%)</td>
</tr>
<tr>
<td>50-59</td>
</tr>
<tr>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>40-49</td>
</tr>
<tr>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>≤ 39</td>
</tr>
<tr>
<td>9 (56.3%)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>7 (43.8%)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>9 (56.3%)</td>
</tr>
<tr>
<td>Exposure history</td>
</tr>
<tr>
<td>Living in Wuhan</td>
</tr>
<tr>
<td>7 (43.8%)</td>
</tr>
<tr>
<td>Exposure to infected patients</td>
</tr>
<tr>
<td>8 (50%)</td>
</tr>
<tr>
<td>Unknown origin</td>
</tr>
<tr>
<td>1 (6.2%)</td>
</tr>
<tr>
<td>Number of new cases</td>
</tr>
<tr>
<td>Jan 25 to Jan 31, 2020</td>
</tr>
<tr>
<td>6 (37.5%)</td>
</tr>
<tr>
<td>Feb 5 to Feb 10, 2020</td>
</tr>
<tr>
<td>10 (62.5%)</td>
</tr>
<tr>
<td>Time (d)</td>
</tr>
<tr>
<td>Interval from onset to admission</td>
</tr>
<tr>
<td>4 (2, 6)</td>
</tr>
<tr>
<td>Hospital stay</td>
</tr>
<tr>
<td>17 (14, 20)</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>13 (81.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>10 (62.5%)</td>
</tr>
<tr>
<td>Dry cough</td>
</tr>
<tr>
<td>13 (37.5%)</td>
</tr>
<tr>
<td>Cough and expectoration</td>
</tr>
<tr>
<td>13 (37.5%)</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>4 (25%)</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>3 (18.7%)</td>
</tr>
<tr>
<td>Pharyngalgia</td>
</tr>
<tr>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Running nose</td>
</tr>
<tr>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Chill</td>
</tr>
<tr>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Muscle soreness</td>
</tr>
<tr>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>1 (6.3%)</td>
</tr>
<tr>
<td>Chest distress</td>
</tr>
<tr>
<td>1 (6.3%)</td>
</tr>
<tr>
<td>Underlying disease</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>1 (6.3%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>1 (6.3%)</td>
</tr>
<tr>
<td>Bronchitis</td>
</tr>
<tr>
<td>1 (6.3%)</td>
</tr>
<tr>
<td>Treatments</td>
</tr>
<tr>
<td>Antiviral treatment</td>
</tr>
<tr>
<td>16 (100%)</td>
</tr>
<tr>
<td>Traditional Chinese Medicine</td>
</tr>
<tr>
<td>16 (100%)</td>
</tr>
<tr>
<td>Recombinant human interferon</td>
</tr>
<tr>
<td>16 (100%)</td>
</tr>
</tbody>
</table>
The median time interval from illness onset to admission was 4 (IQR: 2-6) d. Fever (81.3%), fatigue (62.5%), dry cough (37.5%), cough and expectoration (37.5%), and anorexia (25%) were the most common symptoms of COVID-19 infection. Additionally, headache (18.7%), chills (12.5%), pharyngalgia (12.5%), runny nose (12.5%), muscle soreness (12.5%), chest distress (6.3%), and diarrhea (6.3%) were found in some patients. A few patients had comorbidities such as hypertension (12.5%), diabetes mellitus (12.5%), cardiovascular disease (6.3%), cerebrovascular disease (6.3%) or bronchitis (6.3%) at admission. All patients received antiviral (lopinavir and ritonavir), traditional Chinese medicine (oral administration) and recombinant human interferon (aerosol inhalation) treatments; more than half of the patients (56.3%) required high-flow oxygen therapy; a few patients received anticoagulant (heparin sodium, 37.5%), digestant (31.3%), antibiotic (25%), glucocorticoid (18.7%) and immunoglobulin (6.3%) treatments if necessary; and two (12.5%) patients needed intensive unit care. All patients were cured to discharge after adequate treatment, including one severe case aged 89 years. The median length of hospital stay of all patients was 17 (IQR: 14-20) d.

**Laboratory tests of patients at admission, upon hospitalization and before discharge**

By comparing the results of routine blood examination at different times (Figure 1), we found that the red blood cell (RBC) count ([4.66 ± 0.51] × 10^12/L), RBC distribution width (RDW), (10.7% ± 0.8%), hemoglobin content (127 ± 34 g/L), white blood cell (WBC) count ([4.75 ± 1.77] × 10^9/L), neutrophil count ([3.3 ± 2.1] × 10^9/L) and percent of neutrophils (55.28% ± 14.65%) were close to the lower end of the normal range (NR) or below at admission and did not change significantly during the three time periods. The platelet count was normal at admission but increased ([241 ± 68] × 10^9/L; \( P = 0.026 \)) significantly after treatment. The lymphocyte count ([1.39 ± 0.37] × 10^9/L) was lower at admission but increased ([1.93 ± 0.60] × 10^9/L; \( P = 0.024 \)) significantly after treatment. The eosinophil (EO) count ([0.0145 ± 0.009] × 10^9/L) and percent of EO% (0.36% ± 0.29%) were below the NR at admission but increased significantly after treatment, although they were still at the lower end of the NR. Additionally, the percentage of lymphocytes, monocyte count, percentage of monocytes, basophil count and percentage of basophils were nearly in the NR and did not change at different times.

The ESR was always close to the middle upper end of the NR or above at different times (Figure 2). However, most patients who had undergone examination of the high sensitivity CRP (hs-CRP) test at admission had obviously increased levels (4.0 ± 2.7 mg/L), and all patients returned to the NR before discharge (1.2 ± 0.8 mg/L; \( P = 0.005 \)). A similar change trend was found for the CRP levels (\( P = 0.035 \)). The indices associated with the function of coagulation (Figure 3) - i.e., the prothrombin time, prothrombin activity, international normalized ratio, prothrombin ratio, activated partial thromboplastin time, thrombin time and D-dimer level were always in the NR for all patients, except for the fibrinogen (FIB) level, which was above the NR (4.3 ± 1.4 g/L) and returned to the NR (\( P = 0.117 \)) after anticoagulant treatment.

Among the fifteen blood biochemistry indices reflecting the liver function of patients (Figure 4), glutamyl transpeptidase (GGT), alkaline phosphatase, cholinesterase and total bile acid were nearly in the NR at different times. The total protein (TP) level (72 ± 6 g/L), albumin (ALB) level (42 ± 6 g/L), ratio of ALB and globulin (GLO) (1.5 ± 0.4), and prealbumin (PA) level (280 ± 110 mg/L) were close to the middle lower end of the NR or below at admission, and the total bilirubin (TBIL) (17 ± 9 μM), direct bilirubin (DBIL) (4.0 ± 1.8 μM), and indirect bilirubin (IBIL) (11.7 ± 6.1 μM) levels and aspartate transferase (AST) activity (33 ± 14 U/L) were close to the middle upper end of the NR or above at admission; these findings predicted the impaired liver function of patients after developing COVID-19. Even worse, alanine transaminase (ALT) activity (51 ± 27 U/L; \( P = 0.038 \)) and AST activity (44 ± 11 U/L; \( P = 0.083 \)) increased, whereas the GLO level (23.6 ± 3.8 g/L; \( P = 0.014 \)) decreased after hospitalization, observations that predicted aggravated liver dysfunction after treatment. These data are consistent with the obviously increased levels of total cholesterol (TC) (4.9 ± 1.1 mmol/L; \( P = 0.069 \)), triglyceride (TG) (2.56 ± 0.93 mmol/L; \( P = 0.0003 \)), and apolipoprotein B (APOB) (1.0 ± 0.1 g/L; \( P = 0.040 \)), slightly decreased level of high-density lipoprotein cholesterol (HDL-C) (\( P = 0.217 \)) and slightly increased level of low-density lipoprotein cholesterol (LDL-C) (\( P = 0.200 \)) after treatment (Figure 5). We speculated that the most substantial reason was the secondary liver injury likely induced by virus infection as well as overdosed medicines used during the treatment.
Figure 1 Dynamic changes in routine blood examination indices for patients with coronavirus disease 2019 at admission, upon hospitalization and before discharge. RBC: Red blood cell; RDW.CV: RBC distribution width.CV; HGB: Hemoglobin; PLT: Platelet; WBC: White blood cell; NEUT: Neutrophil; LYM: Lymphocyte; MONO: Monocyte; EO: Eosinophil; BASO: Basophil; NR: Normal range.
Figure 2 Dynamic changes in the serum erythrocyte sedimentation rate and C-reactive protein levels of patients with coronavirus disease 2019 at admission, upon hospitalization and before discharge. ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; hs-CRP: High-sensitivity C-reactive protein; NR: Normal range.

Figure 3 Dynamic changes in coagulation function indices for patients with coronavirus disease 2019 at admission, upon hospitalization and before discharge. PT: Prothrombin time; PTA: Prothrombin activity; INR: International normalized ratio; PTR: Prothrombin ratio; APTT: Activated partial thromboplastin time; FIB: Fibrinogen; TT: Thrombin time; NR: Normal range.

We next evaluated the renal function of patients at different times (Figure 6). Serum urea, uric acid, total CO₂, and cystatin C levels were nearly in the NR at different times. The level of serum creatinine (66 ± 9 μM) was close to the lower end of the NR at admission and further reduced (56 ± 13 μM, \( P = 0.050 \)) after treatment, which may indirectly reflect liver injury during virus infection. Additionally, the serum β2-MG (3.2 ± 1.0 mg/L) level in most patients was above the NR at admission and gradually returned to the normal level after treatment (\( P = 0.040 \)), predicting kidney injury in patients after developing COVID-19. The serum biochemical indices associated with cardiac function (Figure 7) - i.e., creatine
Figure 4 Dynamic changes in liver function indices for patients with coronavirus disease 2019 at admission, upon hospitalization and before discharge. TP: Total protein; ALB: Albumin; GLO: Globulin; PA: Prealbumin; TBIL: Total bilirubin; DBIL: Direct bilirubin; IBIL: Indirect bilirubin; ALT: Alanine
transaminase; AST: Aspartate transferase; GGT: Glutamyl transpeptidase; ALP: Alkaline phosphatase; CHE: Cholinesterase; TBA: Total bile acid; NR: Normal range.

Figure 5 Dynamic changes in blood lipid indices for patients with coronavirus disease 2019 at admission, upon hospitalization and before discharge. TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; APOA1: Apolipoprotein A1; APOB: Apolipoprotein B; NR: Normal range.

Figure 6 Dynamic changes in renal function indices for patients with coronavirus disease 2019 at admission, upon hospitalization and before discharge. UA: Uric acid; CREA: Creatinine; TC02: Total CO2; Cys-c: Cystatin C; β2-MG: β2-microglobulin; NR: Normal range.

phosphokinase isoenzyme activity - were always in the NR at different times. However, the activities of creatine kinase (CK), lactic dehydrogenase (LDH) and a-hydroxybutyric dehydrogenase (α-HBDH) gradually decreased after treatment, indicating potentially slight heart damage in patients after developing COVID-19. Among the five blood biochemical markers associated with immunity (Figure 8),
immunoglobulin M (IgM) and complement C4 were in the NR at admission, but IgA (181 ± 60 mg/dL), IgG (845 ± 193 mg/dL) and complement C3 (93 ± 17 mg/dL) were close to the middle lower end of the NR at admission, indicating low immunity for most patients after developing COVID-19.

CT imaging analysis of patients at admission, upon hospitalization and before discharge
According to chest CT image analysis of all patients at the three time periods, we found dynamic changes in CT characteristics for most patients (Figure 9). During the initial stage, ground-glass opacity was observed in the lungs. During the progressive stage, the lesions became larger, more consolidated or increased in number, more pulmonary lobes were affected, and fibrous stripes and the paving stone sign were observed. During the severe stage, consolidated lesions diffusely distributed in double lungs, enlarged fibrous stripes, signs of white lung and air bronchogram were observed. During the recovery stage, partial absorption of lesions was observed in the pulmonary lobes, and patients were in recovery. Representative CT images (2 cases) with various lesions are shown in Figure 9.

DISCUSSION
In the present study, we reported the epidemiological and clinical characteristics of 16 cases of laboratory-confirmed COVID-19 infections admitted to the People’s Hospital of Hebi (Hebi, China), a representative agricultural city in North China with one-fifth of the population working in other places year around. The first 6 confirmed cases returned from Wuhan after the Chinese Lunar New Year holiday began. Because the latency of COVID-19 has been reported to be as short as 2 d[15], a rapid increase in confirmed cases emerged in Hebi in the following week, followed by zero cases in the subsequent four days. These cases were likely imported and linked to the cases that appeared in Wuhan, China. From February 5, another 10 cases were confirmed, and 9 cases were identified in four family clusters; one case was of unknown origin. The latency of patients infected in Hebi ranged from 6 to 10 d, which was longer than that of the Wuhan exposure or Shenzhen exposure[15,16]. Notably, one patient who had returned from Wuhan had a latency as long as 22 d, and the onset of this patient was even later than that of his family member. No new cases were identified after February 11, 2020. Overall, COVID-19 is an efficient person-to-person transmission disease with different latencies and can be spread through asymptomatic patients. Therefore, the most effective precautionary measures for general areas were the lockdown and screening of people from epidemic areas and avoiding crowded areas, and more stringent public health measures should be implemented in epidemic areas before universal vaccination can be reached or effective medicines are developed.
Fever and the resulting fatigue were the typical symptoms for most patients at admission in Hebi, a finding similar to that reported for patients in Wuhan[17]. Therefore, the simplest approach to screen potential infections is the monitoring of body temperature. Additionally, respiratory infection symptoms such as dry cough, cough and expectoration and digestive system symptoms such as anorexia were the common symptoms in our study. The median time of hospital stay was 17 (14, 20) d in this study, and all the patients were cured to discharge. We predicted that the high cure rate might be associated with the relatively young age of the patients. These findings agree with most of the study findings showing that patients aged older than 60 years are more likely to become critical cases[18,19].

According to the laboratory test results, the WBC count, neutrophil count, percent of neutrophils, and lymphocyte count were close to the lower end of the NR or below at admission. Among these, leukopenia is a significant laboratory index for COVID-19 infection and its increase often predicts an improvement of this disease[20]. In our study, the lymphocyte count of most patients increased after adequate treatment and nearly recovered to the NR before discharge. Notably, the EO count and percent of EO% in most patients were below the NR at admission and increased to varying degrees after hospitalization. A similar phenomenon is observed in patients with COVID-19 and other severe infections[21], indicating that eosinopenia is associated with lower immune function and is an independent indicator of COVID-19 infection. Based on the available evidence, anemia is associated with severe infection of COVID-19 due to the interaction of SARS-CoV-2 and hemoglobin and resultant hemolysis[22,23]. Consistently, we found that the RBC count, RDW_CV and levels of hemoglobin were always close to the lower end of the NR or below during the entire treatment. Additionally, a previous study revealed that pro-inflammatory cytokines, including interleukin-2 receptor (IL-2R) and IL-6 in serum, increased significantly in severe patients with COVID-19[24], suggesting injury to cytokine storms caused by COVID-19 infection. CRP is a typical inflammatory marker in plasma produced during the acute phase of inflammation[25]. Similarly, our study also found that most patients showed increased levels of CRP, particularly hs-CRP, which recovered to the NR before discharge. ESR, another marker of systemic inflammation and a less expensive alternative to CRP, was also found to be increased in some patients at admission. The hypercoagulable state and secondary hyperfibrinolysis marked by an increased level of D-dimer are important pathological features of severe to critical types of COVID-19 infection[26]. Although increased D-dimer levels were not detected in our study, we still found upregulated plasma FIB levels in most patients at admission and recovery after anticoagulant
Liver damage is common in patients with COVID-19, and severe cases have a higher risk of liver dysfunction[28]. A recent study reported that the expression level of the ACE2 receptor in cholangiocytes is similar to that of alveolar type 2 cells, suggesting that SARS-CoV-2 directly binds to cholangiocytes and leads to liver damage[29]. However, a pathological study on liver tissue from a deceased COVID-19 patient showed that the viral titer was relatively low because no viral inclusion body was observed in the liver, but moderate microvascular steatosis and mild active inflammation of the hepatic lobular portal area were observed[30]. We found that GGT, an accurate diagnostic biomarker for cholangiocyte injury, was not elevated in most patients. However, relatively low levels of TP, ALB and PA, a decreased ratio of ALB/GLO, relatively high levels of TBIL, DBIL, and IBIL, and high AST activity were detected in most patients at admission, indicating that SARS-CoV-2 might directly damage liver function. Furthermore, the ALT and AST activities further increased, and the GLO level decreased after hospitalization. Additionally, increased levels of TC, TG, and APOB, slightly decreased levels of HDL-C and increased levels of LDL-C were detected in most patients after treatment. We predicted that the aggravated liver impairment and elevated blood lipids may be due to hepatotoxicity induced by both viruses and overdosed medicines used during hospitalization. Therefore, patients with severe liver dysfunction at admission may develop liver failure and must be given personalized medication to protect the liver, and patients should undergo regular evaluation of liver function even after discharge.

Renal dysfunction or even acute kidney injury occurs in approximately half of patients with COVID-19, the main features of which are proteinuria, hematuria, increased levels of blood urea nitrogen and serum creatinine[31]. This finding implies the possibility that cells in the kidney may be directly infected by SARS-CoV-2. Based on the online analysis of ACE2 expression in different human organs and immunohistochemistry tests, Fan et al[32] proved that ACE2 is highly expressed in renal tubular cells. Similarly, our study also demonstrated that more than half of patients showed a sustainable increase in β2-MG levels at admission and a decrease after treatment. Considering this evidence, renal function evaluation of confirmed cases should be performed at admission, and more intensive surveillance and potential interventions should be given for severe patients to prevent fatality. Additionally, SARS-CoV-2 can cause fatal consequences for patients who have underlying cardiovascular diseases or cardiac risk...
Nie XB et al. Biochemical indices dynamic changes of COVID-19 factors and cardiac injury for patients without potential cardiovascular disease[33]. For more detailed information on the relationship between COVID-19 and the cardiovascular system, please refer to the review elaborately summarized by Kwenandr et al[34]. In our study, the myocardial enzyme activities associated with cardiac function were nearly in the NR at admission, but the activities of CK, LDH and α-HBDH were reduced to varying degrees after the treatment. To our knowledge, the human population has no immunity to SARS-CoV-2, and older people are susceptible to COVID-19 and may develop more severe symptoms than younger people[19], indirectly indicating that immunity is the most effective way to block and fight against COVID-19 infection. According to the results of immunity-associated tests, the levels of IgA, IgG and complement C3 were relatively low for most patients at admission, demonstrating the low immunity of these cases.

This retrospective study still has significant limitations. First, we had a relatively small number of confirmed cases, and not all patients were examined for the above laboratory tests during the three time periods (at admission, upon hospitalization and before discharge) because of condition limitation; hence, the number of cases in some figures was less than 16. Second, the specific Ct values of RT-PCR to identify the genes of SARS-CoV-2 were largely lacking, and no method exists to analyze the correlation of virus titers with the severity of symptoms and data concerning laboratory tests. Third, follow-up studies on most patients at discharge regarding abnormal phenomena such as eosinopenia and aggravated liver function were also lacking. Thus, a stricter experimental design and complete data collection are required in future studies.

CONCLUSION
Collectively, our study indicated that COVID-19 is a highly contagious disease; hence, stringent public health measures are the most effective strategy to cut off its transmission before universal vaccination is reached or effective antivirals are developed. Leukopenia, eosinopenia, decreased EO%, elevated hs-CRP and FIB levels, and abnormal liver and renal function are valuable biochemical indices for most patients with COVID-19 infection, and aggravated liver dysfunction will be detected for most patients during treatment. Therefore, adequate laboratory tests, CT scanning at admission and dynamic monitoring of blood biochemical indices will be beneficial to identify and predict the response of patients to various treatment modalities. We hope our study on the 16 cases in Hebi will provide useful information to understand the prevention, diagnosis and treatment of COVID-19.

ARTICLE HIGHLIGHTS

Research background
There are no studies on the dynamic changes of biochemical indices of patients with coronavirus disease 2019 (COVID-19) at admission, upon hospitalization and before discharge.

Research motivation
The epidemiological features and dynamic changes in blood biochemical indices for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients in Hebi, a representative city with a large floating population in North China, have not been well characterized.

Research objectives
This retrospective study aimed to analyze the data of patients with COVID-19 at admission, upon hospitalization and before discharge in order to clarify the epidemiological features and dynamic changes in blood biochemical indices of this disease.

Research methods
All available medical information, especially the laboratory data, was collected from 16 cases of laboratory-confirmed COVID-19 infection at admission, upon hospitalization and before discharge.

Research results
Fever and fatigue were the common symptoms of COVID-19 infection. Leukopenia, eosinopenia, decreased percentage of eosinophils, elevated high sensitivity C-reactive protein and fibrinogen levels, abnormal liver and renal function were valuable biochemical indices for patients with COVID-19. Aggravated liver dysfunction could be detected in most patients during treatment.

Research conclusions
Patients with COVID-19 have certain common symptoms at admission and dynamic changes in blood biochemical indices at admission, upon hospitalization and before discharge. Dynamic monitoring of
blood biochemical indices can be beneficial to identify and predict the response of patients to various treatment modalities.

**Research perspectives**

Further investigations on stricter experimental design, larger samples and complete data collection are required to confirm whether the findings of this study could be applied on a broader scale.

**FOOTNOTES**

**Author contributions:** Nie XB and Hou RF designed the research study; Shi BS, Zhang L, Niu WL, Xue T, Li LQ and Wei XY performed the research; Wang YD and Chen WD contributed analytic tools; Nie XB analyzed the data and wrote the manuscript; Hou RF revised the manuscript; all authors have read and approve the final manuscript.

**Institutional review board statement:** The study was reviewed and approved by the (Ethics Committee of People’s Hospital of Hebi) Institutional Review Board (Approval No. 2020004).

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

**Conflict-of-interest statement:** (Nie XB, Xue T, Li LQ, Wei XY, Wei-Dong Chen) are employees of (Key Laboratory of Receptors-Mediated Gene Regulation, School of Basic Medical Sciences, Henan University). Hou RF is an employee of (Hebi Key Laboratory of Liver Disease, The People’s Hospital of Hebi, Henan University). (Shi BS, Zhang L, Niu WL) are employees of (The Third People’s Hospital of Hebi). Wang YD is an employee of (State Key Laboratory of Chemical Resource Engineering, College of Life Science and Technology, Beijing University of Chemical Technology). The authors declare that they have no conflicts of interest to disclose.

**Data sharing statement:** Technical appendix, statistical code, and dataset available from the corresponding author at dr_rfhou@126.com. Participants gave informed consent for data sharing.

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Clinical Trials Study

Identification and predictive analysis for participants at ultra-high risk of psychosis: A comparison of three psychometric diagnostic interviews

Peng Wang, Chuan-Dong Yan, Xiao-Jie Dong, Lei Geng, Chao Xu, Yun Nie, Sheng Zhang

Abstract

BACKGROUND
An accurate identification of individuals at ultra-high risk (UHR) based on psychometric tools to prospectively identify psychosis as early as possible is required for indicated preventive intervention. The diagnostic comparability of several psychometric tools, including the comprehensive assessment of at risk mental state (CAARMS), the structured interview for psychosis-risk syndrome (SIPS) and the bonn scale for the assessment of basic symptoms (BSABS), is unknown.

AIM
To address the psychometric comparability of CAARMS, SIPS and BSABS for subjects who are close relatives of patients with schizophrenia.

METHODS
In total, 189 participants aged 18-58 years who were lineal relative by blood and collateral relatives by blood up to the third degree of kinship of patients with schizophrenia were interviewed in the period of May 2017 to January 2019. Relatives of the participants diagnosed schizophrenia were excluded. All the participants were assessed for a UHR state by three psychometric tools (CAARMS, SIPS and BSABS). The psychometric diagnosis results included at risk of psychosis (UHR+), not at risk of psychosis (UHR-) and psychosis. Demographic and clinical characteristics were also measured. The inter-rater agreement was assessed for evaluation of the coherence of the three scales. Transition rates for UHR+ subjects to psychosis within 2 years were also recorded.
RESULTS
The overall agreement percentages were 93.12%, 92.06% and 93.65% of CAARMS and SIPS, SIPS and BSABS and CAARMS and BSABS, respectively. The overall agreement percentage of the relative functional impairment of the three groups (UHR+, not at risk of psychosis and psychosis) were 89.24%, 86.36% and 88.12%, respectively. The inter-rater reliability of the CAARMS, SIPS and BSABS total score was 0.90, 0.89 and 0.85. The inter-rater reliability was very good to excellent for all the subscales of these three instruments. For CAARMS, SIPS and BSABS, the kappa coefficient about UHR criteria agreement was 0.87, 0.84 and 0.82, respectively ($P < 0.001$). The transition rates of UHR+ to psychosis within 2 years were 16.7% (CAARMS), 10.0% (SIPS) and 17.7% (BSABS).

CONCLUSION
There is good diagnostic agreement between the CAARMS, SIPS and BSABS towards identification of UHR participants who are close relatives of patients with schizophrenia.

Key Words: Psychosis; Ultra-high risk; Psychosis-Risk syndrome; Psychometric diagnostic; Predictive analysis

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INTRODUCTION
Indicated preventive intervention brings new hope for impacting the course of psychosis since treatments for psychosis substantially improve outcomes[1,2]. Therefore, an accurate identification of individuals at clinical high risk (CHR) based on psychometric tools to prospectively identify psychosis as early as possible is required to allow preventative screening, diagnosis and interventions[3-5].

During the development of psychiatry, psychometric tools were created, analyzed and confirmed. These tools include the comprehensive assessment of at risk mental state (CAARMS), the Structured Interview for Psychosis-Risk Syndrome (SIPS) and the Basel Screening Instrument for Psychosis for the assessment of “ultra-high risk” (UHR) patients. The Bonn Scale for the Assessment of Basic Symptoms (BSABS) and the Schizophrenia Proneness Instruments are used to assess basic symptoms.

A screening test should identify those potential individuals developing the disease[6], and a prognostic test is necessary for prediction of the future disease development when a patient has ominous signs or symptoms. However, criteria for UHR as a screening test rely on subjectively experienced disturbances of perception, thinking, language and attention[7].

Both the CAARMS and the SIPS can distinguish UHR subjects from large group of individuals with high-risk services for potential UHR symptoms. Moreover, the CAARMS and the SIPS demonstrate the similar construct and criteria, which show same predictive values in the follow-up[8,9]. Meanwhile, the prevalence of the condition would affect the predictive values which are not fixed indicators[6].

However, there is little evidence of a single recognized standard among these instruments for UHR identification in China, especially in participants who are lineal relative or collateral relatives of schizophrenia patients. The development of future large-scale UHR multicenter studies was affected significantly by psychometric uncertainty because of amplifying heterogeneity across individual sites. These concerns and conjecture have never been examined practically.

We present this study of UHR assessment in participants who are lineal relative or collateral relatives by blood up to three generations of patients with schizophrenia by using the CAARMS, SIPS and
BSABS. Our principal aim was to address the psychometric comparability of the CAARMS, SIPS and BSABS for these participants. Our secondary aim was to verify the viability and reliability of these three instruments for these participants.

**MATERIALS AND METHODS**

**Samples**

For the research group, we included participants who were a lineal relative by blood and collateral relative by blood up to the third degree of kinship of patients with schizophrenia diagnosed in the Affiliated Wuhan Mental Health Center, Tongji Medical College of Huazhong University of Science & Technology from May 2017 to January 2019. All the participants were assessed for UHR by three psychometric tools, including CAARMS, SIPS and BSABS. Participants were recruited from the Wuhan Mental Health Center and were able to be contacted by telephone or an internet homepage.

**Procedure and clinical measures**

The CAARMS, a semi-structured clinical interview, covers different aspects of attenuated psychopathology or functioning. It consists of 27 items, each item rated in terms of intensity from 0 to 6 and frequency/duration from 0 to 6, which can be classified into seven subscales, including positive symptoms, cognitive change, attention/concentration/emotional disturbance, negative symptoms, behavioral change, motor/physical changes and general psychopathology. Positive symptoms, including delusions, hallucinations and thought disorder, of the CAARMS are used to determine both the UHR criteria and the threshold for psychosis.

The SIPS, a semi-structured clinical interview, consists of six parts, including Family History Questionnaire, The scale of psychosis-risk symptoms, the global assessment of functioning (GAF), schizotypal personality disorder checklist (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition), Summary of SIPS data and Summary of SIPS syndrome criteria. The symptoms score from 0 to 6 in terms of intensity, frequency/duration, influence and degree of conflict.

The BSABS, a semi-structured clinical interview, consists of 92 items classified into six rating scales, including adynamia (A + B), cognitive disorder (C), cenesthesia experience (D), dysfunction of central autonomic nerve (E) and self-protection (F).

All the participants participated in the CAARMS, SIPS and BSABS assessments for early detection of schizophrenia. At the end of the diagnostic interview assessment, the psychometric diagnosis results included at risk of psychosis, not at risk of psychosis, and psychosis. Demographic and clinical characteristics were also measured.

The inter-rater agreement was assessed for the evaluation of the coherence of the three instruments. The transition rates of psychosis from at risk of psychosis individuals within 2 years were also recorded.

**Statistical analysis**

All statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, United States). Intraclass correlation coefficients were calculated to estimate intra-scale reliability, and the kappa coefficient was calculated to evaluate the inter-scale and inter-rater agreement on the diagnosis. Comparisons among groups were examined using the Kruskal-Wallis test, and post-hoc analyses were performed using the Mann-Whitney U test with Bonferroni correction. P < 0.05 indicated statistical significance.

**RESULTS**

**Samples and raters characteristics**

The research group consisted of 189 participants who were lineal or collateral relatives of schizophrenia patients who were diagnosed between May 2017 and January 2019.

Of the research group participants, 68 were females (35.98%). The mean age was 35.54 years (standard deviation = 4.15, range = 18-58 years).

**Diagnostic comparison of CAARMS, SIPS and BSABS**

Diagnostic comparison of CAARMS and SIPS (Table 1): The overall agreement percent was 93.12% (expected agreement by chance: 35.12%), and the kappa was a substantial 0.745 [95% confidence interval (CI): 0.663-0.859]. The analysis weighted for the relative functional impairment of the three groups (at risk of psychosis, not at risk of psychosis and psychosis) was determined. The overall agreement percent was 89.24% (expected agreement: 46.38%), and the kappa was 0.796 (95%CI: 0.681-0.895).

Diagnostic comparison of SIPS and BSABS (Table 2): The overall agreement percent was 92.06% (expected agreement by chance: 31.93%), and the kappa was a substantial 0.728 (95%CI: 0.648-0.825). The relative functional impairment of the three groups was analyzed. The overall agreement percent
Table 1 Diagnostic comparison between the comprehensive assessment of at-risk mental states and the structured interview for psychosis-risk syndrome outcomes in participants of the research group (P < 0.001)

<table>
<thead>
<tr>
<th>CAARMS outcomes</th>
<th>SIPS outcomes</th>
<th>UHR-</th>
<th>UHR+</th>
<th>Psychosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>UHR-</td>
<td>Count</td>
<td>162</td>
<td>0</td>
<td>0</td>
<td>162</td>
</tr>
<tr>
<td></td>
<td>Ratio, %</td>
<td>85.71</td>
<td>0</td>
<td>0</td>
<td>85.71</td>
</tr>
<tr>
<td>UHR+</td>
<td>Count</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Ratio, %</td>
<td>2.11</td>
<td>2.65</td>
<td>1.59</td>
<td>6.35</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Count</td>
<td>1</td>
<td>5</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Ratio, %</td>
<td>0.53</td>
<td>2.65</td>
<td>4.76</td>
<td>7.94</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>167</td>
<td>10</td>
<td>12</td>
<td>189</td>
</tr>
<tr>
<td></td>
<td>Ratio, %</td>
<td>88.36</td>
<td>5.3</td>
<td>6.35</td>
<td>100</td>
</tr>
</tbody>
</table>


Table 2 Diagnostic comparison between the structured interview for psychosis-risk syndrome and the bonn scale for the assessment of basic symptoms outcomes in participants of the research group (P < 0.001)

<table>
<thead>
<tr>
<th>BSABS outcomes</th>
<th>SIPS outcomes</th>
<th>UHR-</th>
<th>UHR+</th>
<th>Psychosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>UHR-</td>
<td>Count</td>
<td>159</td>
<td>0</td>
<td>0</td>
<td>159</td>
</tr>
<tr>
<td></td>
<td>Ratio, %</td>
<td>84.13</td>
<td>0</td>
<td>0</td>
<td>84.13</td>
</tr>
<tr>
<td>UHR+</td>
<td>Count</td>
<td>6</td>
<td>7</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Ratio, %</td>
<td>3.17</td>
<td>3.7</td>
<td>2.12</td>
<td>8.99</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Count</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Ratio, %</td>
<td>1.06</td>
<td>1.59</td>
<td>4.23</td>
<td>6.88</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>167</td>
<td>10</td>
<td>12</td>
<td>189</td>
</tr>
<tr>
<td></td>
<td>Ratio, %</td>
<td>88.36</td>
<td>5.29</td>
<td>6.35</td>
<td>100</td>
</tr>
</tbody>
</table>

SIPS: Structured interview for psychosis-risk syndrome; BSABS: Bonn scale for the assessment of basic symptoms; UHR: Ultra-high risk; UHR+: At risk of psychosis; UHR-: Not at risk of psychosis.

was 86.36% (expected agreement: 44.27%), and the kappa was 0.759 (95%CI: 0.676-0.854).

Diagnostic comparison of CAARMS and BSABS (Table 3): The overall agreement percent was 93.65% (expected agreement by chance: 34.07%), and the kappa was a substantial 0.767 (95%CI: 0.678-0.881). The analysis for the relative functional impairment of all the groups was performed. The overall agreement percent and the kappa was 88.12% (expected agreement: 45.52%) and 0.778 (95%CI: 0.680-0.873), respectively.

Inter-rater correlation coefficients of CAARMS, SIPS and BSABS subscales
The inter-rater reliability of the CAARMS, SIPS and BSABS total score were 0.90, 0.89 and 0.85, respectively. The inter-rater reliability of these three scales ranged from very good to excellent for the seven subscales of CAARMS, six subscales of SIPS and five subscales of BSABS. The kappa coefficient for the agreement on the UHR criteria among three raters of these three scales were 0.87, 0.84 and 0.82, respectively (P < 0.001) (Table 4).

Transition rates of at risk of psychosis subjects to psychosis within 2 years
The transition rates of at risk of psychosis to psychosis within 2 years were 16.7% (CAARMS), 10.0% (SIPS) and 17.7% (BSABS) (Table 5).
### DISCUSSION

An accurate identification of individuals at CHR, which is the preventive intervention for psychosis, will substantially improve the outcomes of these individuals. The use of accurate and proper tools to detect psychosis as early as possible for prognosis is very necessary[2]. The aim of this study was to test the comparability of three psychometric instruments (CAARMS, SIPS and BSABS) most frequently used in China to interview participants who were lineal or collateral relatives of patients with schizophrenia. The results indicated that these three instruments have good psychometric properties, and all were reliable and valid for early identification and prospective analysis in this population. Moreover, there were good inter-rater correlation coefficients of each scales.

A prodromal phase named the at-risk mental state (ARMS) precedes most psychotic disorders. Though it is unclear about the most effective therapies, the remained time of and sustained effects, the potential intervention for ARMS groups may take effect on preventing or delaying the onset of psychosis and then improve the outcome for the reduction of untreated psychosis period. In some earliest UHR studies, transition rates of first year from ARMS to psychosis were about 40%[10,11], while a later study reported the transition rate of ARMS to psychosis as 7%-16% within 2 years[12].

Specific psychometric interviews that assess validated CHR criteria are usually accomplished with prognostic testing[13], such as the CAARMS[14], the SIPS[15] and the BSABS[16]. These instruments make a comprehensive analysis for CHR through age, social function, family history of psychosis, symptom score, frequency and duration of symptoms.

Daneault et al.[17] claimed that the development of the SIPS was influenced by the CAARMS. The first aim of this study was to verify the diagnostic comparability of CAARMS vs SIPS and BSABS in 189 participants who were lineal relatives and collateral relative of patients with schizophrenia. There was overall substantial agreement (kappa) between the CAARMS and SIPS, SIPS and BSABS and CAARMS and BSABS. These three instruments show similar psychometric parameters, such as excellent reliability properties. A parallel proportion of true positives over time was shown in a previous study about CAARMS and SIPS[9]. In a recent meta-analysis, help-seeking individuals interviewed with CAARMS and SIPS showed similar excellent prognostic accuracy in ruling out psychosis risk[18].

Different CAARMS or SIPS versions in different countries were compared in previous studies. An excellent reliability was shown in these CHR scales used by trained raters: the overall inter-rater agreement was 0.95, 0.85 and 0.91 for the SIPS[19], the CAARMS[20] and the Schizophrenia Proneness Instruments Adult version[21], respectively. Pelizza et al.[22] tested the reliability and validity for the help-seeking population evaluated by the authorized Italian version of the CAARMS. The results indicated that CAARMS version may assess and detect ARMS reliably and validly in an Italian population, which may also predict transition to psychosis helpfully. Another study observed that there was overall substantial diagnostic agreement between the CAARMS 12/2006 and the SIPS 5.0 in the identification of UHR subjects[23]. We also observed in this study that the CAARMS and the SIPS had similar reliability and validity when used to interview the special population of close relatives of patients with schizophrenia.

Moreover, reliability of the CAARMS, SIPS and BSABS in this study was assessed by inter-rater reliability and internal consistency. The intra-class correlation coefficients of three scales subscale displayed good to excellent reliability, which was similar to the original validation study[12]. The inter-rater reliability for the overall score was 0.90 for total subscales. These findings demonstrate that all the
Table 4 Inter-rater correlation coefficients of the comprehensive assessment of at-risk mental states, the structured interview for psychosis-risk syndrome and the bonn scale for the assessment of basic symptoms subscales (n = 30, P < 0.001)

<table>
<thead>
<tr>
<th></th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAARMS Subscale</td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>0.93</td>
</tr>
<tr>
<td>Cognitive change</td>
<td>0.75</td>
</tr>
<tr>
<td>Attention/concentration/emotional disturbance</td>
<td>0.74</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>0.88</td>
</tr>
<tr>
<td>Behavioral change</td>
<td>0.75</td>
</tr>
<tr>
<td>Motor/physical changes</td>
<td>0.85</td>
</tr>
<tr>
<td>General psychopathology</td>
<td>0.93</td>
</tr>
<tr>
<td>Total</td>
<td>0.9</td>
</tr>
<tr>
<td>SIPS Subscale</td>
<td></td>
</tr>
<tr>
<td>Family History Questionnaire</td>
<td>0.9</td>
</tr>
<tr>
<td>The Scale of Psychosis-Risk Symptoms</td>
<td>0.8</td>
</tr>
<tr>
<td>The Global Assessment of Functioning</td>
<td>0.72</td>
</tr>
<tr>
<td>Schizotypal Personality Disorder Checklist (DSM-5)</td>
<td>0.81</td>
</tr>
<tr>
<td>Summary of SIPS data</td>
<td>0.92</td>
</tr>
<tr>
<td>Summary of SIPS syndrome criteria</td>
<td>0.88</td>
</tr>
<tr>
<td>Total</td>
<td>0.89</td>
</tr>
<tr>
<td>BSABS Subscale</td>
<td></td>
</tr>
<tr>
<td>Adynamia (A + B)</td>
<td>0.87</td>
</tr>
<tr>
<td>Cognitive disorder</td>
<td>0.76</td>
</tr>
<tr>
<td>Cenesthesia experience (D)</td>
<td>0.82</td>
</tr>
<tr>
<td>Dysfunction of central autonomic nerve</td>
<td>0.88</td>
</tr>
<tr>
<td>Self-protection (F)</td>
<td>0.89</td>
</tr>
<tr>
<td>Total</td>
<td>0.85</td>
</tr>
</tbody>
</table>


Table 5 Transition rates of at risk of psychosis participants to within 2 years

<table>
<thead>
<tr>
<th></th>
<th>UHR+</th>
<th>Outcomes after 2 years follow-up</th>
<th>Transition rates, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Psychiatry</td>
<td>No psychosis</td>
</tr>
<tr>
<td>CAARMS</td>
<td>12</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>SIPS</td>
<td>10</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>BSABS</td>
<td>17</td>
<td>3</td>
<td>14</td>
</tr>
</tbody>
</table>

CAARMS: Comprehensive assessment of at-risk mental states; SIPS: Structured interview for psychosis-risk syndrome; BSABS: Bonn scale for the assessment of basic symptoms; UHR+: At risk of psychosis.

three instruments can be evaluate the early identification of schizophrenia in the population of lineal relative of these patients clinically. Furthermore, the inter-rater reliability of the UHR inclusion criteria of the three scales was also approving. Cronbach’s alpha coefficient reflecting internal consistency for the CAARMS total score was 0.89.
In this study, a 2-year follow-up showed that the transition rates of UHR to psychosis were 16.7% (CAARMS), 10.0% (SIPS) and 17.7% (BSABS). These rates were slightly higher than in previous studies [10-12]. We hypothesize that the participants selected for this study were at a higher risk of psychosis because they were lineal relatives or collateral relatives in three generations of patients with schizophrenia.

If comparability, viability, reliability and practicability are considered, then we suggest that CAARMS and BSABS are easier and more convenient for interviewing participants who are close relatives including lineal or collateral relatives by blood up to three generations of schizophrenia patients in China.

This study had some limitations. First, a long-term follow-up was not performed. Second, the recruitment type may have impacted the observed substantial agreement between the three instruments [24]. Also, it is possible that the UHR patients who did not meet the SIPS criteria were undetected by the referrers. This may have inflated the observed agreement. In one study, there were significant differences between the CAARMS and the SIPS in other epidemiological samples of non-help-seeking subjects [25].

**CONCLUSION**

There is good diagnostic agreement between the CAARMS, SIPS and BSABS towards identification of CHR participants who are close relatives of patients with schizophrenia. Also, the three instruments are reliable and valid for assessing and detecting at-risk mental states in these subjects.

**ARTICLE HIGHLIGHTS**

**Research background**

Indicated preventive intervention is the new hope for affecting the psychosis progress since treatments for psychosis substantially improve outcomes. Therefore, an accurate identification of individuals at ultra-high risk (UHR) based on psychometric tools to prospectively identify psychosis as early as possible is required to allow preventative screening, diagnosis and interventions. With the development of psychiatry, psychometric tools have been created, analyzed and confirmed. There is little evidence of a single recognized standard among these instruments for UHR identification in China.

**Research motivation**

In total, 189 participants who were the lineal relative or collateral relatives by blood up to the third degree of kinship of schizophrenia patients were interviewed to identify a UHR state by three psychometric tools, including the comprehensive assessment of at-risk mental states (CAARMS), the Structured Interview for psychosis-risk syndrome (SIPS) and the bonn scale for the assessment of basic symptoms (BSABS), which are the most common instruments in China.

**Research objectives**

To address the psychometric comparability of the CAARMS, SIPS and BSABS for assessment of close relative of schizophrenia patients and to verify the viability and reliability of these three instruments for these participants.

**Research methods**

All of the participants were assessed for a UHR state by the CAARMS, SIPS and BSABS. The psychometric diagnosis results included at risk of psychosis, not at risk of psychosis and psychosis. Demographic and clinical characteristics were also measured. The inter-rater agreement was assessed for evaluation of the coherence of the three instruments. The transition rates of at risk of psychosis to psychosis within 2 years were also recorded.

**Research results**

The overall agreement percentages were 93.12% for CAARMS and SIPS, 92.06% for SIPS and BSABS and 93.65% for CAARMS and BSABS. Moreover, the inter-rater reliability of the CAARMS, SIPS and BSABS total score was 0.90, 0.89 and 0.85, respectively. For all the subscales of these three scales, the inter-rater reliability varied from very good to excellent. The transition rates of at risk of psychosis to psychosis within 2 years were about 16.7% (CAARMS), 10.0% (SIPS) and 17.7% (BSABS).

**Research conclusions**

It showed a good diagnostic agreement between the CAARMS, SIPS and BSABS in identification of UHR participants who are close relative of patients with schizophrenia. Also, these three instruments
are reliable and valid tools for at-risk mental states assessment and detection in these participants.

**Research perspectives**

The lineal and collateral relatives by blood up to the third generations of schizophrenia patients are clinical high-risk participants. Early detection aids in initiation of preventive intervention and can provide substantially improved outcomes. A multicenter interview and follow-up of these participants by different instruments will provide more experience and value for clinical high-risk participants.

**FOOTNOTES**

**Author contributions:** Wang P designed the research; Dong XJ, Geng L, Nie Y, and Xu C helped to collect the patient's clinical data; Yan CD and Zhang S analyzed the data; Wang P and Zhang S wrote the paper and revised the manuscript; all authors read and approved the final manuscript.

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**Institutional review board statement:** The study was approved by the Ethics Committee of Affiliated Wuhan Mental Health Center, Tongji Medical College of Huazhong University of Science & Technology (No. ky2018.45).

**Clinical trial registration statement:** This study is registered at ClinicalTrials.gov, registration number NCT05042739 (https://clinicaltrials.gov/ct2/show/NCT05042739).

**Informed consent statement:** Informed written consent was obtained from the patients for publication of this study.

**Conflict-of-interest statement:** The authors declare having no conflicts of interest.

**Data sharing statement:** No additional data are available.

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

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S-Editor: Ma YJ
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P-Editor: Ma YJ

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Wang P et al. Early identification for risk of psychosis


Clinical Trials Study

Prognostic significance of peritoneal metastasis from colorectal cancer treated with first-line triplet chemotherapy

Shouki Bazarbashi, Abdulrahman Alghabban, Mohamed Aseafan, Ali H Aljubran, Ahmed Alzahrani, Tusneem AM Elhassan

Abstract

BACKGROUND
Peritoneal metastasis from colorectal cancer (CRC) carries a poor prognosis in most studies. The majority of those studies used either a single-agent or doublet chemotherapy regimen in the first-line setting.

AIM
To investigate the prognostic significance of peritoneal metastasis in a cohort of patients treated with triplet chemotherapy in the first-line setting.

METHODS
We retrospectively evaluated progression-free survival (PFS) and overall survival (OS) in 51 patients with metastatic CRC treated in a prospective clinical trial with capecitabine, oxaliplatin, irinotecan, and bevacizumab in the first-line setting according to the presence and absence of peritoneal metastasis. Furthermore, univariate and multivariate analyses for PFS and OS were performed to assess the prognostic significance of peritoneal metastasis at the multivariate level.

RESULTS
Fifty-one patients were treated with the above triplet therapy. Fifteen had peritoneal metastasis. The patient characteristics of both groups showed a significant difference in the sidedness of the primary tumor (left-sided primary tumor in 60% of the peritoneal group vs 86% in the nonperitoneal group, \( P = 0.03 \)) and the presence of liver metastasis (40% for the peritoneal group vs 75% for the nonperitoneal group, \( P = 0.01 \)). Univariate analysis for PFS showed a statistically significant difference for age less than 65 years (\( P = 0.034 \)), presence of liver metastasis (\( P = 0.046 \)), lung metastasis (\( P = 0.011 \)), and those who underwent metastasectomy (\( P = 0.001 \)). Only liver metastasis and metastasectomy were
statistically significant for OS, with $P$ values of 0.001 and 0.002, respectively. Multivariate analysis showed that age (less than 65 years) and metastasectomy were statistically significant for PFS, with $P$ values of 0.002 and 0.001, respectively. On the other hand, the absence of liver metastasis and metastasectomy were statistically significant for OS, with $P$ values of 0.003 and 0.005, respectively.

**CONCLUSION**

Peritoneal metastasis in patients with metastatic CRC treated with first-line triple chemotherapy does not carry prognostic significance at univariate and multivariate levels. Confirmatory larger studies are warranted.

**Key Words:** Colorectal cancer; Peritoneal carcinomatosis; Triplet chemotherapy; Survival; Prognostic factors; Metastasectomy

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**INTRODUCTION**

Globally, colorectal cancer (CRC) is the third most-common cancer and the second-most-common cause of cancer death in males and third in females[1]. There has been a significant improvement in overall survival (OS) for patients with metastatic CRC secondary to the introduction of several new chemotherapy and targeted agents[2-5]. Although no major improvement in survival was observed with first-line doublet chemotherapy regimens compared to single-agent regimens[6-8], triplet chemotherapy apparently resulted in improved OS compared to doublets in the first-line setting[9-12].

Several studies have shown that patients with peritoneal carcinomatosis in metastatic CRC have poor survival, and this was an independent poor prognostic factor[13,14]. However, the majority of those studies used either single-agent or doublet chemotherapy with or without targeted therapy[13,14]. It is unclear whether peritoneal carcinomatosis continues to be a poor prognostic factor in patients with metastatic CRC treated with triplet regimens.

We have previously reported the results of our phase I/II trial of triplet chemotherapy using capecitabine, oxaliplatin, and irinotecan with bevacizumab in patients with advanced CRC[15]. Here, we report the post hoc analysis of the efficacy of the above combination in patients with and without peritoneal metastasis and examined the different prognostic factors for progression-free survival (PFS) and OS in these groups of patients.

**MATERIALS AND METHODS**

**Study design**

The present study represents a post hoc analysis of the previously published phase I/II trial of triplet therapy in patients with unresectable metastatic or locally advanced CRC. Efficacy data were analyzed according to the presence vs the absence of peritoneal metastasis.

**Patients**

Patients with metastatic CRC not amenable to surgical resection were enrolled in a phase I/II trial of triplet chemotherapy consisting of capecitabine, oxaliplatin, irinotecan, and bevacizumab. The study procedures have been published earlier[15]. Briefly, patients were eligible for inclusion if they were...
more than 18 years old, had histologically confirmed CRC adenocarcinoma with no prior chemotherapy or targeted therapy for metastatic disease, had Eastern Cooperative Oncology Group performance status 0-2, had measurable disease [defined by response evaluation criteria in solid tumors (RECIST) V1.1] [16], and had adequate organ function (defined as absolute neutrophil count ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, normal serum bilirubin, serum transaminases ≤ 2.5 times the upper limits of normal, normal serum creatinine, and urine dipstick for proteinuria ≤ 2 +). Patients who had prior adjuvant oxaliplatin or fluoropyrimidine therapy were eligible if the last chemotherapy was ≥ 12 mo. Exclusion criteria included central nervous system metastasis, severe cardiovascular dysfunction, prior malignancy within 5 years (except for adequately treated nonmelanoma skin cancer or in situ cervical cancer), active infection, bleeding diathesis, major surgery within 28 d of starting therapy, uncontrolled hypertension, prior history of dihydropyrimidine deficiency, and pregnancy or breastfeeding. The study was approved by the institutional review board under the number RAC2081068 and was listed on clinicaltrials.gov (NCT01311050). All patient signed informed consent.

Treatment
The phase I part of the trial has been described earlier in a previous publication[15]. According to phase I, the recommended doses for phase II were capecitabine 1000 mg/m^2 orally on days 1 to 14, oxaliplatin 130 mg/m², irinotecan 150 mg/m², and bevacizumab at 7.5 mg/kg of body weight, all on day 1 of each cycle. Treatment cycles were repeated every 21 d. Patients were given 5-8 cycles of a triplet regimen with bevacizumab. Responding patients were placed on maintenance capecitabine and bevacizumab at the above doses until disease progression or unacceptable toxicity.

Statistics and efficacy endpoints
The statistical design of the phase I and II parts of this study was described earlier[15]. The number of patients planned for the phase II part of the trial was 46. All patients were assessed for response according to RECIST criteria V1.1 by computed tomography scans or magnetic resonance imaging performed after the second, fifth, and eighth cycles of chemotherapy and every 2 mo thereafter.

Patient characteristics were summarized using frequencies with percentages, while continuous variables were summarized using medians with interquartile ranges. Patient characteristics were further retrospectively compared according to the presence or absence of peritoneal metastasis. Categorical variables were compared using the chi-square test, while continuous variables were compared using the Mann-Whitney test.

OS was defined as the time to death of any cause, while PFS was defined as the time to disease progression, recurrence, or death from any cause. Surviving patients were censored at last follow-up. Probabilities of OS and PFS were calculated using the Kaplan-Meier estimator with variance calculated using the Greenwood formula. Survival curves were compared using log-rank test. Multivariate analysis was performed using the cox proportional hazard regression model. The proportional hazards assumption was tested, and covariates that violated the proportional hazards assumption were added as time-dependent covariates. P value < 0.05 was considered significant. Analysis was conducted using RStudio. Version 1.4.1106 © 2009-2021 RStudio, PBC. The statistical methods of this study were performed and reviewed by Tusneem Elhassan from King Faisal Specialist Hospital and Research Center.

RESULTS
A total of 53 patients with metastatic or locally advanced unresectable CRC were enrolled in a phase I/II trial of combination chemotherapy with capecitabine, oxaliplatin, irinotecan, and bevacizumab (6 in the phase I part and 47 in the phase II part). Among those, two withdrew. Therefore, a total of 51 patients were available for evaluation. Patient characteristics are illustrated in Table 1. Fifteen patients (29.4%) had peritoneal metastasis. Forty (78.4%) had left-sided colon cancer. Thirty-three (64.7%) had liver metastasis; 20 (39.2%) had lung metastasis, and 32 (62.7%) patients had more than one site of metastasis.

The characteristics of patients with peritoneal metastasis vs no peritoneal metastasis are illustrated in Table 1. Of note, 31 (86%) patients with no peritoneal metastasis had left-sided primary tumors, while only 9 (60%) patients in the peritoneal metastasis group had left-sided primary tumors (P = 0.03). Additionally, 25 (75%) of the patients with no peritoneal disease had liver metastasis, while only 6 (40%) of the patients with peritoneal metastasis had liver metastasis (P = 0.01).

The median PFS and OS for the whole group were 10.8 mo [95% confidence interval (CI): 5.1-16.5] and 31.3 mo (95%CI: 16.9-45.6), respectively. The median PFS for the peritoneal metastasis group vs the group without peritoneal metastasis was 9.4 (95%CI: 8.6-10.1) mo vs 13.7 (95%CI: 4.4-22.9) mo (P = 0.401). The median OS for the group with peritoneal metastasis vs the group without peritoneal metastasis was not reached vs 31.3 (95%CI: 19.5-43.1) mo (P = 0.368) (Figures 1 and 2).

Univariate analysis of known prognostic factors is shown in Table 2. Age (less than 65 years), presence of liver/lung metastasis, and metastasectomy were statistically significant for PFS, with P values of 0.034, 0.046, 0.011, and 0.001, respectively. Only liver metastasis and metastasectomy were
Table 1 Characteristics of 51 patients with metastatic colorectal cancer, with and without peritoneal metastasis treated with triplet chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Whole group</th>
<th>Peritoneal metastasis N (%)</th>
<th>No peritoneal metastasis N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>52 (23-74)</td>
<td>52 (23-74)</td>
<td>50 (32-73)</td>
<td>0.97</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>Male</td>
<td>27 (52.9%)</td>
<td>8 (53.3%)</td>
<td>19 (52.8%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24 (47.1%)</td>
<td>7 (46.7%)</td>
<td>17 (47.1%)</td>
<td></td>
</tr>
<tr>
<td>Site of primary</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Left</td>
<td>40 (78.4%)</td>
<td>9 (60%)</td>
<td>31 (86.1%)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>11 (21.6%)</td>
<td>6 (40%)</td>
<td>5 (13.9%)</td>
<td></td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>0-1</td>
<td>40 (78.4%)</td>
<td>12 (80%)</td>
<td>28 (77.8%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11 (21.6%)</td>
<td>3 (20%)</td>
<td>8 (22.2%)</td>
<td></td>
</tr>
<tr>
<td>Liver metastasis</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Yes</td>
<td>33 (64.7%)</td>
<td>6 (40%)</td>
<td>27 (75%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18 (35.3%)</td>
<td>9 (60%)</td>
<td>9 (25%)</td>
<td></td>
</tr>
<tr>
<td>Lung metastasis</td>
<td></td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>Yes</td>
<td>20 (39.2%)</td>
<td>3 (20%)</td>
<td>17 (47.2%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>31 (60.8%)</td>
<td>12 (80%)</td>
<td>19 (52.8%)</td>
<td></td>
</tr>
<tr>
<td>KRAS status</td>
<td></td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Wild</td>
<td>20 (39.2%)</td>
<td>3 (20%)</td>
<td>17 (47.2%)</td>
<td></td>
</tr>
<tr>
<td>Mutant</td>
<td>21 (41.2%)</td>
<td>9 (60%)</td>
<td>12 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (19.6%)</td>
<td>3 (20%)</td>
<td>7 (19.4%)</td>
<td></td>
</tr>
<tr>
<td>Prior surgery to primary</td>
<td></td>
<td></td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>Yes</td>
<td>29 (55.9%)</td>
<td>10 (66.7%)</td>
<td>19 (52.8%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22 (44.1%)</td>
<td>5 (33.3%)</td>
<td>17 (47.2%)</td>
<td></td>
</tr>
<tr>
<td>No of metastatic sites</td>
<td></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>1</td>
<td>19 (37.2%)</td>
<td>4 (28.6%)</td>
<td>13 (41.9%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 1</td>
<td>32 (62.7%)</td>
<td>10 (71.4%)</td>
<td>18 (58.1%)</td>
<td></td>
</tr>
<tr>
<td>Metastasectomy</td>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Yes</td>
<td>13 (25.5%)</td>
<td>5 (33.3%)</td>
<td>8 (22.2%)</td>
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</tr>
<tr>
<td>No</td>
<td>38 (74.5%)</td>
<td>10 (66.7%)</td>
<td>28 (77.8%)</td>
<td></td>
</tr>
</tbody>
</table>

statistically significant for OS, with P values of 0.001 and 0.002, respectively.

Multivariate analysis showed that age (less than 65 years) and metastasectomy were statistically significant for PFS, with P values of 0.002 and 0.001, respectively. On the other hand, the absence of liver metastasis and metastasectomy were statistically significant for OS, with P values of 0.003 and 0.005, respectively (Table 3).

**DISCUSSION**

To our knowledge, this is the first study to evaluate the prognostic significance of peritoneal metastasis in patients with metastatic CRC treated primarily with triplet first-line chemotherapy. Historically, the presence of peritoneal carcinomatosis in patients with metastatic CRC has resulted in poor prognosis[13, 14]. The median OS in patients treated with modern chemotherapy regimens, including targeted therapy, has ranged from 8 to 12 mo[17]. Bakkers et al[17] reported a population-based study with 7233 patients with metastatic CRC, of which 743 had peritoneal carcinomatosis. The median OS for the 409
Table 2 Univariate analysis of progression-free survival and overall survival in 51 patients with metastatic colorectal cancer treated with triplet therapy

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mo (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>12.4 (5-19.9)</td>
<td>0.034</td>
</tr>
<tr>
<td>≥ 65</td>
<td>5.7 (3-6.3)</td>
<td>0.429</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10.8 (4.3-17.3)</td>
<td>0.068</td>
</tr>
<tr>
<td>Female</td>
<td>9.4 (0-19.3)</td>
<td>0.046</td>
</tr>
<tr>
<td>Site of primary</td>
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<td></td>
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<tr>
<td>Left</td>
<td>10.8 (4.1-17.5)</td>
<td>0.011</td>
</tr>
<tr>
<td>Right</td>
<td>9.1 (0.5-17.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Performance status</td>
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<td></td>
</tr>
<tr>
<td>0-1</td>
<td>15.9 (7-24.8)</td>
<td>0.401</td>
</tr>
<tr>
<td>2</td>
<td>6.9 (2.8-11)</td>
<td>0.957</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8.9 (7-10.9)</td>
<td>0.928</td>
</tr>
<tr>
<td>No</td>
<td>15.9 (5.7-26.1)</td>
<td>0.565</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>8.9 (6.4-11.4)</td>
<td>0.011</td>
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<tr>
<td>No</td>
<td>13.7 (5.8-21.6)</td>
<td>0.928</td>
</tr>
<tr>
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<tr>
<td>Yes</td>
<td>9.4 (8.6-10.1)</td>
<td>0.056</td>
</tr>
<tr>
<td>No</td>
<td>13.7 (4.4-22.9)</td>
<td>0.957</td>
</tr>
<tr>
<td>KRAS</td>
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<tr>
<td>Wild</td>
<td>13.7 (0-30.7)</td>
<td>0.957</td>
</tr>
<tr>
<td>Mutant</td>
<td>10.8 (5.2-16.4)</td>
<td>0.565</td>
</tr>
<tr>
<td>Unknown</td>
<td>9.4 (8.2-10.5)</td>
<td>0.928</td>
</tr>
<tr>
<td>Prior surgery to primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10.8 (3-18.6)</td>
<td>0.056</td>
</tr>
<tr>
<td>No</td>
<td>10.2 (3.4-17)</td>
<td>0.056</td>
</tr>
<tr>
<td>No of metastatic sites</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>12.4 (6.7-18.2)</td>
<td>0.056</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>8.9 (6.6-11.3)</td>
<td>0.928</td>
</tr>
<tr>
<td>Metastasectomy</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>18.6 (0-NR)</td>
<td>0.056</td>
</tr>
<tr>
<td>No</td>
<td>8 (5.4-10.6)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

PFS: Progression-free survival; OS: Overall survival; CI: Confidence interval; NR: Not reached.

...patients with synchronous peritoneal carcinomatosis was 8.1 mo compared to 12 mo for those with metachronous peritoneal metastasis. This difference was not statistically significant in multivariate analysis, with a hazard ratio of 1.03 (95% CI: 0.83-1.27). Since this was a population-based study, treatment consisted of palliative chemotherapy, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) and best supportive care. The percentage of patients who had CRS-
Figure 1  Kaplan–Meier curve for progression-free survival for patients with metastatic colorectal cancer with (blue curve) and without (green curve) peritoneal carcinomatosis ($P = 0.401$).

Figure 2  Kaplan–Meier curve for overall survival for patients with metastatic colorectal cancer with (blue curve) and without (green curve) peritoneal carcinomatosis ($P = 0.368$).

HIPEC in the above study was 16% in the metachronous group and 8% in the synchronous group. Palliative chemotherapy was given to 55% and 69% of patients in the metachronous and synchronous groups, respectively.

A more similar cohort to our study was the pooled analysis reported by Franko et al[13], wherein they looked at the survival and prognostic significance of patients with peritoneal metastasis vs other organ metastasis from two large north central cancer treatment group phase III studies (N9741 and N9841). Since those patients were entered in a prospective clinical trial, all had good performance status from 0 to 1 and expected survival of more than 3 mo with no negative prognostic factors such as ascites or malignant bowel obstruction. All patients were treated with doublet regimens (FOLFOX vs IFL vs IROX). There was no differential impact of the type of systemic chemotherapy used on the basis of the presence or absence of peritoneal carcinomatosis. Expectedly, peritoneal carcinomatosis in this pooled
Table 3 Multivariate analysis of progression-free survival and overall survival in 51 patients with metastatic colorectal cancer treated with triplet therapy

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65</td>
<td>1*</td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>0.22 (0.08-0.57)</td>
<td>0.002</td>
</tr>
<tr>
<td>Liver metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1*</td>
<td>0.076</td>
</tr>
<tr>
<td>No</td>
<td>0.5 (0.23-1.07)</td>
<td></td>
</tr>
<tr>
<td>Metastasectomy</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>1*</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.23 (0.09-0.57)</td>
<td></td>
</tr>
</tbody>
</table>

*Represent the reference group.

PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval.

analysis had a negative prognostic impact on survival, with a hazard ratio (HR) of 1.316 (95% CI: 1.152-1.504, \( P < 0.0001 \)). Other investigators at an earlier date found no benefit of infusional 5-fluorouracil (5-FU) as opposed to bolus 5-FU in patients treated for CRC with peritoneal metastasis[18].

Our cohort was treated uniformly with the combination of capecitabine, oxaliplatin, irinotecan, and bevacizumab. The PFS was 9.4 mo for patients with no peritoneal metastasis vs 13.7 mo in patients with peritoneal carcinomatosis. A difference was not statistically significant in univariate and multivariate analyses. Similarly, OS in our cohort was not reached for patients with peritoneal carcinomatosis compared to 31.3 mo in the no peritoneal metastasis group (\( P = 0.0368 \), univariate analysis). The median follow-up for the whole group was 89 mo.

Generally, survival in patients with peritoneal carcinomatosis from CRC metastasis has improved with the introduction of CRS-HIPEC. The benefit of CRS-HIPEC has been proven in randomized controlled clinical trials using older chemotherapy regimens (fluoropyrimidine alone)[19]. There are, however, multiple prospective phase II and retrospective studies reporting a 3-year survival of 30% to 60% in patients with isolated peritoneal carcinomatosis treated with CRS-HIPEC[20-24]. In our cohort, the percentage of metastasectomy that could have influenced the efficacy of our therapy was 33.3% in the peritoneal carcinomatosis group vs 22.2% in the no peritoneal carcinomatosis group, a difference that did not reach statistical significance. We accordingly believe that surgery played a partial role in the good results seen in the group of peritoneal metastases.

The presence of other site involvement in patients with CRC peritoneal metastasis has been examined by Franko et al[14]. A total of 10553 patients treated with systemic therapy in prospective randomized trials were reported by the ARCAD database. Of those, 9178 (87%) had nonperitoneal metastasis, 194 (2%) had isolated peritoneal metastasis, and 1181 (11%) had peritoneal and other organ metastases. Survival was better in the nonperitoneal metastasis group (adjusted HR 0.75, 95% CI: 0.63-0.91, \( P = 0.003 \)). Patients with peritoneal metastasis and one other site had similar survival to those with isolated peritoneal metastasis (adjusted HR 1.10, 95% CI: 0.89-1.37, \( P = 0.37 \)). Two of 14 trials reported in the above pooled analysis used triplet regimens as an investigational arm; however, none of them reported a subgroup analysis based on peritoneal metastasis[11,25]. In our study, the patients with peritoneal metastasis had a higher percentage of more than 1 metastatic site involvement (71.4%) than the nonperitoneal metastasis group (58.1%), a difference that was not statistically significant (\( P = 0.39 \)).

Our study has several limitations, firstly the retrospective nature of the study. Additionally, the small number of patients included makes interpretations of the data difficult. On the other hand, our patient cohort was treated in a prospective phase I/II study with a uniform treatment plan.

CONCLUSION

In conclusion, our data showing equal survival in metastatic CRC patients with peritoneal metastasis vs no peritoneal metastasis and the absence of a negative prognostic impact of peritoneal carcinomatosis when patients are treated with a triplet chemotherapy regimen as a first-line therapy is hypothesis-generating. These data need to be confirmed in large prospective studies.
ARTICLE HIGHLIGHTS

Research background
Peritoneal metastasis has been shown to be a poor prognostic factor in metastatic colorectal cancer (CRC). In all published literature citing the above, the patients were treated with either single or doublet first-line chemotherapy. There are no data on the prognostic significance of peritoneal carcinomatosis in patients treated with first-line triplet chemotherapy.

Research motivation
We have shown before that triplet first-line chemotherapy in metastatic CRC overcomes the poor prognosis of right-sidedness. We wanted to examine whether the same applies to peritoneal metastasis in CRC.

Research objectives
We wanted to examine the progression-free survival (PFS) and overall survival (OS) of patients with peritoneal vs no peritoneal metastasis treated with first-line triplet chemotherapy and to confirm the lack of a statistically significant difference in the two groups on univariate and multivariate analysis.

Research methods
This was a post hoc analysis of a phase I/II trial evaluating the efficacy and toxicity of triplet chemotherapy in the first-line treatment of metastatic CRC. Patient characteristics, PFS, and OS were examined for the groups with and without peritoneal metastasis. Univariate and multivariate analyses were performed to include other known prognostic factors in metastatic CRC.

Research results
No statistically significant difference was found in the PFS and OS in the group with or without peritoneal metastasis. Peritoneal metastasis was confirmed not to be an independent prognostic factor in patients with metastatic CRC treated with first-line triplet chemotherapy based on multivariate analysis.

Research conclusions
The study suggests that first-line triplet chemotherapy overcomes the poor prognostic significance of patients with metastatic CRC. This needs to be confirmed in large prospective trials.

Research perspectives
Treatment of patients with metastatic CRC should be personalized based on prognostic clinical and molecular factors. The benefit of triplet chemotherapy might outweigh the excess toxicity in certain subgroups, such as those with peritoneal carcinomatosis.

FOOTNOTES

Author contributions: Bazarbashi S contributed to designing the study; Bazarbashi S, Alghabban A and Aseafan M contributed to data analysis; Bazarbashi S, Alghabban A, Aseafan M, Aljubran AH and Alzahrani A contributed to write the manuscript; Elhassan TA has contributed to the statistical analysis.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Board at King Faisal Specialist Hospital and Research Center under the number RAC2081068.

Clinical trial registration statement: This study is registered at https://clinicaltrials.gov/ct2/show/NCT01311050?term=bazarbashi&draw=2&rank=4. The registration identification number is: NCT01311050.

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

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

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and since the study is not randomized trial, the CONSORT 2010 statement do not apply.

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REFERENCES


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

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Bazarbashi S et al. Colorectal peritoneal metastasis prognosis with triplet chemotherapy

10.1200/JCO.2011.37.1039


Observational Study

Effect of intraoperative cell rescue on bleeding related indexes after cesarean section

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Abstract

BACKGROUND
Obstetric hemorrhage is the leading cause of maternal mortality globally, especially in China. The key to a successful rescue is immediate and rapid blood transfusion. Autotransfusion has become an integral part of clinical blood transfusion, with intraoperative cell salvage (Iocs) being the most widely used.

AIM
To investigate the application of Iocs in cesarean section.

METHODS
A total of 87 patients who underwent cesarean section and blood transfusion in our hospital from March 2015 to June 2020 were included in this prospective controlled study. They were divided into the observation (43 cases) and control (44 cases) groups using the random number table method. The patients in both groups underwent lower-segment cesarean section. The patients in the control group were treated with traditional allogeneic blood transfusion, whereas those in the observation group were treated with Iocs. Hemorheology [Red blood cell count, platelet volume, and fibrinogen (FIB)] and coagulation function (partial prothrombin time, prothrombin time (PT), platelet count, and activated coagulation time) were measured before and 24 h after transfusion. In the two groups, adverse reactions, such as choking and dyspnea, within 2 h after cesarean section were observed.

RESULTS
Before and after transfusion, no significant differences in hemorheology and coagulation function indices between the two groups were observed (P > 0.05). About 24 h after transfusion, the erythrocyte count, platelet ratio, and FIB value
significantly decreased in the two groups \( P < 0.05 \); the PLT value significantly decreased in the two groups; the activated partial thromboplastin time, PT, and activated clotting time significantly increased in the two groups \( P < 0.05 \); and no statistical differences were observed in hemorheology and coagulation function indices between the two groups \( P > 0.05 \). Furthermore, there was no significant difference in the incidence of adverse reactions between the two groups \( P > 0.05 \).

**CONCLUSION**

In patients undergoing cesarean section, intraoperative cell salvage has a minimum effect on hemorheology and coagulation function and does not increase the risk of amniotic fluid embolism.

**Key Words:** Intraoperative cell salvage; Cesarean section; Amniotic fluid embolism; Hemorheology; Coagulation function

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**Core Tip:** A total of 87 patients who underwent cesarean section and blood transfusion in our hospital from March 2015 to June 2020 were included in this prospective controlled study. The patients were divided into the observation (43 cases) and control (44 cases) groups using the random number table method. Intraoperative cell salvage (IOCS) was found to have a minimum effect on hemorheology and coagulation function in patients with cesarean section and does not increase the risk of amniotic fluid embolism. These findings indicate that the principle of IOCS should be strictly followed during operation, which is worth promoting.

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**URL:** https://www.wjgnet.com/2307-8960/full/v10/i8/2439.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i8.2439

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**INTRODUCTION**

Obstetric hemorrhage is the leading cause of maternal mortality globally, accounting for 27.1% of all maternal deaths\[^1,2\]. It has also been recently reported to be the leading cause of death among pregnant women in China. With the liberalization of China’s birth policy, there are more and more elderly pregnant women, and their risk of postpartum hemorrhage increases accordingly\[^3\]. The key to a successful rescue is immediate and rapid blood transfusion; however, traditional allogeneic blood transfusion involves safety problems, including blood shortage, transfusion-related infection, and immune suppression\[^4,5\], which poses great safety risks to puerpera and babies. In recent years, with the development of the blood transfusion concept and the maturity of blood transfusion technology, autotransfusion has become an integral part of clinical blood transfusion. In addition, it has attracted a considerable amount of attention owing to its ability to effectively relieve the increasingly tight blood supply and prevent the occurrence of homoimmune reaction and disease transmission\[^6\]. According to different sources, autologous blood transfusion is divided into storage type of autologous blood transfusion which was to store your own blood in advance for use when you need it in the future, diluted autotransfusion which was collected and preserved before operation and diluted with plasma substitutes, and intraoperative cell salvage (IOCS), with the latter being the most widely used. In IOCS, the blood recovery device is used to recover, anticoagulate and filter the intraoperative blood loss and postoperative bleeding. Then, the blood is reinfused to the patient. IOCS is also widely used in orthopedics, cardiothoracic surgery, etc.\[^7-9\]. However, due to the limitations of traditional technology, the application of IOCS in obstetrics was previously believed to increase the risk of amniotic fluid embolism. In recent years, with the advancement of technology, blood recovery devices and leukocyte filters can effectively eliminate the risk factors of amniotic fluid embolism\[^10-12\]. Therefore, the use of IOCS in cesarean section has been given a considerable amount of attention. In this paper, the application of IOCS in cesarean section, monitoring of amniotic fluid embolization, and other related indications are discussed, demonstrating its safety in cesarean section.
MATERIALS AND METHODS

General information
A total of 87 patients who underwent cesarean section and blood transfusion in our hospital from March 2015 to June 2020 were included in this prospective controlled study. The patients were divided into the observation and control groups using the random number table method. The observation group consists of 43 patients (age, 23 to 50 years; average age, 35.21 ± 7.85 years; body mass index, 19–26 kg/m²; average body mass index, 22.57 ± 2.25 kg/m²; and gestational age, 37.2 ± 1.3 wk). In this group, there were 29 and 14 primiparas and multiparas, respectively. Conversely, the control group consisted of 44 patients (age, 22 to 50 years; average age, 34.64 ± 8.02 years; body mass index, 18–27 kg/m²; average body mass index, 22.39 ± 2.82 kg/m²; and gestational age, 37.2 ± 1.2 wk). In this group, there were 26 and 18 primiparas and paras, respectively. No significant difference was observed in the general clinical data between the two groups (P > 0.05), thus indicating clinical comparability. This study was approved by the ethics committee of our hospital, and signed informed consent was obtained from all the parturients and/or their families.

Inclusion and exclusion criteria
The inclusion criteria were meeting the conditions of cesarean section, American Society of Anesthesiologists Grades II–III, stable physical signs and clear consciousness, and normal preoperative blood system, heart, liver, and kidney.

The exclusion criteria were the presence of pregnancy complications such as cardiovascular and immune system diseases, made worse by malignant tumor, and expected anticoagulant treatment before operation. Cognitive and mental disorders, the contraindications to blood transfusion, and participation in other clinical studies during pregnancy.

Methods of operation and postoperative blood transfusion
The patients in both groups underwent lower-segment cesarean section. The patients in the control group were treated with traditional allogeneic blood transfusion, whereas those in the observation group were treated with IOCS.

Anesthesia
Routine oxygen mask inhalation and continuous monitoring of electrocardiogram, respiration, and other vital signs were performed. L3-4 lumbar anesthesia combined with epidural anesthesia were performed, and 1% ropivacaine was diluted with cerebrospinal fluid and injected into the subarachnoid space. The lumbar anesthesia and puncture needles were removed, and an epidural catheter was fixed to control the anesthesia block level to T6. If the parturient women have intraspinal anesthesia taboo syndrome, they shall be induced in a rapid sequence and then subjected to endotracheal intubation general anesthesia If the heart rate is ≤ 55 beats/min and the systolic blood pressure is ≤ 80 mmHg, ephedrine and atropine should be administered, respectively.

Intraoperative cell salvage
The amount of blood loss was measured using the volume method combined with the weighing method. The Cell saver type five blood recovery system (American Blood Technology Company) was used. Before surgery, pipes, blood storage tanks, blood storage bags, etc. were installed. The recovery system was pre-washed with 200 mL of normal saline containing 50000 U of heparin sodium, and the blood recovery system turned on 10 min before surgery. After the amniotic fluid was exhausted and the fetus was delivered, the blood in the surgical field was sucked into the blood storage tank using a negative-pressure suction device. Mix the blood with 50 U/mL heparin sodium normal saline in a volume ratio of 1:5, filter, wash, separate and clean it, and then enter the circulation tank. Based on the condition of the patient, transfusion was performed through a white blood cell filter, and the vital signs and adverse reactions of the patient were closely monitored during the process.

Blood transfusion indications
The indications for allogeneic transfusion were as follows: the red blood cells (RBCs) were transfused when the hemoglobin level was < 80 g/L and/or the RBC ratio was < 0.21; fresh frozen plasma was transfused when the prothrombin time (PT) and activated partial thromboplastin time (APTT) were > 1.5 times the reference value and the international standardized ratio was > 1.5; and the platelet was transfused when the platelet count was less than 50 × 10^9/L.

The indications for autologous blood transfusion were as follows: the amount of blood loss was less than 20% of the body blood volume, and autologous blood was transfused after abdominal closure; the amount of blood loss was ≥ 20% of the total body blood volume; autologous blood was immediately infused; and allogeneic blood was infused when the patient’s vital signs could not be maintained after intraoperative autologous blood transfusion.
Observation indicators and evaluation criteria

**Hemorheology:** 2 mL of femoral vein blood was collected from the patients before and 24 h after transfusion, and ethylenediaminetetraacetic acid anticoagulation was employed to detect the RBC count, platelet volume, and fibrinogen (FIB) value (FIB normal value: 2.4–3.7 g/L).

**Blood coagulation function:** Before and 24 h after blood transfusion, 2 mL of fasting venous blood was collected from the patients’ forearm in the morning and then centrifuged at 3000 r/min for 10 min to separate the plasma. The APTT, PT, PLT, and activated clotting time (ACT) values were determined using an automatic hemagglutination instrument.

**Adverse reactions:** Adverse reactions such as choking, dyspnea, vomiting, postpartum hemorrhage, and shock within 2 h after cesarean section were observed in the two groups.

**Statistical analysis**
SPSS version 22.0 was used for the data analysis. The data were expressed as mean ± SE of the mean, and t-test was employed. Count data were expressed as case (%), and a χ² test was employed. P < 0.05 was considered statistically significant.

**RESULTS**

**Comparison of hemorheology between the two groups**
No significant differences were observed in the RBC count, platelet volume, and FIB value between the two groups before and after transfusion (P > 0.05). About 24 h after transfusion, the erythrocyte count, platelet volume, and FIB value significantly decreased (P < 0.05) in both groups, and no statistical difference was observed between the two groups (P > 0.05) (Table 1).

**Comparison of the coagulation function between the two groups**
No significant differences in the APTT, PT, PLT, and ACT values were observed between the two groups after transfusion (P > 0.05). About 24 h after transfusion, the PLT value significantly decrease; the APTT, PT, and ACT significantly increased (P < 0.05), and no statistical significance was observed between the two groups (P > 0.05) (Table 2).

**Comparison of adverse reactions between the two groups**
No significant difference was observed in the incidence of adverse reactions between the two groups (P > 0.05) (Table 3).

**DISCUSSION**
The entry of the amniotic fluid substance to the maternal blood circulation during delivery can cause amniotic fluid embolism, which manifests as disseminated intravascular coagulation, shock, acute pulmonary embolism, etc. They pose a serious threat to maternal safety. In addition, autotransfusion is thought to increase the risk of amniotic fluid embolism in women undergoing cesarean section. In this study, the safety of IOCS in cesarean section was investigated. Our results indicated no significant changes in hemorheology and the coagulation function of parturients when IOCS was employed compared with that when traditional allogeneic transfusion was employed (P > 0.05). Along with the pathogenesis of amniotic fluid embolism, (1) Fetal substances contained in the amniotic fluid block the microorgans of various maternal organs, and (2) Maternal allergic reaction to fetal components in the amniotic fluid causes pulmonary vasoconstriction, platelet and white blood cell excitation, and activation of complement components, which are highly likely to cause amniotic fluid embolism[15,16].

The results of this study indicate that IOCS does not increase the risk of maternal amniotic fluid embolism. The reason may be that the circulating blood recovery device for autologous blood transfusion can deal with body cavity bleeding, intraoperative blood loss and postoperative drained blood through circulation, anticoagulation, filtration and washing. At the same time, the technology can wash platelets, tissues, blood, anticoagulants and plasma proteins as much as possible, reduce platelet count and improve coagulation function[17].

Furthermore, alpha-fetoprotein, phosphatidylglycerol, fetal squamous epithelial cells, and some inflammatory factors can be entirely removed from the blood to reduce the risk of amniotic fluid embolism[18].

In clinical practice, IOCS has the following advantages[19-21]: (1) It can relieve the increasingly tight blood supply and does not require blood type identification and cross-matching, which is convenient and safe; and (2) It can prevent the spread of infectious diseases and adverse reactions caused by allogeneic blood transfusion. If IOCS has high operational requirements, the collection and transfusion...
Table 1 Comparison of the hemorheology indices between the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Red blood cell count (×10^12/L) Before transfusion</th>
<th>Red blood cell count (×10^12/L) After transfusion</th>
<th>t</th>
<th>P value</th>
<th>Platelet volume (%) Before transfusion</th>
<th>Platelet volume (%) After transfusion</th>
<th>t</th>
<th>P value</th>
<th>FIB (g/L) Before transfusion</th>
<th>FIB (g/L) After transfusion</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>44</td>
<td>4.35 ± 0.62</td>
<td>3.56 ± 0.55</td>
<td>6.323</td>
<td>&lt; 0.001</td>
<td>0.51 ± 0.17</td>
<td>0.40 ± 0.10</td>
<td>3.7</td>
<td>&lt; 0.001</td>
<td>3.32 ± 0.50</td>
<td>2.31 ± 0.41</td>
<td>10.361</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Observation</td>
<td>43</td>
<td>4.19 ± 0.53</td>
<td>3.45 ± 0.55</td>
<td>6.353</td>
<td>&lt; 0.001</td>
<td>0.55 ± 0.14</td>
<td>0.38 ± 0.08</td>
<td>6.913</td>
<td>&lt; 0.001</td>
<td>3.28 ± 0.53</td>
<td>2.27 ± 0.36</td>
<td>10.337</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>t</td>
<td>1.292</td>
<td>0.933</td>
<td>1.197</td>
<td>1.029</td>
<td>0.362</td>
<td>0.483</td>
<td>0.718</td>
<td>0.63</td>
<td></td>
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</tr>
<tr>
<td>P value</td>
<td>0.1997</td>
<td>0.354</td>
<td>0.235</td>
<td>0.307</td>
<td>0.718</td>
<td>0.63</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

FIB: Fibrinogen.

Table 2 Comparison of the coagulation function indices between the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>APTT (s) Before transfusion</th>
<th>APTT (s) After transfusion</th>
<th>t</th>
<th>P value</th>
<th>PT (s) Before transfusion</th>
<th>PT (s) After transfusion</th>
<th>t</th>
<th>P value</th>
<th>PLT (×10^12/L) Before transfusion</th>
<th>PLT (×10^12/L) After transfusion</th>
<th>t</th>
<th>P value</th>
<th>ACT (s) Before transfusion</th>
<th>ACT (s) After transfusion</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>44</td>
<td>34.75 ± 2.95</td>
<td>42.65 ± 6.78</td>
<td>7.087</td>
<td>&lt; 0.001</td>
<td>14.15 ± 3.41</td>
<td>18.02 ± 5.35</td>
<td>4.046</td>
<td>&lt; 0.001</td>
<td>212.55 ± 35.15</td>
<td>166.57 ± 26.17</td>
<td>6.93</td>
<td>&lt; 0.001</td>
<td>91.21 ± 15.75</td>
<td>124.14 ± 23.12</td>
<td>7.808</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Observation</td>
<td>43</td>
<td>35.25 ± 3.06</td>
<td>40.67 ± 5.21</td>
<td>5.882</td>
<td>&lt; 0.001</td>
<td>14.45 ± 3.26</td>
<td>18.35 ± 4.85</td>
<td>4.376</td>
<td>&lt; 0.001</td>
<td>219.45 ± 32.16</td>
<td>168.54 ± 29.35</td>
<td>7.668</td>
<td>&lt; 0.001</td>
<td>90.75 ± 16.54</td>
<td>121.76 ± 25.37</td>
<td>6.714</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>t</td>
<td>0.776</td>
<td>1.536</td>
<td>0.419</td>
<td>0.301</td>
<td>0.982</td>
<td>0.331</td>
<td>0.133</td>
<td>0.458</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.44</td>
<td>0.128</td>
<td>0.676</td>
<td>0.764</td>
<td>0.329</td>
<td>0.742</td>
<td>0.895</td>
<td>0.649</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

APTT: Activated partial thromboplastin time; PT: Prothrombin time; ACT: Activated clotting time.

of blood should follow the principles of aseptic operation to reduce the risk of cross-infection. To prevent excessive negative pressure resulting in the formation of excessive blood foam, which causes hemolysis and destruction of RBC, the suction pressure should be controlled below 20 kPa during blood recovery.

This study has certain limitations, including the relatively small sample size, which may be insufficient to evaluate the overall differences in the use of the two transfusion methods. Another limitation is the cross-sectional design of this study, which could only infer an association, not a cause. Thus, more studies in the future are needed to confirm the effect of intraoperative cell rescue on cesarean hemorrhage.
### Table 3 Comparison of adverse reactions between the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Choking</th>
<th>Dyspnea</th>
<th>Restless</th>
<th>Vomiting</th>
<th>Shock</th>
<th>cyanosis</th>
<th>Postpartum hemorrhage</th>
<th>Total</th>
</tr>
</thead>
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<td>Control</td>
<td>44</td>
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<td>1</td>
<td>1</td>
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<td>0</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Observation</td>
<td>43</td>
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<td>0</td>
<td>2</td>
<td>1</td>
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</table>

### CONCLUSION

In summary, IOCS has a negligible effect on hemorheology and the coagulation function in patients with cesarean section and does not increase the risk of amniotic fluid embolism. However, the principle of IOCS should be strictly followed during operation, which is worth promoting.

### ARTICLE HIGHLIGHTS

#### Research background

Obstetric hemorrhage is the leading cause of maternal mortality globally, especially in China. The key to a successful rescue is immediate and rapid blood transfusion. Autotransfusion has become an integral part of clinical blood transfusion, with intraoperative cell salvage (IOCS) being the most widely used.

#### Research motivation

In this paper, the application of IOCS in cesarean section, monitoring of amniotic fluid embolization, and other related indications are discussed, demonstrating its safety in cesarean section.

#### Research objectives

This study aimed to investigate the application of IOCS in cesarean section.

#### Research methods

A total of 87 patients who underwent cesarean section and blood transfusion in our hospital from March 2015 to June 2020 were enrolled in this prospective controlled study.

#### Research results

Before and after transfusion, no significant differences were observed in hemorheology and the coagulation function indices between the two groups. About 24 h after transfusion, the erythrocyte count, platelet ratio, and fibrinogen value significantly decreased in the two groups; the PLT value significantly decreased in the two groups; the activated partial thromboplastin time, prothrombin time, and activated clotting time significantly increased in the two groups; and no statistical differences were observed in the hemorheology and coagulation function indices between the two groups. Furthermore, there was no significant difference in the incidence of adverse reactions between the two groups.

#### Research conclusions

IOCS has a negligible effect on hemorheology and coagulation function in patients undergoing cesarean section and does not increase the risk of amniotic fluid embolism.

#### Research perspectives

The principle of IOCS should be strictly followed during operation, which is worth promoting.

### FOOTNOTES

**Author contributions:** Yu YF wrote the manuscript; Cao YD participated in data analysis.

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**REFERENCES**


Prospective Study

Effectiveness of the combination of workshops and flipped classroom model to improve tube fixation training for nursing students

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Abstract

BACKGROUND
Tube indwelling is a key procedure in modern medicine. Careful tube setup is necessary to prevent unplanned extubation. The training for tube fixation is time- and resource-consuming, and optimal modes of training are currently being sought. Previous studies have compared workshops and flipped classroom models separately using conventional teaching strategies, but no study has examined a combination of both teaching models in nursing training.

AIM
To compare the effectiveness of workshops vs workshops combined with the flipped classroom model for improving tube fixation training for nursing students.

METHODS
This was a prospective cohort study. In this study, 149 nurses who joined our hospital in 2019 underwent training using workshops combined with the flipped classroom model (experimental group), while 159 nurses who joined the hospital in 2018 received only workshop-based training (control group). The combination of workshops with the flipped classroom training model was divided into two
modules: pre-class and in-class training. The participation of nurses in the training activities, on-site assessment of training, nurses’ evaluation of their training, and related indicators of tube quality management were evaluated.

RESULTS
The average age of nurses in the control group was 22.94 ± 0.94 years and that of nurses in the experimental group was 25.42 ± 3.23 years ($P < 0.01$). The qualified rate of after-class assessments for the experimental and control groups was 100.00% (average score: 94.01 ± 2.78 points) and 91.82% (average score: 84.24 ± 2.94 points), respectively ($P < 0.01$). Most nurses in the experimental group completely agreed that the combined training was helpful to cultivate clinical thinking and independent learning ability and to master knowledge of tube fixation. In addition, the training content within the pre-class teaching video, pre-class tube atlas, pre-class main instructor guidance, in-class demonstration, and in-class practice was very informative. The experimental group had higher evaluation scores than the control group (4.88 ± 0.38 vs 4.67 ± 0.64; $P < 0.01$). Comparison of tube quality management before and after training in 2018 to 2019 revealed that the unplanned ureteral tube removal rate dropped from 0.25‰ to 0.06‰, the unplanned chest tube removal rate dropped from 1.07‰ to 0.78‰, and the unplanned gastric tube removal rate dropped from 0.36‰ to 0.17‰. The incidence rate of pressure ulcers caused by the tube decreased from 0.78‰ to 0.45‰.

CONCLUSION
The combination of workshop and flipped classroom training is effective in improving tube fixation training of nurses, cultivating nurses’ active learning abilities and clinical thinking, and improving the safety of the procedure.

Key Words: Flipped classroom teaching; Nursing; Tube fixation; Workshop

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Core Tip: This was a prospective study, in which 149 nurses participated in a new skill-training method for tube fixation training. The workshop combined with flipped classroom training was helpful in improving tube fixation training, cultivating nurses’ active learning abilities and clinical thinking, and improving the safety of the procedure.

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INTRODUCTION
Tube indwelling is a key and complex procedure in modern medicine. It is a vital means and basis for treatment, observation, and prognosis of patients[1,2]. Unplanned extubation (UEX) refers to extubation intentionally caused by patients or by accident and one that is not planned by a healthcare worker[1-3]. Careful tube setup is necessary to prevent UEX[1,2], which requires appropriate training. Proper training is time- and resource-consuming, because tube indwelling is an invasive procedure and cannot be performed without adequate practice by student nurses or healthcare workers. Hence, optimal training models are being currently sought.

At present, the most effective approaches for learning medical techniques are eagerness of the trainees to learn the material, active participation of the students in class, and collaboration with classmates and instructors[4-8]. The workshop model first appeared during research in the field of education and psychology. It is a participatory, experiential, and interactive training model that can enhance the interest and enthusiasm of the participants to learn techniques through skill practice, which is essential to improve their ability to perform operations[7-10]. Another training model that is gaining popularity in healthcare is the flipped classroom model, in which the trainees are provided with learning resources (including paper materials, video, or audio lecture content, etc.) before attending the class, dedicating the classroom time for engaging and interactive discussion and experiential practices [11-16]. In workshop or teacher-focused training, trainers should stimulate learners’ interest from
The training effect largely depends on nurses' interest and participation. As shown in several previous studies in the field of nursing, appropriate training methods can have a positive effect on nurses' participation in training. Several studies have explored the application of the flipped classroom model alone in nursing training. For example, Yi and Ding implemented flipped classroom teaching in nursing management, and 96.8% of the students believed that it could promote learning and recognized this teaching mode. Yang et al. applied the flipped classroom model in geriatric nursing courses, and the results showed that there was no significant difference in the scores of comprehension and memory questions between groups, but the case analysis ability and autonomous learning ability were significantly improved. Liu et al. found that implementing the flipped classroom mode in nursing teaching in higher vocational colleges can improve students' autonomous learning ability, and their theoretical and operational assessment scores are significantly improved.

Previous studies have compared using workshops and flipped classroom models separately with conventional teaching methods; however, to date, no study has examined the effectiveness of the combination of workshops and flipped classroom teaching techniques in medical education, although the concept theoretically exists in education. The only literature on such an approach was a report that was published in the context of a flipped classroom workshop, during a conference. It has been suggested that the flipped classroom technique engages trainees for a longer period and improves knowledge retention as well as performance of trainees, compared to more conventional teaching methods that are usually teacher-focused and theory-centered.

Our hospital set up a tube nurse specialist team in 2018. The workshop model was used to train 159 nurses who joined the hospital in 2018. After comprehensively evaluating the effectiveness of the workshop, the structure of the training model was reformed and the nurses who joined the hospital in 2019 received training based on a blended learning approach involving, a combination of the workshop with the flipped classroom model; this model was based on the hypothesis that the combination of the two methods could enhance the effectiveness of the training. Therefore, our study aimed to compare the effectiveness of workshop-only training with the combination of workshop and flipped classroom training on improving the teaching technique of tube fixation for nursing students. The findings of our study could provide new teaching methods to improve the effectiveness and safety of tube indwelling in clinical nursing.

**MATERIALS AND METHODS**

**Study design and subjects**
This was a prospective cohort study involving 149 newly graduated trainee nurses who joined the Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University in 2019 and received blended training, based on the combination of the workshop and flipped classroom (experimental group), and 159 nurses who joined the hospital in 2018 and received only workshop-based training (control group). All trainees were newly graduated nurses and were in their first year of working as registered nurses; they had no previous work experience or tube-related training. Biostatistics is not covered in this manuscript.

**Training methods**
Tube fixation training is part of the standardized training course for new nurses at Sun Yat-Sen Memorial Hospital. The student nurses are required to complete the training and assessment course of this technique before working independently, in order to safely perform the procedure as well as meet the needs of clinical nursing work.

The control group received only in-class training using the traditional workshop model, including on-site explanation, on-site demonstration, group exercises, and summary assessments. The experimental group received tube fixation training using workshops in combination with a flipped classroom approach. The workshop combined with the flipped classroom model was led by a group of tube specialists from the hospital and was designed as two modules: Pre-class teaching and in-class training (Figure 1).

**Pre-class training content and requirements**
The pre-class training content was divided into three components.

**Training design and requirements:** Before the lecture, the training instructors designed the overall training objectives and content. The resources were then provided to the newly recruited nurses to study in advance. Furthermore, the instructors briefed the nurses on the combined approach that would be used for the tube fixation training and explained the study content and importance of pre-class training to facilitate independent learning. The training instructors regularly sent the trainees learning notices every week through a network communication platform, to encourage them to complete the pre-class self-study, following which they collected feedback.

**Design and distribution of the pre-class training content:** The training instructors sent the nurses pre-
class training content that included a video operation guide of tube fixation and the fixation chart. The commonly used clinical tubes are divided into two categories: venous tubes and non-venous tubes. Non-venous tube fixation methods are further subdivided into gastric tube fixation, tracheal intubation fixation, I-shaped fixation, one-shaped fixation, and knot fixation methods. There are a total of seven tube fixation methods, and seven videos were recorded by the tube specialist group, each being 3-6 min in length. The nurses were required to watch the videos and were encouraged to engage in group discussions and ask questions in class. The tube fixation guide atlas was compiled by the tube specialist group, printed in large color pages, and distributed as a reference to the new nurses.

Observation and practice: The chief clinical instructor who approved the training and assessment designed by the tube specialist group provided guidance to the new nurses while they observed and practiced the tube fixation technique in a clinical setting.

In-class training content and requirements
The in-class training of the newly graduated nurses from the control and experimental groups was divided into two sessions, each session being 4 h long. After the training, each nurse was assessed for 0.5 h, totaling 4.5 h. The assessment mainly included three modules for the control group, including on-site demonstration, independent group practice and Q&A guidance, and on-the-spot examination. For the experimental group, a summary module was added.

On-site demonstration: The tube specialist group demonstrated the abovementioned seven fixation methods with physical projection equipment. The time to demonstrate each method was limited to 10-20 min, and the instructors simultaneously explained the methods. The key points, difficulties, and details of the methods were focused on. For the experimental group, theory and knowledge were supplemented based on actual cases.

Independent group exercise and Q&A guidance: The new nurses were organized in groups of 8-10. The instructors provided the trainees with tube models and exercise consumables. All nurses participated in the exercise and were encouraged to discuss the key difficulties and problems. The instructors answered any questions that the nurses had and guided each of them to practice independently.

Summary: The instructors answered any queries that the nurses had and summarized the advantages and disadvantages experienced during the practical application.

On-the-spot examination: All new nurses participating in the training had to complete the assessment by performing all seven fixation methods. The instructors worked in groups of two, and each group was responsible for the assessment and scoring of a fixation method.

Outcomes of the assessments
The participation of the new nurses in the training activities, on-site assessment of the training, nurses’ evaluation of the training, and related indicators of tube quality management were evaluated. The nurses in the control group only participated in the on-site assessment of tube fixation methods and training satisfaction surveys.
Participation of nurses in training activities: For pre-class training, based on the observations of the chief instructors in each ward, the understanding of the nurses when learning to use the tube fixation atlas, the methods of tube fixation, and the participation of the nurses in the actual practice of tube fixation were recorded. For in-class training, the participation of the nurses was recorded through their participation in group exercises and discussions.

On-site assessment of the training: The assessment was conducted immediately after completing the on-site training and independent exercises. Instructors worked in teams of two and were responsible for the assessment of a fixation method. The nurses were required to complete the assessment and scoring of all fixation methods. The methods were scored using the percentile system, with ≥ 80 points indicating that the methods qualified; the fixation methods were deemed qualified only if they met the standards.

Evaluation of the training by the nurses: After class, a self-designed questionnaire was used to understand the evaluation of the training models by the trainee nurses. The questionnaire included the evaluation of the training models and the training content. Likert’s 5-level scoring scale was used to evaluate the training models. The responses were scored on a scale of 1-5, ranging from “completely disagree” to “completely agree” and “very bad” to “very good.” The questionnaire was completed on-site after training.

Relevant indices of tube quality management

The standard clinical tube fixation rate, UEX rate, and incidence of tube-related pressure ulcers were recorded after the training. The standard clinical tube fixation rate was calculated as the number of fixed standard tubes/total number of tubes × 100%[1-3]. The UEX rate refers to the proportion of UEX of catheters occurring in hospitalized patients to the total number of days of indwelling of a catheter or to the total number of cases of catheter insertion during the same study period. The incidence of pressure ulcers is equal to the number of new cases of pressure injuries in hospitalized patients in the same period/total number of hospitalized patients in the same period × 100%.

Statistical methods

All analyses were performed using the SPSS 20.0 software (IBM, Armonk, NY, United States). Continuous variables are presented as means ± SD and were analyzed using the Student’s t-test. Categorical data were presented as n (%) and were compared using a chi-square test. Ordinal data were presented as n (%) and were compared using the Mann–Whitney U-test. P values of < 0.05 were considered to be statistically significant.

RESULTS

Characteristics of the nurses

The average age of nurses in the control group was 22.94 ± 0.94 years and that of those in the experimental group was 25.42 ± 3.23 years (P < 0.01). There were no significant differences in sex and educational background between the two groups (Table 1).

Training assessment

The qualified rate of the after-class assessment for the experimental group was 100.00%, with an average score of 94.01 ± 2.78 points, compared to a qualified rate of 91.82% for the control group, with an average score of 84.24 ± 2.94 points (both P < 0.01; Table 2).

Nurses’ evaluation of the workshops combined with a flipped classroom

All 149 nurses in the experimental group completed the evaluation questionnaire. Most nurses completely agreed that the training model based on the combination of workshops and a flipped classroom was beneficial for cultivating clinical thinking (59.73%, score of 4.50 ± 0.68), encouraging independent learning ability (62.41%, score of 4.56 ± 0.62), and mastering knowledge (66.44%, score of 4.52 ± 0.76) (Table 3). In the experimental group, 52.35% nurses found that the pre-class training video helpful (score of 4.28 ± 0.89), 72.48% nurses found the pre-class tube atlas helpful (score of 4.68 ± 0.54), 59.06% nurses found the pre-class chief-instructor guidance helpful (score of 4.51 ± 0.65), 88.59% nurses found the in-class demonstration helpful (score of 4.87 ± 0.37), and 84.56% nurses found the in-class practice helpful (score of 4.84 ± 0.39) (Table 4). The evaluation score of the tube fixation training was higher in the experimental group compared to that in the control group (4.88 ± 0.38 vs 4.67 ± 0.64, P < 0.01; Table 2).

Relevant indices of tube quality management

After analysis and training, the clinical tube fixation methods were retrospectively analyzed at the end
of 2019, and the standard fixation compliance rate was 96.03%. On comparing the rate of UEX events at our hospital in 2018 and 2019, we observed that the rate of unplanned ureteral tube removal decreased from 0.25‰ to 0.06‰, the rate of unplanned chest tube removal decreased from 1.07‰ to 0.78‰, and the rate of unplanned gastric tube removal decreased from 0.36‰ to 0.17‰ (Figure 2). Retrospective analysis of the pressure ulcers in the 2 years before and after training revealed that they mainly occurred with gastric tubes. The number of cases of pressure ulcers decreased from 33 to 22, and the incidence decreased from 0.78‰ to 0.45‰.

**DISCUSSION**

In this study, we compared the effectiveness of workshop-only training and the combined training model for improving the tube fixation training of nursing students. Our results strongly demonstrate that a blended learning approach using the combination of the workshop training and the flipped classroom training models was effective in improving the quality of teaching and learning the tube fixation methods. In addition, using this model encouraged the nurses’ enthusiasm and eagerness for interactive and independent learning and clinical thinking as well as improved the safety of the
The instructors should stimulate the nurses’ interest from multiple perspectives in order to influence as many trainees as possible[24]. The effectiveness of the training depends, to a large extent, on the training methods along with interest and participation of the nurses, which can have a positive effect on the quality of their participation in training. Some studies showed that the workshop training model could more effectively stimulate the nurses’ interest in learning compared to traditional teaching methods[28,29]. The flipped classroom model is focused on the students, and a large number of studies have shown that flipped classrooms can effectively improve the independent learning ability of students [19,25-27,30-31]. In this study, using the combination of the two learning models, the nurses were required to self-study before the class by watching videos and an atlas. Then, while in class, they were required to observe and practice the operations, find problems and solutions, and seek advice and clarifications regarding doubts from the clinical guidance teachers. The tube specialists then conducted practical ability training for all nurses through the workshop and finally completed the assessment. During the entire training process, as the main body of learning, not only did the nurses develop an interest in learning and cultivate the ability of independent learning, they also ensured the final effect of training. After completing the training course, some nurses commented the following: “this form of training is different from the inflexible classroom theoretical study. It enables us to learn on our own, has more opportunities for practical practice, engages in more exchanges and discussions, and improves our ability to think about clinical problems.” This response is reflected by the high satisfaction scores of the experimental group with regard to the training course.

In addition, as a result of the high quality of training, our study shows that combining the workshop and flipped classroom training models helps in improving the safety of using tubes in clinical practice. The nurses in our study provided good evaluation scores for the content of the training model, especially its ease of use, operation demonstration, and operation practice with the guidance of the tube fixation atlas; this proved to greatly improve the enthusiasm and eagerness of the nurses during training as well as the outcomes of training. Furthermore, analysis of clinical data after training showed that the fixation rate of clinical tubes reached 96.03%, and the busy work schedules of the nurses did not hamper their understanding and the effectiveness of tube fixation. When analyzing the UEX events at our hospital 1 year before and after the training, tube UEX rates decreased and the incidence of pressure ulcers caused by tubes decreased from 0.78‰ to 0.45‰; these rates indicate a better understanding of clinical tube fixation, which ensures that the tubes do not cause harm to the patients while playing effective roles in their treatment.

Despite the improvements observed with the novel combined training model, our study has some limitations. The participants in our study were inexperienced, newly graduated nurses, and this training model should be applied to assess the continuous education of experienced nurses as well. Although good training results have been achieved using the combined training model for tube fixation, several problems need to be addressed. First, the inadequate training conditions cannot be ignored, and access to basic training equipment must be considered[32]. Due to the lack of literature on tube fixation training, this study has a theoretical and exploratory disadvantage. Furthermore, the number of nurses are higher than the number of trainers, and training efficacy cannot be guaranteed. Second, it is necessary to understand the adaptability of the trainers and nurses to the flipped classroom approach. To smoothly apply the flipped classroom model, it is necessary to encourage the nurses to...
become the main body of learning; change the traditional teacher-student relationship; and encourage nurses to find problems, raise issues, and think about problems that may be encountered during learning. Third, attention should be paid to effectively combine and promote the two training models. This study suggests that the pre-class training on tube fixation can be adequately conducted by using the flipped classroom model, but the in-class training should be conducted using the workshop model to ensure that the nurses have enough time to practice their skills. Further studies are required to refine and optimize the training content.

One limitation of this study is that the combined training model was in its first year of implementation. Similarly, the instructors responsible for designing the training were themselves exploring the course whilst conducting it. Moreover, the research scheme was immature. Due to the limitation of information technology, the pre-class contents could not be well mastered, and the pre-class training could not be effectively conducted. Furthermore, we did not record the observation of the instructors, so there was no effective evaluation of the differences in the training models by supervisors. Information from only the nurses was obtained by individually talking to them at the training site. Therefore, our study lacks robust quantitative results. The two groups in our study comprised nurses of different ages, and the training sessions were conducted at two different periods, which may have led to biases. Additional studies are necessary to address these limitations.

CONCLUSION

In conclusion, our results prove that a combined approach using workshop along with flipped classroom training is helpful in improving tube fixation training for student nurses. This novel combined model of a workshop and flipped classroom is in line with the development of modern informatization and innovation in sciences. Using the flipped classroom approach is particularly helpful to encourage nurses to become the main body of learning by active and interactive participation. In addition, it ensures the integration of theory with practical application, so as to achieve optimum effective training.

ARTICLE HIGHLIGHTS

Research background
Nurse training for tube fixation is necessary to prevent unplanned extubation.

Research motivation
No study has examined a combination of both workshop and flipped classroom models in tube fixation training for nurses.

Research objectives
This study aimed to compare workshops plus flipped classroom model with workshops alone to deliver tube fixation training for nurses.

Research methods
Nurses were trained according to the two models, and the quality indicators of the training were then evaluated.

Research results
Nurses in the combined training group scored higher than nurses who received workshop training alone.

Research conclusions
Workshop plus flipped classroom models are effective in improving tube fixation training in nurses.

Research perspectives
Future studies can investigate class content, record trainers’ observations, and devise an effective method to evaluate the training model.

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Wang YC et al. Training method for tube fixation

FOOTNOTES

**Author contributions**: Wang YC contributed to methodology, writing- original draft preparation; Wang YC and Zhou XZ contributed to conceptualization; Cheng HL contributed to software, validation, writing- original draft preparation; Deng YM contributed to data curation, investigation; Li BQ contributed to data curation, investigation; Zhou XZ contributed to supervision; all authors have read and agreed to the published version of the manuscript.

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Mortality in patients with COVID-19 requiring extracorporeal membrane oxygenation: A meta-analysis

Ye Zhang, Lei Wang, Zhi-Xian Fang, Jing Chen, Jia-Lian Zheng, Ming Yao, Wen-Yu Chen

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Abstract

BACKGROUND
Coronavirus disease 2019 (COVID-19) has become a worldwide pandemic and significant public health issue. The effectiveness of extracorporeal membrane oxygenation (ECMO) in treating COVID-19 patients has been called into question.

AIM
To conduct a meta-analysis on the mortality of COVID-19 patients who require ECMO.

METHODS
This analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) and has been registered at the International Prospective Register of Systematic Reviews (number CRD42020227414). A quality assessment for all the included articles was performed by the Newcastle-Ottawa Scale (NOS). Studies with ten or more COVID-19 patients undergoing ECMO were included. The random-effects model was used to obtain the pooled incidence of mortality in COVID-19 patients receiving ECMO. The source of heterogeneity was investigated using subgroup and sensitivity analyses.

RESULTS
We identified 18 articles with 1494 COVID-19 patients who were receiving ECMO. The score of the quality assessment ranged from 5 to 8 on the NOS. The majority
Core Tip: Coronavirus disease 2019 (COVID-19) has become a worldwide pandemic and significant public health issue. The effectiveness of extracorporeal membrane oxygenation (ECMO) in treating COVID-19 patients has been called into question. Therefore, we conducted this meta-analysis on the mortality of COVID-19 patients who require ECMO. We identified 18 articles with 1494 COVID-19 patients who were receiving ECMO. With more resource assessment and risk-benefit analysis, our data reveal that ECMO might be a feasible and effective treatment for COVID-19 patients.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has become a global pandemic. As of October 25, 2021, there have been over 243 million infections and approximately 4.9 million deaths[1]. It was characterized by rapid disease progression and a high risk of acute respiratory distress syndrome (ARDS) due to severe or fatal pneumonia[2]. Although the majority of COVID-19 patients have very moderate disease, current studies suggest that approximately 18% of them have serious disease[3] with a mortality rate of up to 53%-67%[4,5].

Extracorporeal membrane oxygenation (ECMO), which can support gas exchange in patients failing conventional mechanical ventilation[6], has been proven to be effective in the treatment of severe respiratory failure and cardiovascular compromise caused by ARDS, based on the experience of previous viral outbreaks, such as Middle East Respiratory Syndrome and H1N1 influenza[7-9]. There are two primary ECMO therapy methods: Veno-venous ECMO (VV-ECMO) and veno-arterial ECMO (VA-ECMO). For the vast majority of COVID-19 patients who need ECMO treatment, we adopted VV-ECMO. The World Health Organization (WHO) and Chinese experts have recommended that ECMO can be used as a salvage therapy for severe COVID-19 patients who are not responding to conventional ARDS treatments[10-14]. Although there are still numerous complications, research has revealed that 63% of patients recovered from ARDS and were weaned from ECMO.

Despite such optimism for a possible role for ECMO in COVID-19, concerns have been raised due to the high mortality rate observed in studies[15]. Venerable age, late ECMO initiation time, and multiple complications (diabetes, heart disease, obesity, etc.) are all independent risk factors that increase the 90-d mortality rate. The role of ECMO in the treatment of diseases caused by this new virus is still uncertain and controversial. Currently, there is insufficient worldwide evidence to assess the effectiveness of ECMO. The majority of prior studies were based on retrospective cohort studies and case reports in a specific population, making it difficult to analyze the impact of ECMO on COVID-19 patients in a systematic manner[6]. Therefore, we conducted a meta-analysis focusing on the mortality of COVID-19 patients requiring ECMO in order to guide current clinical practice and future research efforts.
MATERIALS AND METHODS

Search strategy
To identify articles concerning ECMO and COVID-19, a comprehensive literature search was undertaken utilizing the PubMed, EMBASE, Web of Science, Cochrane Library, and Clinical Trials databases. On December 9, 2020, all searches were updated, and the search strategy was divided into two categories: (1) COVID-19; and (2) ECMO. The following keywords were used: “COVID-19”, “2019 novel coronavirus disease”, “2019-nCoV”, and “Extracorporeal membrane oxygenation.” The articles were limited to English literature. To prevent missing relevant records, reference lists from the selected
studies and systematic reviews were thoroughly searched. Furthermore, this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines, and it was registered at the International Prospective Register of Systematic Reviews (number CRD42020227414) prior to submission.

**Inclusion and exclusion criteria**

Original studies that matched the following criteria were included in the meta-analysis: (1) Studies with ten or more patients; (2) Patients with laboratory-confirmed COVID-19 receiving ECMO; (3) Studies with primary data; and (4) Studies with more than 5 points on the Newcastle-Ottawa scale (NOS). The exclusion criteria were: (1) Duplicate publication or dataset; and (2) Animal and in vitro experiments, case reports, letters, editorials, comments, conference summaries, meta-analyses, and reviews were excluded.

**Data extraction**

Data from the included articles were extracted, including authors' names, publication year, study location, study design, sample size, patient baseline characteristics, clinical parameters, management, primary outcome, and complications. The article search, selection, data extractions, and quality assessment were all conducted independently by two reviewers (ZY and CWY), and any disagreements were resolved after consensus.

**Quality assessment**

The NOS was applied for a quality assessment on all of the included papers. All included papers were classified as poor (scores 0–3), moderate (scores 4–6), or high (scores 7–9) quality studies, with papers with more than 5 points being considered for further analysis.

**Statistical analysis**

The pooled estimates of the event rate were obtained using the random-effects model. Each study had its own underlying effect size. The random-effects model assumes that there is a mean population effect size that varies depending on the study. We used the inconsistency statistic ($I^2$) to evaluate the extent of heterogeneity. An $I^2$ value greater than 50% was considered to indicate substantial heterogeneity. The Egger's and Begg's tests were used to assess publication bias and a visual funnel plot for asymmetry was presented. Sensitivity analysis and subgroup analysis were also utilized to investigate the source of heterogeneity and a two-sided test at the 5% level was considered statistically significant. Moreover, Stata 15.1 (Stata Corporation, College Station, TX, United States) was utilized to conduct the meta-analysis.

**RESULTS**

In the initial search, 1821 potentially relevant articles were identified. After eliminating duplicates, 1153 studies were assessed based on title and abstract. Following a full-text review of the remaining 56 studies, 38 studies were excluded. Finally, the meta-analysis comprised 18 articles representing 1494 verified COVID-19 patients treated with ECMO (Figure 1). Since EuroELSO was a subset of centers participating in the international ELSO registry, we eliminated the previous study on EuroELSO to avoid data duplication\cite{16,17}.

**Studies characteristics and quality assessment**

The characteristics of these studies are summarized in Table 1. All of the studies were observational in design, with the majority of them being retrospective (94.2%). The score of the quality assessment ranged from 5 to 8 on the NOS. All studies were rated as “moderate to high quality.” In the majority of cases, VV-ECMO was utilized (93.8%). Table 2 summarizes the sample characteristics of the included studies.

The in-hospital or short-term mortality ranged between 0.04 and 0.57. Overall pooled mortality was estimated to be 0.31 [95% confidence interval (CI): 0.24-0.39; $I^2 = 84.8\%$] using random-effect pooled estimates (Figure 2). Two studies found that the mortality rate in the ECMO group was lower than that in the mechanical ventilator group (57.1% vs 63.2% and 46.2% vs 47.8%).

**Subgroup analysis**

Figure 3 depicts the outcomes of the random effects model and subgroup analysis. There were significant differences in mortality between location groups (Figure 3A; 33.0% vs 55.0% vs 37.0% vs 18.0%, $P < 0.001$), setting groups (Figure 3B; 28.0% vs 34.0%, $P < 0.001$), sample size group (Figure 3C; 37.0% vs 31.0%, $P < 0.001$), and NOS groups (Figure 3D; 39.0% vs 19.0%, $P < 0.001$). There was no source of heterogeneity in any of the subgroups.
Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Location</th>
<th>Study design</th>
<th>Sample size</th>
<th>Type of ECMO (VV%)</th>
<th>Follow-up</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al[31]</td>
<td>2020</td>
<td>United Kingdom</td>
<td>Retrospective/Single center</td>
<td>43</td>
<td>100%</td>
<td>In-hospital</td>
<td>7</td>
</tr>
<tr>
<td>Yang et al[21]</td>
<td>2020</td>
<td>China</td>
<td>Retrospective/Multicenter</td>
<td>21</td>
<td>NA</td>
<td>In-hospital</td>
<td>8</td>
</tr>
<tr>
<td>Barbaro et al[16]</td>
<td>2020</td>
<td>ELSO</td>
<td>Retrospective/Multicenter</td>
<td>1035</td>
<td>94.49%</td>
<td>3 mo</td>
<td>7</td>
</tr>
<tr>
<td>Alnababteh et al[32]</td>
<td>2021</td>
<td>United States</td>
<td>Retrospective/Single center</td>
<td>13</td>
<td>100%</td>
<td>In-hospital</td>
<td>8</td>
</tr>
<tr>
<td>Le Breton et al[27]</td>
<td>2020</td>
<td>France</td>
<td>Retrospective/Single center</td>
<td>13</td>
<td>100%</td>
<td>In-hospital</td>
<td>5</td>
</tr>
<tr>
<td>Guilhaire et al[33]</td>
<td>2020</td>
<td>France</td>
<td>Retrospective/Single center</td>
<td>24</td>
<td>100%</td>
<td>In-hospital</td>
<td>5</td>
</tr>
<tr>
<td>Jackel et al[34]</td>
<td>2020</td>
<td>Germany</td>
<td>Retrospective/Single center</td>
<td>15</td>
<td>100%</td>
<td>1 mo</td>
<td>8</td>
</tr>
<tr>
<td>Jang et al[19]</td>
<td>2020</td>
<td>Korea</td>
<td>Retrospective/Multicenter</td>
<td>19</td>
<td>84.21%</td>
<td>In-hospital</td>
<td>7</td>
</tr>
<tr>
<td>Schmidt et al[35]</td>
<td>2020</td>
<td>France</td>
<td>Retrospective/Multicenter</td>
<td>83</td>
<td>97.59%</td>
<td>3 mo</td>
<td>7</td>
</tr>
<tr>
<td>Riera et al[36]</td>
<td>2020</td>
<td>Spain</td>
<td>Retrospective/Single center</td>
<td>19</td>
<td>100%</td>
<td>In-hospital</td>
<td>5</td>
</tr>
<tr>
<td>Jacobs et al[24]</td>
<td>2020</td>
<td>United States</td>
<td>Retrospective/Multicenter</td>
<td>32</td>
<td>78.13%</td>
<td>In-hospital</td>
<td>6</td>
</tr>
<tr>
<td>Beintgen et al[37]</td>
<td>2021</td>
<td>Germany</td>
<td>Prospective/Single center</td>
<td>11</td>
<td>100%</td>
<td>28 d</td>
<td>8</td>
</tr>
<tr>
<td>Cousin et al[20]</td>
<td>2021</td>
<td>France</td>
<td>Retrospective/Multicenter</td>
<td>30</td>
<td>100%</td>
<td>3 mo</td>
<td>8</td>
</tr>
<tr>
<td>Sultan et al[28]</td>
<td>2020</td>
<td>United States</td>
<td>Retrospective/Multicenter</td>
<td>10</td>
<td>100%</td>
<td>26 d</td>
<td>5</td>
</tr>
<tr>
<td>Yankah et al[38]</td>
<td>2021</td>
<td>Germany</td>
<td>Retrospective/Multicenter</td>
<td>42</td>
<td>100%</td>
<td>1 mo</td>
<td>5</td>
</tr>
<tr>
<td>Kon et al[29]</td>
<td>2021</td>
<td>United States</td>
<td>Retrospective/Single center</td>
<td>27</td>
<td>100%</td>
<td>In-hospital</td>
<td>6</td>
</tr>
<tr>
<td>Zayat et al[39]</td>
<td>2021</td>
<td>Germany</td>
<td>Retrospective/Single center</td>
<td>17</td>
<td>94.12%</td>
<td>In-hospital</td>
<td>7</td>
</tr>
<tr>
<td>Mustafa et al[40]</td>
<td>2020</td>
<td>United States</td>
<td>Retrospective/Multicenter</td>
<td>40</td>
<td>100%</td>
<td>In-hospital</td>
<td>7</td>
</tr>
</tbody>
</table>

ECMO: Extracorporeal membrane oxygenation; NOS: Newcastle-Ottawa Scale; NA: Not available.

**Publication bias and sensitivity analysis**
Funnel plots showed no obvious asymmetry. The Egger’s ($P = 0.95$) and Begg’s tests ($P = 0.14$) further revealed no significant publication bias. The recalculated pooled results did not change significantly after removing each study sequentially, showing that there was no outlier study that influenced the overall result.

**DISCUSSION**
ECMO is an essential instrument for treating severe respiratory and heart failure, and it was widely employed in the treatment of critically ill patients during the COVID-19 pandemic. However, previous research found that the impact of ECMO in critically ill COVID-19 patients was controversial due to the high mortality rate. Therefore, we conducted this meta-analysis that included 18 original independent studies to examine the effectiveness of ECMO in the treatment of COVID-19. The mortality rate of COVID-19 patients treated with ECMO in our investigation was 31%, which was lower than the mortality rate of severe COVID-19 patients in the prior study. These data imply that ECMO treatment may decrease the mortality rate of COVID-19 patients who are severely ill.

Although some studies reported that the mortality rate of COVID-19 patients treated with ECMO is as high as 53-83.3%[18-22], which is substantially higher than the results of this study, we believe such high mortality may be due to other reasons rather than the ECMO treatment being ineffective. For example, many previous studies conducted in the early stage of the COVID-19 outbreak used a small sample size with a high proportion of patients having pre-existing comorbidities, which may be an important factor contributing to the high mortality.[23]. Additionally, due to a lack of experience in treating COVID-19 at the beginning of the outbreak, ECMO treatment may have been initiated too late. The secondary infection and other complications may also lead to high mortality. These possible reasons of increased mortality are consistent with prior results obtained by certain researchers who discovered that variables such as advanced age (> 65 years old), gender (male), pre-existing diseases, and acute or chronic organ failure may contribute to a poor prognosis[24-26]. Considering these factors, our findings may provide evidence for the future application of ECOM in treating severe COVID-19 patients.
### Table 2 Patient characteristics, clinical parameters, management, and primary complications of the included studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Age (yr)</th>
<th>Proportion of male (%)</th>
<th>Smoke</th>
<th>SOFA</th>
<th>PH</th>
<th>PaO₂/FiO₂ (mmHg)</th>
<th>Comorbidities</th>
<th>ECMO duration (d)</th>
<th>Pre-ECMO MV (d)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al [31]</td>
<td>46 (35.5-52.5)</td>
<td>76.7%</td>
<td>NA</td>
<td>7 (4-10)</td>
<td>7.30 (7.19-7.36)</td>
<td>67.5 (58.9-77.8)</td>
<td>(1), (2), (3), (4), (5)</td>
<td>13 (8-20)</td>
<td>5 (2-6)</td>
<td>1, 2, 4, 5</td>
</tr>
<tr>
<td>Yang et al [18]</td>
<td>45.2 ± 14.5</td>
<td>57.1%</td>
<td>NA</td>
<td>6.5 (4.8-8.0)</td>
<td>7.30 (7.19-7.41)</td>
<td>60 (55.6-72.0)</td>
<td>(3), (4), (6)</td>
<td>NA</td>
<td>9.1 (5.9-24.8)</td>
<td>1.5 (0.5-3.5)</td>
</tr>
<tr>
<td>Barbaro et al [16]</td>
<td>49 (41-57)</td>
<td>73.8%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>72 (59-94)</td>
<td>(2), (3), (4), (5), (6)</td>
<td>13.9 (7.8-23.3)</td>
<td>4 (1.8-6.4)</td>
<td>1, 3, 7, 8</td>
</tr>
<tr>
<td>Alnasabteh et al [32]</td>
<td>44.5 ± 9.5</td>
<td>61.5%</td>
<td>1</td>
<td>9.3 ± 4.5</td>
<td>7.32 (7.23-7.39)</td>
<td>81.3 ± 20.3</td>
<td>(1), (2)</td>
<td>12 (10.4-16.2)</td>
<td>NA</td>
<td>1, 2, 6</td>
</tr>
<tr>
<td>Le Breton et al [27]</td>
<td>49.3</td>
<td>69.2%</td>
<td>4</td>
<td>9.9</td>
<td>7.28</td>
<td>59</td>
<td>(1)</td>
<td>13 (3-34)</td>
<td>6</td>
<td>1, 2</td>
</tr>
<tr>
<td>Gualaire et al [33]</td>
<td>48.8 ± 8.9</td>
<td>83.3%</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>67 (52-78)</td>
<td>(1), (2)</td>
<td>19 ± 10.1</td>
<td>6.3 (1-11)</td>
<td>1, 3</td>
</tr>
<tr>
<td>Jäckel et al [34]</td>
<td>60.8 (54.1-67.0)</td>
<td>26.7%</td>
<td>3</td>
<td>10 (8-11)</td>
<td>7.30 (7.23-7.40)</td>
<td>NA</td>
<td>(1), (2), (3), (4)</td>
<td>11.3 (7.8-23.8)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Jang et al [19]</td>
<td>63 (60-66)</td>
<td>79.0%</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>7.30 (7.20-7.40)</td>
<td>92 (62.4-138.7)</td>
<td>(1), (2), (3), (4), (5), (6)</td>
<td>15.9 (7.7-28.2)</td>
<td>3.1 (0.8-5.5)</td>
</tr>
<tr>
<td>Schmidt et al [35]</td>
<td>49 (41-56)</td>
<td>73.5%</td>
<td>2</td>
<td>12 (9-13)</td>
<td>7.32 (7.24-7.38)</td>
<td>60 (54-68)</td>
<td>(1), (3), (4), (5), (6), (7)</td>
<td>NA</td>
<td>4 (3-6)</td>
<td>1, 2, 3, 5, 8</td>
</tr>
<tr>
<td>Riera et al [36]</td>
<td>50.5 (31-64)</td>
<td>84.2%</td>
<td>NA</td>
<td>NA</td>
<td>7.2 (6.9-7.4)</td>
<td>70.8 (57-118)</td>
<td>(1), (3)</td>
<td>10.7 (2-33)</td>
<td>NA</td>
<td>1, 3</td>
</tr>
<tr>
<td>Jacobs et al [24]</td>
<td>52.4 ± 12.5</td>
<td>68.8%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>(2), (3), (4), (5)</td>
<td>7.3 ± 3.3</td>
<td>4.3 ± 2.4</td>
<td>NA</td>
</tr>
<tr>
<td>Bemtgen et al [37]</td>
<td>59.4 (49.8-61.3)</td>
<td>63.6%</td>
<td>NA</td>
<td>14 (13-16)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>17.9 (7.8-23.8)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cousin et al [20]</td>
<td>57 (47-62)</td>
<td>80.0%</td>
<td>1</td>
<td>10 (7-12)</td>
<td>7.37 (7.32-7.41)</td>
<td>69 (63-75)</td>
<td>(1), (3), (4), (5), (7)</td>
<td>11 (7-14)</td>
<td>6 (4-9)</td>
<td>1, 2, 3, 6, 8</td>
</tr>
<tr>
<td>Sultan et al [28]</td>
<td>NA</td>
<td>70.0%</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>(3), (4)</td>
<td>11 (4-14)</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Yankah et al [38]</td>
<td>51 (25-73)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10.6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kon et al [29]</td>
<td>40 (30.5-47)</td>
<td>85.2%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7.28 (7.22-7.39)</td>
<td>84 (70-118)</td>
<td>(1), (3), (4), (5), (6), (7)</td>
<td>11 (10-14)</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>Zayat et al [39]</td>
<td>57 (39-67)</td>
<td>64.7%</td>
<td>4</td>
<td>11.9 ± 9.4</td>
<td>7.3 (7.2-7.4)</td>
<td>53-75</td>
<td>(1), (3), (5), (6), (7)</td>
<td>16 (11-21)</td>
<td>3 (3-15)</td>
<td>1, 3, 5, 8</td>
</tr>
<tr>
<td>Mustafa et al [40]</td>
<td>48.4 (22-62)</td>
<td>75%</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>(1), (2), (3), (4), (5), (6)</td>
<td>13.0 ± 2.6</td>
<td>4.0 ± 0.5</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA: Not available; SOFA: Sequential Organ Failure Assessment score; MV: Mechanical ventilation; CNS: Central nervous system.
Mean ± SD or median (interquartile range).
Comorbidities: (1)-Hypertension; (2)-Diabetes; (3)-Lung disease; (4)-Obesity; (5)-Heart disease; (6)-Kidney disease; (7)-Immunosuppression.
Complications: 1-Hemorrhage; 2-Infection; 3-Thrombosis; 4-Pneumothorax; 5-Cardiovascular complications; 6-Renal complications; 7-Respiratory failures; 8-Neurological complications.

According to the studies with a low mortality rate among patients who received ECMO treatment, we recommend that ECMO should be combined with the use of other therapies, such as antiviral, immunosuppressive, anticoagulant, and supportive therapies, as well as the collaboration of professional multidisciplinary teams and professional nursing[27-29]. Additionally, the timing of ECMO intervention may also be a critical factor affecting the prognosis. Previous studies have confirmed that early ECMO intervention after mechanical ventilation can enhance the survival rate of patients with HINI pneumonia and ARDS[26]. The majority of patients with severe ARDS and severe SARS-CoV-2 pneumonia received delayed treatment and rapidly worsened. Yang et al[21] showed that among COVID-19 patients treated with ECMO, the average time from mechanical ventilation to ECMO in the survival group was shorter than that in the death group. The use of early ECMO may be associated with...
Figure 3 Subgroup forest plot of in-hospital or short-term mortality in patients with coronavirus disease 2019 requiring extracorporeal membrane oxygenation. There were significant differences in mortality between location, study setting, sample size, and Newcastle-Ottawa scale (NOS) score groups. A: Location; B: Study setting; C: Sample size; D: NOS score groups. COVID-19: Coronavirus disease 2019; ECMO: Extracorporeal membrane oxygenation; NOS: Newcastle-Ottawa Scale.

a better prognosis[18]. Despite the fact that the PaO$_2$/FiO$_2$ ratio is less than 80 mm Hg and the MV treatment has been administered, we believe that ECMO should be initiated as soon as possible. Moreover, research has shown that prolonged ECMO treatment may be associated with an increased risk of death and multiple organ failure[30]. Therefore, both the timing and duration of ECMO treatment are critical to consider when treating critically ill patients with COVID-19.

We acknowledge that our study has several limitations. To begin with, the power of the study is limited by the small sample size. Biases in patient selection and indication may have existed due to the small sample size. Additionally, the majority of the included studies were observational with retrospective designs, and more than half of the studies were single-center ones, which may lead to selection and reporting bias. Finally, the survival analyses for mortality were based on a short-term follow-up and varied death observation time, which might have underestimated the reported prevalence of mortality and complications.
CONCLUSION

Despite the fact that ECMO is approved as a rescue treatment for severe COVID-19, its application during the COVID-19 pandemic is currently restricted due to high treatment costs and an unclear usage procedure. Our findings suggested that ECMO might be a feasible and effective treatment for COVID-19 patients with more resource evaluation and risk-benefit analysis. Further research with a large sample size and multi-center designs is needed to examine the effectiveness of ECMO in the treatment of COVID-19 patients.

ARTICLE HIGHLIGHTS

Research background
Patients with moderate to severe coronavirus disease 2019 (COVID-19) infection often have severe acute respiratory distress syndrome, with a poor prognosis, limited treatment options, and high mortality. Extracorporeal membrane oxygenation (ECMO) has been proven to have the advantages of improving symptoms and reducing mortality in previous studies. However, existing studies lack strong evidence and disagreement whether ECMO can reduce the mortality of patients with moderate to severe COVID-19 infection. This article intends to summarize the mortality of COVID-19 patients treated with ECMO in order to evaluate the efficacy of ECMO in COVID-19 patients.

Research motivation
To summarize the mortality and comorbidities of COVID-19 patients treated with ECMO, to evaluate the efficacy and adverse reactions of ECMO in COVID-19 patients, and to clarify the effectiveness of ECMO treatment, in order to provide a basis for future treatment options for patients with moderate to severe COVID-19.

Research objectives
To evaluate the efficacy and adverse reactions of ECMO in COVID-19 patients.

Research methods
This research was conducted through the method of meta-analysis. A random effects model was adopted to assess the mortality of COVID-19 patients treated with ECMO.

Research results
The mortality rate of COVID-19 patients treated with ECMO was 31%, which was lower than the mortality rates of severe COVID-19 patients in previous studies, suggesting that ECMO treatment can reduce the mortality rate of severe COVID-19 patients. Previous studies have not yet given clear answers to when ECMO should be used and the duration of ECMO treatment.

Research conclusions
ECMO may be a feasible and effective treatment for COVID-19 patients.

Research perspectives
Prospective, large-sample, multi-center studies are needed to have a more comprehensive understanding of the effectiveness and safety of ECMO treatment.

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FOOTNOTES

Author contributions: Zhang Y, Wang L, and Fang ZX conceptualised and designed the protocol, drafted the initial manuscript, and reviewed the manuscript; Chen J and Zheng JL defined the concepts and search items, data extraction process, as well as methodological appraisal of the studies; Yao M planned the data extraction and statistical analysis; Chen WY provided critical insights; all authors have approved and contributed to the final written manuscript.

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Zhang Y et al. ECMO for patients with COVID-19


CASE REPORT

Escitalopram-induced hepatitis: A case report

Guillaume Wabont, Laurie Ferret, Nicolas Houdre, Antoine Lepied, Johana Bene, Etienne Cousein

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Abstract

BACKGROUND
The antidepressant escitalopram is widely prescribed for the treatment of depression. It is generally well-tolerated, and cholestasis is not mentioned in its summary of product characteristics (SmPC). We present a case of cholestatic and cytolysis liver injury due to escitalopram and a VigiBase® study.

CASE SUMMARY
A 68-year-old man was admitted to our emergency unit due to clinical jaundice associated with hepatitis, pruritus and dark urine. We tested the patient for the most common etiologies of jaundice, including hemolysis, viral hepatitis, cirrhosis, carcinoma, cholangitis, cholelithiasis and intrahepatic or extrahepatic obstruction. The etiological study was negative, and an adverse drug reaction was the sole possible explanation. The patient was receiving treatment with escitalopram. Two days after its withdrawal, pruritus was resolved. Ten days after withdrawal, clinical jaundice disappeared. It took a month and three weeks after withdrawal for the patient to have normalized liver function tests. To our knowledge, this is the first reported case of cholestasis where treatment with escitalopram was the only possible cause, with a highly probable causality. In addition, we determined whether escitalopram is associated with hepatotoxicity and cholestasis by performing a disproportionality analysis. All cases of hepatobiliary disorders induced by escitalopram and reported in the World Health Organization pharmacovigilance database (VigiBase®) were analyzed to characterize this toxicity. We found that patients treated with escitalopram had an increased risk of hepatitis [odds ratio (OR) = 1.938 (1.186-3.166)] and cholestasis [OR = 1.866 (1.279-2.726)] [OR (95% confidence interval)]. The median duration between the introduction of escitalopram and the occurrence of acute hepatitis and/or
cholestasis was ten days +/- seven days.

CONCLUSION
Although extremely rare, this case report, the review of the literature and the pharmacovigilance update confirm that escitalopram can cause drug-induced hepatotoxicity and cholestasis, generally within a week after initiation. Thus, escitalopram should be withdrawn immediately if an iatrogenic cause cannot be excluded. If its responsibility is ascertained, escitalopram should be consequently contraindicated. In addition, serotoninergic antidepressants in patients with non-severe depression are ineffective and harmful. Finally, the SmPC of escitalopram should be updated to alert for this risk and give clear clinical guidelines.

Key Words: Escitalopram; Hepatitis; Cholestasis; Pharmacovigilance; Case report

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INTRODUCTION
Depression is a common mental disorder worldwide and a leading cause of non-fatal health loss, affecting more than 264 million people[1]. Among the antidepressants, selective serotonin reuptake inhibitors are often prescribed as a first-line treatment. They increase the intrasynaptic levels of serotonin by inhibiting the neurotransmitter’s reuptake into the presynaptic neuron. However, the benefits of antidepressants are known to be minimal or even non-existent in patients with mild to moderate symptoms, uselessly exposing them to potential adverse drug reactions[2]. Drug-induced liver injury is a rare complication of antidepressants and is a concern mainly for tricyclic and tetracyclic antidepressants[3].

Here we present a case of cholestatic and cytolysis liver injury due to escitalopram, a selective serotonin reuptake inhibitor, and a VigiBase® study.

CASE PRESENTATION
Chief complaints
The 68-year-old Caucasian male patient, was prescribed escitalopram 5 mg/d by his general practitioner for a minor depressive episode; the posology rose to 10 mg/d one week later. The patient developed clinical icterus with pale stools and dark urine three days later, without any pain or hyperthermia.

History of present illness
The patient was admitted to the emergency unit three days later. He was then transferred to the gastroenterology and hepatology unit, where an etiologic investigation was performed[4].

The moderate daily intake of alcohol (less than 10 g/d) and the absence of damaged hepatocytes, cirrhosis or carcinoma excluded hepatocellular jaundice.

History of past illness
The patient had no history of past illness, chronic treatment or known allergies.

Personal and family history
No notable personal or family history.
**Physical examination**
A physical examination was unremarkable, except for palpable hepatomegaly, eliminating an obstructive cause. Etiologies such as cholangitis, pancreatic carcinoma or edema, cholelithiasis and trauma were not found.

**Laboratory examinations**
Normochromic and normocytic anemia, a subtle inflammatory syndrome, cholestasis with conjugated hyperbilirubinemia and cytolytic hepatitis were observed (Table 1). The presence of conjugated bilirubin and the absence of hemolysis excluded pre-hepatic jaundice. A viral cause was improbable due to the absence of hyperthermia, and human immunodeficiency virus (HIV), hepatitis viruses (HAV, HBV, HCV, HEV), cytomegalovirus (CMV) and herpes simplex viruses (HSV) serologies were negative. Autoantibodies and serum immunoglobulin levels were not screened.

**Imaging examinations**
Hepatic ultrasonography was unremarkable.

**FINAL DIAGNOSIS**
Considering the lack of probing results from the etiologic investigation and the spontaneous resolution of symptoms after treatment was withdrawn, the only possible remaining cause was drug-induced cholestatic and cytolytic hepatitis due to escitalopram.

**TREATMENT**
Treatment with escitalopram was immediately stopped.

**OUTCOME AND FOLLOW-UP**
The chronopathology was as follows: The symptoms started to appear ten days after initiation of treatment. Pruritus resolved two days after escitalopram withdrawal. Clinical jaundice disappeared ten days after withdrawal. Liver function tests normalized a month after withdrawal. It should be noted that bilirubin levels normalized more rapidly than transaminase levels, which is not common in clinical practice, especially in drug-induced liver injury (DILI)[5]. However, we are unable to explain this phenomenon.

**DISCUSSION**

**Case report description**
We used the Roussel Uclaf Causality Assessment Method (RUCAM) to quantify the strength of the association between cholestatic hepatitis and treatment with escitalopram[6,7]. The RUCAM comprises seven criteria: The time to onset of reaction after drug start, clinical course, risk factors, concomitant drugs with hepatotoxic properties, non-drug causes, and published information on hepatotoxicity and the response to any new administration to the suspected drug. The RUCAM score ranges from -8 to +14. A higher score means a higher probability of DILI as it is collapsed into the following five-category scale: Highly probable (> 8), probable (6-8), possible (3-5), unlikely (1-2), and excluded (≤ 0).

According to the RUCAM, the iatrogenic cause of both hepatitis (10/14) and cholestasis (9/14) in our case was highly probable (Supplementary material).

**Literature review**
Eligible studies were identified through electronic searches of Medline and Embase (1966 to May 2020), using different sets of keywords. The first set consisted of “escitalopram” and “citalopram”; the second set of “cholestasis” and “hepatitis”, the third one (optional) of “iatrogeny” and “drug-induced”.

In addition, we reviewed the reference lists in the articles. Voican et al[3] wrote a review for clinicians on antidepressant-induced liver injury. Helmut et al[11] described a case of cholestasis and acute hepatitis three weeks after introducing citalopram in a 56-year-old woman. Milkiewicz et al[12] described a case of cholestasis and acute hepatitis two months after introducing citalopram 10 mg/d (posology rose to 20 mg/d one month later). Finally, Ng et al[13] described a case of cholestasis two weeks after the introduction of escitalopram and olanzapine in a 56-year-old woman.
Few cases have proved that hepatic cholestasis can rarely be caused by citalopram[11,12]. Since citalopram is a racemic composed of 50% R-citalopram and 50% escitalopram, it was plausible that such a rare adverse event could be due to escitalopram. Only recently, Ng et al[13] described a case of cholestasis due to escitalopram in a 56-year-old woman: The first clinical signs of cholestasis appeared two weeks after escitalopram was initiated. The RUCAM score showed a probable iatrogenic cause. The patient was treated with other drugs, and olanzapine was introduced four days before escitalopram. Olanzapine is also labelled as a cause a cholestasis[14], and up to 28% of patients experience elevated hepatic enzymes. Therefore, in the case presented by Ng et al[13], it may well have participated in hepatic toxicity. In our case, escitalopram was the only drug taken by the patient, and thus its sole contribution to hepatic toxicity is certain, making this case unique.

Milkiewicz et al[12] have made assumptions on the pathophysiological mechanism involving the hepatocellular redistribution of multidrug-resistant protein 2, one of the key canalicular proteins responsible for transporting several organic anions, including bilirubin glucuronides, from the hepatocyte to bile. However, the exact mechanism of such hepatotoxicity remains unclear and needs to be investigated.

Pharmacovigilance analysis of hepatitis and cholestasis induced by escitalopram was investigated using Vigibase®, which is the most extensive pharmacovigilance database. It contains more than 24 million individual case safety reports (ICSRs) submitted by national pharmacovigilance centers from countries all over the world within the World Health Organization pharmacovigilance program.

We used Vigibase® to describe the characteristics of the hepatobiliary disorders associated with escitalopram[8]. We searched for all ICSRs presenting at least one adverse drug reaction from a defined list related to escitalopram with a minimal set of data (Table 2), submitted from the 14 November 1967 to 7 May 2020. A total of 481 ICSRs were analyzed, but only 127 ICSRs matched our specific criteria of cholestasis and/or hepatitis (Table 2), presumably caused by escitalopram. For each of those 127 ICSRs, we collected the following data: Age and sex of the patient, time between the introduction of escitalopram and the hepatobiliary disorder, withdrawal of escitalopram, necessity for hospitalization and the recovery from hepatobiliary disease after it was diagnosed.

We also performed a disproportionality analysis from the data extracted from Vigibase® between the adverse reactions “hepatitis acute (PT)” or “cholestasis (PT)” and escitalopram treatment using the case/non-case method. The strength of the association was quantified by crude reporting OR with their 95% confidence interval[9,10]. Statistical methods are detailed in Supplementary material.

Statistical significance was defined as a P-value threshold of 0.05. Statistical analyses were performed in SAS 9.4 (SAS Institute, Cary NC, United States).

With regard to the 127 ICSRs included for the characterization of hepatitis or cholestasis secondary to the intake of escitalopram, most of the patients were women (64.6%). The median (interquartile) age was 35(40-70) years old.

The mean duration between the introduction of escitalopram and the occurrence of hepatitis or cholestasis was ten days +/- seven days.

Cases of cytolytic hepatitis (28 ICSRs - 22.0%) seemed to be more frequent than cases of cholestasis (19 ICSRs - 15.0%). Only 2 ICSRs (1.6%) corresponded to mixed cholestatic and cytolytic hepatitis.

The toxicity of escitalopram did not seem to be dose-dependent: In almost half of cases the prescribed posology was 10 mg/d (49.0%), followed by 20 mg/d (17.6%), 5 mg/d (8.6%) and 15 mg/d (5.5%).

The vast majority of cases included in the international pharmacovigilance database lacked data such as the chronology of healing after the withdrawal of escitalopram. However, from our case, we can hypothesize that clinical recovery occurs within a few days and biological normalization within a few
Among the 9372588 ICSRs included in the disproportionality analysis, 13071 involved escitalopram. Most of the patients were women (69.3%). Patient age was mainly between 45 and 64 years old (57.0%) followed by 65 and 74 years (21.3%), 18 and 44 years (13.9%), and ≥ 75 years (7.8%). A signal was found between acute hepatitis or cholestasis and exposure to escitalopram (Table 3).

Cholestasis is not mentioned in the summary of product characteristics (SmPC) of escitalopram in the EU or the United States. It should be noted that the American SmPC mentions a risk of delayed hyperbilirubinemia when taking escitalopram, with no further notice (incidence not known). Hepatitis is mentioned in both the European and American SmPC of escitalopram, with an unknown incidence.

Approximately two-thirds (64.6%) of the cases of hepatitis or cholestasis related to escitalopram found in Vigibase® concerned female patients. At first sight, this might indicate gender-based differences in the hepatic toxicity of escitalopram. However, it is well established that depression has a higher prevalence in women than in men: A recent United States national data study found a similar ratio[15]. Furthermore, the exact ratio applies to the number of cases of adverse drug reactions notified with escitalopram (69.3% of cases were female patients): It is unlikely that the hepatotoxicity of escitalopram differs according to gender.

The pharmacovigilance analysis confirmed that escitalopram could rarely cause acute hepatitis and cholestasis. However, the ICSRs in Vigibase® lack data, especially the course of clinical recovery and biological normalization after escitalopram withdrawal. Therefore, when confronted with hepatitis or cholestasis due to escitalopram, health practitioners must spontaneously report it to their local or national pharmacovigilance center and provide as many details as possible.

An interesting aspect of our case is that the general practitioner prescribed escitalopram for a minor depressive episode. A psychiatrist reexamined the patient during his hospitalization and diagnosed mild depression, with no need for an antidepressant drug. Thus, our case highlights something well established: Antidepressants are minimally helpful, if not useless and dangerous, in patients with mild to moderate depressive symptoms[2]. General practitioners and physicians should be aware of the ineffectiveness and harm of serotoninergic antidepressants in patients with non-severe depression.

CONCLUSION

Our case illustrates how inappropriate prescriptions can have severe consequences on both patients (e.g., hospitalizations) and the health care system (evitable social security costs).

Although extremely rare, escitalopram can cause drug-induced hepatitis and cholestasis, generally within a week after initiation. Therefore, physicians must be aware of this rare but severe adverse effect. The SmPC of escitalopram should be updated to alert for this risk and give clear clinical guidelines. In the case of hepatitis or cholestasis, if an iatrogenic cause cannot be excluded, escitalopram must be immediately withdrawn and then contraindicated if its responsibility is ascertained.

Table 2 Search criteria in Vigibase® (characterization of hepatitis or cholestasis)

<table>
<thead>
<tr>
<th>Adverse drug reactions list for extraction</th>
<th>The minimal set of data needed for extraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestasis and jaundice (HLT); Hepatic and hepatobiliary disorders NEC (HLT); Hepatic enzymes and function abnormalities (HLT); Hepatobiliary signs and symptoms (HLT); Cholestatic liver injury (PT); Drug-induced liver injury (PT); Hepatitis (PT); Hepatitis acute (PT); Hepatitis toxic (PT); Hepatocellular injury (PT); Hepatotoxicity (PT)</td>
<td>Patient age above 18 years old; Patient gender specified in the ICSR</td>
</tr>
</tbody>
</table>


Table 3 Reporting odds ratio of acute hepatitis and cholestasis in Vigibase® in patients receiving escitalopram

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hepatitis</td>
<td>1.938</td>
<td>1.186-3.166</td>
<td>0.0083</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>1.866</td>
<td>1.279-2.724</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

OR: Odds ratio; CI: Confidence interval.
FOOTNOTES

Author contributions: Wabont G wrote the manuscript; all authors contributed equally to this work and have read and approved the final manuscript.

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REFERENCES


Fatal community-acquired bloodstream infection caused by
*Klebsiella variicola*: A case report

Da-Li Long, Yu-Hui Wang, Jin-Long Wang, Si-Jie Mu, Li Chen, Xian-Qing Shi, Jian-Quan Li

**BACKGROUND**
*Klebsiella pneumoniae* (*K. pneumoniae*) is an infective microorganism of worldwide concern because of its varied manifestations and life-threatening potential. Genetic analyses have revealed that subspecies of *K. pneumoniae* exhibit higher virulence and mortality. However, infections with *Klebsiella* subspecies are often misdiagnosed and underestimated in the clinic because of difficulties in distinguishing *K. pneumoniae* from its subspecies using routine tests. This case study reports the rapid and fatal effects of *K. pneumoniae* subspecies.

**CASE SUMMARY**
A 52-year-old male patient was febrile and admitted to hospital. Examinations excluded viral and fungal causes along with mycoplasma/chlamydia and parasitic infections. Bacterial cultures revealed blood-borne *K. pneumoniae* sensitive to carbapenem antibiotics, although corresponding treatment failed to improve the patient’s symptoms. His condition worsened and death occurred within 72 h of symptom onset from sepsis shock. Application of the PMseq-DNA Pro high throughput gene detection assay was implemented with results obtained after death showing a mixed infection of *K. pneumoniae* and *Klebsiella variicola* (*K. variicola*). Clinical evidence suggested that *K. variicola* rather than *K. pneumoniae* contributed to the patient’s poor prognosis.

**CONCLUSION**
This is the first case report to show patient death from *Klebsiella* subspecies infection within a short period of time. This case provides a timely reminder of the clinical hazards posed by *Klebsiella* subspecies and highlights the limitations of classical laboratory methods in guiding anti-infective therapies for complex cases. Moreover, this report serves as reference for physicians diagnosing similar
diseases and provides a recommendation to employ early genetic detection to aid patient diagnosis and management.

**Key Words:** Community-acquired bloodstream infection; Mixed infection; *Klebsiella variicola*; *Klebsiella pneumoniae*; High throughput gene detection; Case report

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**Core Tip:** *Klebsiella pneumoniae* infection leads to worldwide concerns with its high mortality and varied manifestation. However, it is difficult to distinguish *Klebsiella pneumoniae* from its subspecies using classic clinical examinations. We here report a case who died with *Klebsiella* subspecies infection within 72 h. This case was diagnosed by genetic detection rather than classic laboratory methods. This case suggests that we should be alert to the clinical hazards and fatal effect of *Klebsiella* subspecies, classic method is limited in guiding the anti-infection therapy for complex cases, and early genetic detection should be performed in the diagnosis and management of complex infection.


**URL:** https://www.wjgnet.com/2307-8960/full/v10/i8/2474.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i8.2474

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**INTRODUCTION**

*Klebsiella pneumoniae* (*K. pneumoniae*) infections are known to be associated with high incidence and mortality. This microorganism causes outbreaks of nosocomial infections and even drug resistance, and can lead to infection in the community among health-care patients or people with underlying immunodeficiency[1]. Based on genetic analysis, *K. pneumoniae* is divided into three phylogroups: *K. pneumoniae* (KpI), *K. quasipneumoniae* (KpII), and *K. variicola* (KpIII)[2]. KpI is the most frequent group encountered in the clinic, followed by KpII and KpIII[1,3]. KpI is usually defined as classic *Klebsiella* (Ck) or hypervirulent *Klebsiella* (Hvkp) according to their invasiveness or virulence, while subspecies of *Klebsiella* (KpII and KpIII) usually present with higher virulence[1]. Currently, approximately 20% of the human isolates assumed to be *K. pneumoniae* are in fact *K. variicola* or *K. quasipneumoniae*[1]. However, since classical laboratory examinations cannot readily distinguish KpI from the KpII and KpIII phylogroups[4], the clinical hazards and importance of KpII and KpIII are often overlooked.

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**CASE PRESENTATION**

**Chief complaints**

A 52-year-old man presented with unexplained high fever, abdominal pain, and headache for 1 d.

**History of present illness**

The patient was subsequently admitted to the intensive care unit with diarrhea and confusion.

**History of past illness**

The patient reported a 5-year history of type 2 diabetes mellitus (T2DM) and 7 years of suffering gout but had no prior medical history related to the current symptoms.

**Personal and family history**

The patient had no particular individual or family history.

**Physical examination**

Physical assessment revealed a body temperature of 40 °C but without other obvious abnormal signs.

**Laboratory examinations**

Laboratory examinations revealed slightly deteriorated hepatorenal function and clotting function and increases in inflammatory parameters (Tables 1-3). Other laboratory biochemical tests proved negative for signs of viral and mycobacterial infections along with mycoplasma/chlamydia and biomarkers of
autoimmune diseases (Table 4). Traditional bacterial culture of the patients’ blood sample showed bacterial infection with *K. pneumoniae* (Table 5).

**Imaging examinations**

Chest radiography showed the manifestations of an inflammatory response, while other imaging results showed no obvious abnormalities (Figures 1-3).
Blood samples were collected on admission and liver and renal function parameters examined. Results were acquired about 2 h after sample collection. TBIL: Total bilirubin; ALB: Serum albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GLU: Glutamate; sCrea: Serum creatinine; UA: Uric acid.

**Table 1 Liver and renal function results**

<table>
<thead>
<tr>
<th>Item</th>
<th>Result (1*)</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBIL (μmol/L)</td>
<td>19.4</td>
<td>3.6-20.5</td>
</tr>
<tr>
<td>TP (μmol/L)</td>
<td>49.8</td>
<td>65-85</td>
</tr>
<tr>
<td>ALB (g/L)</td>
<td>31.4</td>
<td>40-55</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>156</td>
<td>9-50</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>182</td>
<td>15-40</td>
</tr>
<tr>
<td>sCrea (μmol/L)</td>
<td>160</td>
<td>57-97</td>
</tr>
<tr>
<td>Urea (μmol/L)</td>
<td>12.40</td>
<td>3.1-8</td>
</tr>
<tr>
<td>GLU (mmol/L)</td>
<td>13.89</td>
<td>3.9-6.1</td>
</tr>
<tr>
<td>K⁺ (mmol/L)</td>
<td>3.22</td>
<td>3.5-5.5</td>
</tr>
<tr>
<td>UA (μmol/L)</td>
<td>591</td>
<td>210-420</td>
</tr>
</tbody>
</table>

Figure 3 Images of abdominal ultrasonography.

**FINAL DIAGNOSIS**

Based on the patient’s symptoms and laboratory data, sepsis and septic shock were diagnosed according to the diagnostic criteria.

**TREATMENT**

The initial treatment prescribed after the availability of the laboratory results involved a broad-spectrum
Table 2 Clotting function parameters tested after referral

<table>
<thead>
<tr>
<th>Item</th>
<th>Result</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>3P</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>D-D (μg/mL)</td>
<td>60.75↑</td>
<td>0-1</td>
</tr>
<tr>
<td>FDP (μg/mL)</td>
<td>128.5↑</td>
<td>0-5</td>
</tr>
<tr>
<td>PT (s)</td>
<td>18.3↑</td>
<td>9.2-12.2</td>
</tr>
<tr>
<td>INR</td>
<td>1.59↑</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>67.6↑</td>
<td>21.1-36.5</td>
</tr>
<tr>
<td>TT (s)</td>
<td>23.4↑</td>
<td>14-21</td>
</tr>
<tr>
<td>FBG (g/L)</td>
<td>22.58</td>
<td>1.8-3.5</td>
</tr>
</tbody>
</table>

On admission, blood samples were sent for clotting assessment. Results were acquired 1 h after sample collection. FDP: Flexor digitorum profundus; PT: Prothrombin time; INR: International normalized ratio; APTT: Activated partial thromboplastin time; TT: Thromboplastin time; FBG: Fibrinogen.

Figure 4 Bone marrow biopsy result.

regimen for bacterial and fungal infections (intravenous meropenem 1 g per 6 h + intravenous caspofungin 70 mg/initial dose).

OUTCOME AND FOLLOW-UP

The patient's condition rapidly deteriorated within hours of admission with decreased blood pressure
On admission, blood samples were sent for routine examination including C-reactive protein and procalcitonin. Results were acquired 1 h after sample collection. WBC: White blood cells; NEUT: Neutrophils; MONO: Monocytes; LYMPH: Lymphocytes; RBC: Red blood cells; HGB: Hemoglobin; HCT: Hemocrit; PLT: Platelets; CRP: C-reactive protein; PCT: Procalcitonin.

DISCUSSION

*Klebsiella* is a genus of Gram-negative bacterium within the Enterobacteriaceae family. It usually causes opportunistic nosocomial infections among hospitalized patients or outbreaks of community-acquired infections. *Klebsiella* mainly colonizes human gut but it has also been isolated from the skin surfaces such as hands and face, and can be isolated from various environmental sources including water, plants, and soil[1,5]. The genus contains several subspecies that manifest varied clinical outcomes, even death, leading to significant concerns about the accurate and timely identification of the *Klebsiella* subspecies involved together with a better understanding of the patient risk factors involved to reduce mortality risks[6].

Recent research has revealed that diabetes is a significant risk factor for hypervirulent *K. pneumoniae* infection and for causing serious complications[7-9]. In our patient’s case, a medical history of T2DM could have contributed to an underlying immunodeficiency that was responsible for the fatal systemic infection. Although both *K. pneumoniae* and *K. variicola* were detected in the patients’ blood sample, *K. variicola* may have played a more decisive role in the resulting outcome since treatment to target *K. pneumoniae* failed to improve the patient’s condition. Moreover, this is consistent with the notion that *K. variicola* is a frequent cause of bloodstream infections and higher mortality[3,4].

It is difficult to distinguish *K. pneumoniae* and its subspecies by classic bacterial culture methods. This may lead to misdiagnosis or delayed diagnosis and incorrect treatment[4]. As shown in this case, *K. pneumoniae* was found in blood culture and although the clinical isolate was shown to be sensitive to the carbapenem class of antibiotics, the patient did not respond to treatment with meropenem. Similar to *K. pneumoniae*, drug-resistant plasmids in the bacterial structure of *K. variicola* contribute to its virulence and resistance, but the *K. variicola* has the higher-risk antibiotic resistance-related genes sequences, thus giving it higher virulence and resistance[10,11]. Recent clinical observations have shown that tigecycline and polymyxin display higher rates of treatment success in hypervirulent *Klebsiella* infection than other antibacterial drugs such as carbapenem[12]. Moreover, a combination of treatments is preferred to monotherapy in cases of severe infections[13,14]. Unfortunately, treatments to target *K. variicola* infection were not prescribed here because the patients’ illness rapidly progressed before genotyping.

---

**Table 3 Inflammatory parameters**

<table>
<thead>
<tr>
<th>Item</th>
<th>Result</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC ($\times 10^9$)</td>
<td>1.2</td>
<td>3.5-10</td>
</tr>
<tr>
<td>NEUT ($\times 10^9$)</td>
<td>0.63</td>
<td>1.8-6.3</td>
</tr>
<tr>
<td>%NEUT</td>
<td>52.5</td>
<td>40-75</td>
</tr>
<tr>
<td>MONO ($\times 10^9$)</td>
<td>0.05</td>
<td>0.1-0.6</td>
</tr>
<tr>
<td>%MONO</td>
<td>4.2</td>
<td>3-10</td>
</tr>
<tr>
<td>LYMBP ($\times 10^9$)</td>
<td>0.39</td>
<td>1.1-3.2</td>
</tr>
<tr>
<td>%LYMBP</td>
<td>32.5</td>
<td>20-50</td>
</tr>
<tr>
<td>RBC ($\times 10^12$)</td>
<td>1.83</td>
<td>3.5-5.5</td>
</tr>
<tr>
<td>HGB (g/L)</td>
<td>52.0</td>
<td>114-163</td>
</tr>
<tr>
<td>%HCT</td>
<td>15.6</td>
<td>35-50</td>
</tr>
<tr>
<td>PLT ($\times 10^9$)</td>
<td>10</td>
<td>125-350</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>230.33</td>
<td>0-5</td>
</tr>
<tr>
<td>PCT</td>
<td>&gt; 100</td>
<td>0-0.046</td>
</tr>
</tbody>
</table>
### Table 4 Results related to virus, mycobacteria, mycoplasma/chlamydia, and autoimmune disease

<table>
<thead>
<tr>
<th>Item</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV-IGM</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>ADV-IGM</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>IFZA-IGM</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>IFZB-IGM</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HPIVs-IGM</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>MP-IGM</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>CP-IGM</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>CBV-IGM</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>CAV-IGM</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>ECHO-IGM</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>LP-IGM</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>2019-nCoV</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>EB-DNA (copies/mL)</td>
<td>&lt; 5E + 2</td>
<td>&lt; 5E + 2</td>
</tr>
<tr>
<td>EB-DNA</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>CMV DNA DL (copies/mL)</td>
<td>&lt; 5E + 2</td>
<td>&lt; 5E + 2</td>
</tr>
<tr>
<td>CMV DNA DX</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>t1 Test method: Blotting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-PR3</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>A-MP0</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>A-GBM</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>t2 Test method: Fluorescence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cANCA</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>pANCA</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

After admission, blood samples were sent for assessment of infection by virus, mycobacteria, and mycoplasma/chlamydia along with changes in autoimmune disease markers.

results were available.

As well illustrated by our case, *K. pneumoniae* subspecies can be rapidly fatal although their presence may often be overlooked due to the limitations of routine clinical examinations. This case should raise awareness among clinicians to consider *Klebsiella* subspecies infections, especially in cases of unexplained fever or other suspicious clinical presentations that may indicate this condition. Moreover, this case highlights the need to introduce genetic techniques into current clinical practices, especially for the early diagnosis of severe infections.

### CONCLUSION

In summary, we have reported a patient dead with fatal infection caused by *K. variicola*. This fatal infection was identified by PMseq-DNA Pro high throughput gene detection assay. This case calls attention to *Klebsiella* subspecies infections and the need for early introduction of genetic technology in critically ill patients.
Long DL et al. Fatal sepsis caused by subspecies of *K. pneumonia*

### Table 5 Results of bacterial culture and drug sensitivity

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment</td>
<td>Phoenix100</td>
</tr>
<tr>
<td>Items</td>
<td>Bacterial culture + antimicrobial susceptibility</td>
</tr>
<tr>
<td>Results</td>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>MIC</th>
<th>Result interpretation</th>
<th>Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefotaxime</td>
<td>≤ 2</td>
<td>S</td>
<td>S ≤ 1; R ≥ 4</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>≤ 20</td>
<td>S</td>
<td>S ≤ 2/36; R ≥ 4/76</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>≤ 0.5</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>≤ 0.12</td>
<td>S</td>
<td>S ≤ 0.5; R ≥ 2</td>
</tr>
<tr>
<td>Amikacin</td>
<td>≤ 2</td>
<td>S</td>
<td>S ≤ 16; R ≥ 64</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤ 0.25</td>
<td>S</td>
<td>S ≤ 1; R ≥ 4</td>
</tr>
<tr>
<td>Er ertapenem</td>
<td>≤ 0.12</td>
<td>S</td>
<td>S ≤ 0.5; R ≥ 2</td>
</tr>
<tr>
<td>Cefepime</td>
<td>≤ 0.12</td>
<td>S</td>
<td>S ≤ 2; R ≥ 16</td>
</tr>
<tr>
<td>Ce foperazone/sulbactam</td>
<td>≤ 8</td>
<td>S</td>
<td>S ≤ 16; R ≥ 64</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>≤ 0.25</td>
<td>S</td>
<td>S ≤ 1; R ≥ 4</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>≤ 0.12</td>
<td>S</td>
<td>S ≤ 4; R ≥ 16</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>≤ 4</td>
<td>S</td>
<td>S ≤ 8; R ≥ 32</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>4</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>4</td>
<td>S</td>
<td>S ≤ 4; R ≥ 32</td>
</tr>
<tr>
<td>Piperacillin/tatabatam</td>
<td>≤ 4</td>
<td>S</td>
<td>S ≤ 16/4; R ≥ 128/4</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>≤ 2</td>
<td>S</td>
<td>S ≤ 8/4; R ≥ 32/16</td>
</tr>
<tr>
<td>ESBL</td>
<td>Neg</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

A blood sample was collected and examined following the standards of bacterial culture. The results of bacterial growth and antimicrobial susceptibility were acquired 24 h later.

### Table 6 PMseq-DNA Pro high throughput gene detection of blood sample

<table>
<thead>
<tr>
<th>Type</th>
<th>Genus (number of sequences)</th>
<th>Species (number of sequences)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td><em>Klebsiella</em> 68405</td>
<td><em>Klebsiella pneumoniae</em> 243747</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Klebsiella variicola</em> 543</td>
</tr>
</tbody>
</table>

### ACKNOWLEDGEMENTS

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### FOOTNOTES

**Author contributions**: Long DL and Wang YH completed the collection of clinical data; Wang JL, Mu SJ, Chen L, and Shi XQ contributed to the compilation of data and production of charts; Li JQ analyzed all data and wrote the manuscript.

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**Informed consent statement**: Written informed consent was obtained from the patient’s daughter for publication of this case report and any accompanying images.
Fatal sepsis caused by subspecies of K. pneumoniae

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Country/Territory of origin: China

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S-Editor: Yan JP
L-Editor: Wang TQ
P-Editor: Yan JP

REFERENCES


CASE REPORT

Endoscopic extraction of a submucosal esophageal foreign body piercing into the thoracic aorta: A case report

Zhi-Cao Chen, Gui-Quan Chen, Xiao-Chun Chen, Chang-Ye Zheng, Wei-Dong Cao, Gang-Hao Deng

BACKGROUND

Aorto-esophageal injury is a rare but life-threatening complication of esophageal foreign bodies, which typically requires open surgery. The best way to treat patients with this condition remains unclear. To date, few reports have described an aortic wall directly penetrated by a sharp foreign body. Here, we present a rare case of a fishbone completely embedded in the esophageal muscularis propria and directly piercing the aorta, which was successfully treated by endoscopy and thoracic endovascular aortic repair (TEVAR).

CASE SUMMARY

We report the case of a 71-year-old man with a 1-d history of retrosternal pain after eating fish. No abnormal findings were observed by the emergency esophagoscopy. Computed tomography showed a fishbone that had completely pierced through the esophageal mucosa and into the aorta. The patient refused to undergo surgery for personal reasons and was discharged. Five days after the onset of illness, he was readmitted to our hospital. Endoscopy examination showed a nodule with a smooth surface in the middle of the esophagus. Endoscopic ultrasonography confirmed a fishbone under the nodule. After performing TEVAR, we incised the esophageal mucosa under an endoscope and successfully removed the fishbone. The patient has remained in good condition for 1 year.

CONCLUSION

Incising the esophageal wall under endoscope and extracting a foreign body after TEVAR may be a feasible option for cases such as ours.

Abstract

Aorto-esophageal injury is a rare but life-threatening complication of esophageal foreign bodies, which typically requires open surgery. The best way to treat patients with this condition remains unclear. To date, few reports have described an aortic wall directly penetrated by a sharp foreign body. Here, we present a rare case of a fishbone completely embedded in the esophageal muscularis propria and directly piercing the aorta, which was successfully treated by endoscopy and thoracic endovascular aortic repair (TEVAR).

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

P-Reviewer: Cabezuelo AS, Okasha HH

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Revised: November 17, 2021
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Article in press: January 27, 2022
Published online: March 16, 2022
Key Words: Endoscopy; Esophageal foreign body; Esophageal perforation; Aortic penetration; Case report

Core Tip: Aorto-esophageal injury is a rare but life-threatening complication of esophageal foreign bodies, which typically requires open surgery. The best way to treat patients with this condition remains unclear. To date, few reports have described an aortic wall directly penetrated by a sharp foreign body. Here, we present a rare case of a fishbone completely embedded in the esophageal muscularis propria and directly piercing the aorta, which was successfully treated by endoscopy and thoracic endovascular aortic repair.

INTRODUCTION
Esophageal foreign body (EFB) is a common clinical emergency. In the United States, more than 100,000 cases of esophageal foreign bodies occur each year[1]. Because of diet habits, animal bones (such as fish bones, poultry bones, etc.) are among the most commonly encountered foreign bodies in China, and most occur in people over 50 years of age[2]. Aorto-esophageal injury is a rare but life-threatening complication of EFB, which typically requires open surgery[3-6]. The best way to treat patients with this condition remains unclear. To date, there have been few reports of a sharp foreign body in the esophagus penetrating the thoracic aorta[7-16], possibly because this type of injury is extremely rare, and most patients do not receive timely treatment.

Here, we present a case of patient in who a fishbone had completely pierced through the esophageal mucosa and into the aorta; the EFB was successfully extracted by means of endoscopy combined with thoracic endovascular aorta repair (TEVAR).

CASE PRESENTATION
Chief complaints
A 71-year-old man presented to our hospital on October 12, 2020, with a 1-d history of retrosternal pain after eating fish.

History of present illness
The patient did not have fever, dysphagia, hematemesis, hematochezia, melena, or other symptoms.

History of past illness
The patient had no previous medical history.

Personal and family history
The patient had a free personal and family history.

Physical examination
On physical examination, there were no abnormal findings.

Laboratory examinations
Blood tests showed no obvious abnormalities.

Imaging examinations
Emergency thoracic computed tomography (CT) (Figure 1A) revealed a high-density shadow of an EFB (highly suspected to be a fishbone) in the middle thoracic section of the esophagus (eighth thoracic vertebra) involving the wall of the thoracic aorta. The patient was admitted to the department of Ear, Nose, and Throat, and no abnormalities were observed in the esophagus after a careful esophagoscopy examination.
On October 13, 2020, enhanced CT angiography (Figure 1B) revealed that an EFB had directly penetrated the thoracic aorta.

MULTIDISCIPLINARY EXPERT CONSULTATION

Based on previous reports and our experience, our initial plan was to perform TEVAR and then consult with a multidisciplinary team for the next steps. Prior to any treatment, we fully informed the patient of the risk of surgery. It is common for patients and their families to feel hesitant and inquire about alternative treatment options, including by consult with other hospitals. Our patient wished to do such, and was discharged in accordance on October 13, 2020. The other hospital he attended provided an open surgery plan, which the patient chose not to accept. Ultimately, the patient chose to be re-admitted to our hospital, which occurred on October 17, 2020. At that time, we carried out the multidisciplinary team discussion, which led to the choice of a minimally invasive protocol to remove the foreign body using an endoscope after the placement of a thoracic aortic stent.

FINAL DIAGNOSIS

EFB penetrating the thoracic aorta.

TREATMENT

On October 18, 2020, we successfully performed TEVAR (Figure 1C) with placement of an aortic stent.
causing damage to the artery. To accurately locate the fishbone, we performed endoscopic ultrasonography (Figure 2B) after successfully repairing the thoracic aorta with a graft-stent. CT results showed that the fishbone had not injured the aorta, as in our case.

The length of the fishbone was approximately 22 mm (Figure 2F), and there was no breakage. There was also no obvious pus or bleeding at the excision location. As such, the wound was carefully and thoroughly irrigated and then loosely sealed with hemostatic clips. A gastric tube was placed for postoperative drainage, and the patient was continued on antibiotics for the postoperative recovery period. Immediate-postoperative CT scan showed no sign of EFB in the esophagus and mediastinum or aorta, serving as confirmation of successful removal of the fishbone (Figure 3A).

On November 2, 2020, the patient was re-examined with a gastroscope, which showed that the wounds had healed well (Figure 3B), and the gastric tube was removed.

OUTCOME AND FOLLOW-UP
Currently, it has been 1 year since the procedure, and the patient remains in good condition.

DISCUSSION
Aorto-esophageal injury is a rare but life-threatening complication of EFB, which typically requires open surgery. The invasiveness and high cost of that treatment, however, are remarkable determinants. At the same time, the complication rate of EFB removal and secondary outcome/injury increases with the increase of retention time[17,18]. Indeed, the mortality rate can reach 40%–60% if aorto-esophageal fistula arises[19] and such cases need to be treated as soon as possible. With the development of technology, there have been reports of successful minimally invasive treatment of similar patients in recent years. Hanif et al[13] reported a case of a 63-year-old man with a 2.7 cm-long chicken bone penetrating the esophageal wall and transversing into the aorta; treatment via an endoscopic approach with simultaneous endovascular stent-graft repair of the aorta was successful. Choi et al[10] reported a case of a 31-year-old man with a fishbone-induced aortic rupture that was successfully treated with an endovascular stent-graft, with the patient remaining in good condition at the 7-mo follow-up. Xi et al[15] reported a case of a sharp foreign object-induced aortic rupture with mediastinitis and pseudoaneurysm, which was successfully treated by exploratory thoracotomy after endovascular stent-graft repair. Zeng et al[8] reported a case similar to ours, in which a foreign body had lodged in the esophagus and caused a consequent aortic rupture; that case was successfully treated by endovascular stent-graft repair and endoscopic procedure. Ruan et al[20] summarized their experience of 12 patients with EFB combined with aortic injury, 11 of which were successfully removed after TEVAR. These reports highlight that when EFB combined with aortic injury has occurred, it has been safe to remove the EFB after TEVAR.

It is also rare that an EFB is embedded in the wall of the esophagus. Wang et al[21] had reported such a case and they extracted the fishbone using the endoscopic submucosal dissection method; however, the fishbone had not injured the aorta, as in our case.

Our case was unique, with the combination of an EFB embedded in the esophageal wall and causing aortic injury, which increased the difficulty and risk of extraction by standard means of an endoscope. We speculate that the reason why we did not see the fishbone during our initial esophagoscopy is that most fishbones puncturing the esophagus do not transverse it or subsequently puncture other organs, and the foreign body itself was relatively small. The nodules observed by the gastroscope may have resulted from the fishbone being ejected from a blood vessel after the indwelling aortic stent was placed, ultimately bouncing back to the esophageal wall. Consequent local inflammation would have resulted in tissue edema and formed a nodule after 5 d. In multidisciplinary discussions, we established the following four goals: prevention of hemorrhaging, removal of the EFB (suspected fishbone), repair of wounds, and control of infection. The safety of removing the EFB (fishbone) by endoscopy increased after successfully repairing the thoracic aorta with a graft-stent. CT results showed that the fishbone had been pushing outside the lumen of the aorta, which increased our confidence in removing it without causing damage to the artery. To accurately locate the fishbone, we performed endoscopic ultrasono-

(XJZDZ30200; Ankura, Lifetech Scientific Corporation, Shenzhen, China). CT angiography (Figure 1D) after the TEVAR showed that the EFB (suspected fishbone) was pressed against the edge of the blood vessel.

On October 21, 2020, an endoscopic examination (Figure 2A) was performed and a nodule was identified that was about 31 cm away from the incisors, 1.0 cm × 0.8 cm in size and hard, with a fixed position and smooth surface. Endoscopic ultrasonography (Figure 2B) was immediately performed with a 12-MHz probe, revealing a “bone-like image” protruding beyond the muscularis propria under the nodule. Subsequently, endoscopic foreign body removal was performed (Figure 2C–2E) with CO2 gas. First, the nodule was punctured with an injection needle; a small amount of yellow and white pus could be seen. After injection of sodium hyaluronate diluent into the mucous membrane of the superior side, a dual knife and IT knife were used to incise the nodule along the center and the inferior side to the deep part of the esophageal muscularis. The head end of the fishbone (approximately 1.5 mm in length) was found on the distal side of the nodule, and it was pulled out smoothly by use of biopsy forceps.

The length of the fishbone was approximately 22 mm (Figure 2F), and there was no breakage. There was also no obvious pus or bleeding at the excision location. As such, the wound was carefully and thoroughly irrigated and then loosely sealed with hemostatic clips. A gastric tube was placed for postoperative drainage, and the patient was continued on antibiotics for the postoperative recovery period. Immediate-postoperative CT scan showed no sign of EFB in the esophagus and mediastinum or aorta, serving as confirmation of successful removal of the fishbone (Figure 3A).

On November 2, 2020, the patient was re-examined with a gastroscope, which showed that the wounds had healed well (Figure 3B), and the gastric tube was removed.
Figure 2 Images of endoscopy operation. A: Endoscopic examination was performed on October 21, 2020, and a bulge was identified; B: Endoscopic ultrasonography showed a strong echo light cluster protruding beyond the muscularis propria under the bulge; C: The nodule was incised with a dual knife and IT knife to the deep part of the esophageal muscularis; D: A suspicious fishbone with a length of about 1.5 mm was found on the distal side of the nodule; E: The fishbone was pulled out with biopsy forceps; F: The total length of the fishbone was approximately 22 mm.

Figure 3 Images of re-examined computed tomography after the procedure and gastroscope before discharge. A: Computed tomography scan after the procedure show no foreign body in the esophagus and Mediastinum or aorta, which confirmed that we successfully removed the fish bone; B: Re-examined gastroscope before discharge showed that the wounds had healed well.

After removal of the fishbone, preventing infection was the next challenge. To prevent further infection after the surgery, we administered imipenem (1 g intravenous drip twice a day for 10 d) for anti-infection treatment. The patient was discharged on November 2, 2020 and remains in good health.
condition as of the writing of this case report (1 year after the procedure).

There are some limitations to our report that should be considered before applying this knowledge to other cases. In principle, EFBs should be treated urgently (recommended: ≤ 24 h), because the longer duration of presence, the higher the incidence of complications[17,18]. The fishbone in our patient had been retained for 5 d without manifestation of other serious complications, which may have been due to its very small size and the timely application of antibiotics. However, it is still unclear whether the location, shape and size of any foreign body will affect the success rate of TEVAR.

CONCLUSION

In conclusion, aortic injury caused by an EFB can be life-threatening. In rare conditions, the EFB will be embedded in the esophageal wall and pierce into the aorta. Our case suggested that incising the esophageal wall and extracting the foreign body after TEVAR may be a feasible option for this kind of EFB. But, the appropriate timing of the procedure and whether the size and location of foreign bodies in the esophagus affect successful treatment remain unclear.

FOOTNOTES

Author contributions: Chen GQ designed the report and performed the endoscopic surgery; Chen XC collected the patient’s clinical data; Chen ZC analyzed the data and wrote the paper; Zheng CY performed the CT imaging analysis; Cao WD and Deng GH performed the TEVAR surgery.

Informed consent statement: Informed consent was obtained from the patient for publication of this case report and any accompanying images.

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REFERENCES


Severe tinnitus and migraine headache in a 37-year-old woman treated with trastuzumab for breast cancer: A case report

Yong-Zhi Liu, Hai Jiang, Yong-Hua Zhao, Qi Zhang, Shi-Chao Hao, Li-Ping Bao, Wei Wu, Zhao-Bo Jia, Hui-Chuan Jiang

Abstract

BACKGROUND
Trastuzumab is a generally safe agent prescribed in the systemic treatment of breast cancer. Tinnitus is not a currently known adverse event related to trastuzumab. Here, we describe a rare case of severe tinnitus and a migraine headache induced by trastuzumab used for adjuvant therapy.

CASE SUMMARY
A 37-year-old woman was diagnosed with hormone receptor-positive and human epidermal growth factor receptor 2-positive breast cancer. After surgery, she was treated with four cycles of epirubicin and cyclophosphamide; she then received docetaxel and a loading dose of trastuzumab plus pertuzumab. Less than half an hour after trastuzumab infusion, the patient complained of severe tinnitus and left-sided migraine headache. Trastuzumab monotherapy was discontinued immediately, and symptoms disappeared after 10 min. Trastuzumab was readministered, and severe tinnitus and migraine headache recurred. Trastuzumab was stopped, and severe tinnitus diminished after 10 min. Pertuzumab and docetaxel therapy was then administered, and no adverse events were observed. Subsequent infusions of trastuzumab every three weeks did not show the same symptoms.

CONCLUSION
Although trastuzumab is well-tolerated in most patients, we should pay attention to the risk of severe tinnitus and migraine.

Key Words: Breast cancer; Tinnitus; Adverse effects; Trastuzumab; Migraine headache; Case report
Core Tip: Trastuzumab is an important treatment for human epidermal growth factor receptor 2-positive breast cancer and is generally well-tolerated, although both acute and subacute adverse events have been reported. Here, we report a rare case of severe tinnitus and migraine induced by trastuzumab used for adjuvant therapy which may help guide future clinical treatment.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i8.2491

INTRODUCTION
Trastuzumab (Herceptin®) is a humanized monoclonal antibody against the extracellular domain of human epidermal growth factor receptor (HER2) protein and is the first HER2-targeted therapy approved for the treatment of HER2-positive breast cancer[1]. Trastuzumab is generally a well-tolerated drug, although both acute and subacute adverse events such as flu-like syndrome and cardiotoxicity have been observed[2]. Tinnitus has not previously been reported as an adverse event related to trastuzumab. Here, we report a rare case of severe tinnitus and migraine induced by trastuzumab during the first cycle of adjuvant therapy.

CASE PRESENTATION

Chief complaints
A 37-year-old Chinese woman was diagnosed as hormone receptor-positive and HER2-positive infiltrating duct carcinoma in her left breast.

History of present illness
The patient felt a painless lump in the left breast during a physical examination. After several examinations, she underwent breast-conserving surgery, and sentinel lymph node biopsy was resultingly found to be 1/4 positive.

History of past illness
The patient’s prior medical history was unremarkable. The patient did not demonstrate any history of drug allergies and had no history of ear, nose, and throat (ENT), migraine or other central nervous system diseases.

Personal and family history
The patient gave birth at the age of 25 and breastfed her infant. She experienced regular menstrual cycles and had no family history of cancer.

Physical examination
A physical examination of the patient revealed a 1.0 cm × 1.0 cm non-tender mass in the upper outer quadrant of the left breast. Her physical examination confirmed no signs of ENT diseases, central nervous system diseases or cerebral metastasis. And she had a body mass index (BMI) of 30.4.

Laboratory examinations
Laboratory examinations (routine blood analysis, liver biochemical analysis, renal function, tumor markers, etc.) were normal.

Imaging examinations
The patient’s lungs, bones and liver were normal. Imaging examination did not demonstrate any evidence of distant metastases. A cerebral magnetic resonance imaging scan revealed no sign of intracranial or skeletal cranial metastases or any vascular disorders (Figure 1).
Liu YZ et al. Severe tinnitus and migraine headache

Figure 1 Brain magnetic resonance images of the patient. A: Axial view of T1-weighted image shows no brain dysplasia, encephalomalacia or abnormal white matter signal; B: Diffusion-weighted image shows no abnormal signals; C: T2-weighted scan shows that the bilateral internal auditory canal, cochlear, auditory and cranial nerve have no abnormal signals.

FINAL DIAGNOSIS

The final diagnosis of the presented case was primary breast cancer at stage IIB (pT2N1M0). The tumor was estrogen- and progesterone-receptor-positive and HER2-positive. Fluorescent in-situ hybridization revealed HER2 amplification in the patient.

TREATMENT

After surgery, a standard dose regimen of adjuvant chemotherapy and targeted therapy was initiated. This therapy consisted of four cycles of epirubicin (90 mg/m$^2$) and cyclophosphamide (600 mg/m$^2$) administration every three weeks followed by four cycles of docetaxel (100 mg/m$^2$) administration in combination with trastuzumab (8 mg/kg and 6 mg/kg) plus pertuzumab (840 mg and 420 mg) every three weeks. We planned to follow the treatment regimen consisting of trastuzumab plus pertuzumab for one year.

The premedication agent (dexamethasone; 8 mg every 12 h for three doses beginning 12 h before administration of docetaxel) was administered before docetaxel to decrease the occurrences of anaphylactic reactions (ARs). Because ARs have been frequently reported with taxanes, drug administration occurred in the order of trastuzumab, pertuzumab and docetaxel.

During the first cycle of targeted therapy, the patient received 468 mg of trastuzumab monotherapy at a rate of 3 mg/min. Approximately 30 min after the administration of 90 mg of trastuzumab, the patient complained of severe tinnitus and left-sided migraine headache. The infusion of trastuzumab monotherapy was discontinued immediately, and the symptoms disappeared after 10 min. After resolution of severe tinnitus and migraine, the patient was administered trastuzumab for the second time. However, 20 min following trastuzumab re-administration, severe tinnitus and migraine headache again developed, and trastuzumab was therefore stopped. Steroid therapy was successfully used to combat these reactions. Both severe tinnitus and migraine headache diminished after 10 min. The patient’s vital signs were carefully monitored during drug administration, and body temperature, pulse rate, respiratory rate, and blood pressure were normal. Subsequent investigation revealed that the white blood cell count, hemoglobin level, and platelet count as well as the liver and renal functions were also normal. There were no signs of a rash. Other causes of tinnitus were excluded by consultation with an otolaryngologist and a neurosurgeon, and the possibility that the headache could be attributed to a disorder of the ears was also ruled out. External auditory canal was eumorphic, and the ear drum membrane was in keeping with physiological obliquity. The patient’s limbs were not swollen, and she maintained free movement of all four limbs with normal muscle force and strength. No pathological reflection of Babinski’s sign was induced. There was no evidence of acute stroke, intracranial hemorrhage, or hydrocephalus.

Multidisciplinary team members carefully assessed, communicated and informed the patient of appropriate treatment benefit and risk. Subsequently, pertuzumab (840 mg) and docetaxel (100 mg/kg) therapy was initiated, and no adverse events were observed. The patient’s symptoms were not likely a result of bacterial contamination, as the residual liquid bacteria culture was negative. Therefore, the severe tinnitus and migraine headache were significantly associated with trastuzumab rather than with pertuzumab or docetaxel.
OUTCOME AND FOLLOW-UP

Given the HER2-positive nature of the patient’s cancer and the clinical course, administration of trastuzumab retreatment was attempted 21 d later. She received subsequent infusions of trastuzumab every three weeks afterward, and none of the previous adverse reactions recurred.

DISCUSSION

Trastuzumab is a monoclonal antibody used as a standard treatment for breast cancer when the cancer cells overexpress HER2. Trastuzumab is typically well-tolerated; chills, flu-like symptoms, fever, nausea, skin rash, and cardiac toxicity are the most commonly reported adverse effects, and, less frequently, severe thrombocytopenia, hepatotoxicity, and systemic capillary leak syndrome have been described by some studies[3-5].

Here, we describe a case of severe tinnitus and migraine headache induced by trastuzumab. The symptoms recurred on two occasions during trastuzumab usage and re-administration when the patient received her first cycle treatment of trastuzumab. Our case shows, for the first time, that severe tinnitus and migraine headache can be simultaneously induced by trastuzumab infusion. The first case of trastuzumab-related strictly unilateral headache was reported in 2003: a 59-year-old patient experienced severe headache, back pain, fatigue, and a decrease in blood pressure after trastuzumab administration [6]. The second case of trastuzumab-induced throbbing headache was reported in 2009[7]. A 31-year-old woman experienced a very strictly unilateral headache with photophobia, nausea, and vomiting following infusion of trastuzumab. The authors stated that the nature of the migraine headache was not entirely understood[7]. Subsequently, other reports discussed the theory that monoclonal antibodies such as trastuzumab could possibly induce aseptic meningitis, which seemed to be part of an infusion-related reaction or immune-mediated hypersensitivity phenomenon[8,9].

Tinnitus is a subjective complaint defined as a sound in the head or ears that occurs in the absence of any external acoustical source. Studies report tinnitus prevalence ranging from 5.1%-42.7% by different age groups and generally showing an increase in prevalence as age increases. Young adults with migraines are more likely to suffer from tinnitus[10]. There is limited knowledge of direct biological links between migraine and tinnitus. One cross-sectional study showed that headache was associated with tinnitus, and the association was stronger for individuals reporting migraine with aura[11]. Ear injuries, central sensitization, and visual snow can cause tinnitus and may be related to the occurrence of migraines[12,13]. Migraine, tinnitus, anxiety and depression are prevalently comorbid disorders and have been frequently reported in patients with visual snow. Visual snow may start during or shortly after migran aura. One theory suggests that there is a bidirectional relationship among depression, visual snow and migraine[14]. But in this case, the young patient did not have any past histories and clinical symptoms in the later following-up.

Studies suggest that ototoxicity is a possible adverse effect during treatment with taxanes[15]. Although Sarafraz and Ahmadi[16] did not observe tinnitus or hearing loss as the significant side-effects of taxanes, Xuan et al[17] presented two cases of ototoxicity caused by docetaxel-based chemotherapy regimens and speculated that docetaxel may result in degeneration of nerve fibers through disrupted axon transportation. They also suggest that clinicians note the adverse effect on the audiovestibular system caused by neurotoxic chemotherapy[17].

Immunolabeling patterns of HER2 have been described in the utricle and cochlea of rat P3 cultures [18]. Zhang et al[19] showed the pattern of HER2 Labeling in the utricle, saccule, organ of Corti, lateral wall, and spiral ganglion region of adult chinchillas. Whether the severe tinnitus and headache associated with the use of trastuzumab are related to the overexpression of HER2 in the human inner ear remains unclear.

To our knowledge, severe tinnitus and migraine headache with single-agent trastuzumab use are so rare that they had not yet been reported as adverse events in the existing literature. This case therefore has some limitations because only a single case has been reported so far, but more cases may be reported in the future. Because of the widespread use of this drug, we should pay more attention to its adverse reactions, especially because more serious complications may be prevented when adverse events are detected early. Because other patients may experience tinnitus induced by trastuzumab infusion, it is necessary to inform them of the potential adverse events before the use of trastuzumab; these events can also be specified in the drug instructions. The severe tinnitus and migraine headache induced by trastuzumab are noteworthy, and further studies are needed to evaluate whether targeted therapy treatment strategies affect migraine and tinnitus and to determine the mechanisms associated with the symptoms.
CONCLUSION

In conclusion, although trastuzumab is widely used and well-tolerated in most patients, we still should pay attention to the risk of severe tinnitus and migraine induced by trastuzumab. This case report serves as a reminder to be aware of adverse reactions of the breast cancer drugs.

ACKNOWLEDGEMENTS

We thank the patient, her family, and the personnel involved in the treatment of this case.

FOOTNOTES

Author contributions: Liu YZ made contribution to treating the patient, collecting data and writing the article; Jiang H, Zhao YH, Zhang Q, Hao SC, Bao LP, Wu W, Jia ZB, Jiang HC made contribution to treating the patient.

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

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

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Metastatic urothelial carcinoma harboring $ERBB2/3$ mutations dramatically respond to chemotherapy plus anti-PD-1 antibody: A case report

Fei-Fei Yan, Qi Jiang, Xiao-Jie Fei, Jian Ruan, Xiao-Chen Zhang

**Abstract**

**BACKGROUND**

Immune checkpoint inhibitors (ICIs) targeting the programmed death (PD)-1 pathway have substantially changed the clinical management of metastatic urothelial carcinoma (mUC); however, the response rate remains low. There are ongoing efforts to identify robust biomarkers that can effectively predict the treatment response to ICIs. Previous studies have suggested that $ERBB2/3$ mutations are associated with the efficacy of ICIs in gallbladder carcinoma.

**CASE SUMMARY**

We present a 59-year-old man with mUC harboring $ERBB2/3$ mutations (in-frame insertion of $ERBB2$ and $ERBB3$ amplification), negative PD-ligand 1 expression, and low tumor mutation burden. He received anti-PD-1 antibodies and paclitaxel as second-line treatment. After two cycles of treatment, the lung metastases had significantly shrunk, achieving good partial remission. After six cycles of combination therapy, the patient received sindilimab 200 mg once every 3 wk as maintenance monotherapy. At the last follow-up, the patient continued to exhibit a partial response and progression-free survival for as long as 19 mo.
CONCLUSION

ERBB2/3 mutations may represent a predictive biomarker for selecting a subgroup of mUC patients who will benefit from ICIs.

Key Words: Urothelial carcinoma; Bladder cancer; ERBB; Programmed death; Sindilimab; Case report

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INTRODUCTION

Bladder cancer is considered to be one of the most aggressive neoplasms worldwide[1]. For patients with distant metastases, the 5-year survival rate is as low as approximately 5%[2]. Cisplatin based combination regimens have remained the standard first-line treatment for metastatic urothelial carcinoma (mUC) over the past decade. In the past, following the failure of first-line chemotherapy, paclitaxel, docetaxel, ifosfamide or gemcitabine monotherapy have been the most commonly used drugs, but are associated with low efficacy.

Several immune checkpoint inhibitors (ICIs) have been approved in recent years as first-line treatment for patients who ineligible to cisplatin or as second-line treatment for patients with mUC of the bladder. Despite the success of immune checkpoint blockades as a strategy for activating an antitumor immune response and promoting cancer regression, only a subset of patients experienced a durable clinical benefit. However, low objective response rates (13%-31%) have been observed in mUC[3-5].

The level of programmed death (PD)-1 expression and tumor mutation burden (TMB) are the two most commonly used predictive biomarkers but they are not sufficient[6-9]. Therefore, there is an urgent need to identify biomarkers that can predict patient response or resistance to ICIs. Several clinical trials have attempted to identify robust biomarkers that can effectively predict the treatment response to ICIs in a subgroup analysis, including high levels of microsatellite instability (MSI-H), a mismatch repair deficiency (dMMR)[10], or tumor infiltrating cytotoxic T lymphocytes (TILs)[11,12]. It is suggested that ERBB2/3 mutations are associated with the efficacy of ICIs[13].

Here, we report a case of mUC harboring ERBB2/3 mutations, in which the level of PD-1 expression was negative and TMB was 3.4/Mb, demonstrating a durable response to anti-PD-1 antibodies in combination with chemotherapy as second-line therapy.

CASE PRESENTATION

Chief complaints

A 59-year-old man presented to our department complaining of bloody sputum for 2 wk on March 2020. He was diagnosed with urothelial cancer > 13 years ago.

History of present illness

In May 2006, the patient presented with intermittent hematuria for 6 mo. On June 18, 2006, he received transurethral resection of bladder tumor in a local hospital, and immunohistochemistry revealed invasive UC (grade 3). Due to repeated local recurrence, the patient underwent repeated (10 times) transurethral resection of bladder tumor from June 2006 to July 2017. On July 5, 2017, the patients received laparoscopic total cystectomy and ileal neobladder. Postoperative pathology showed high-
grade papillary UC (WHO grade III) with muscularis invasion (rpT2N0M0, stage II). Pathology confirmed that the surgical margin was negative. In July 2018, the patient presented to a local hospital because of intermittent hematuria for 1 mo. Cystoscopy showed urethral neoplasm. Resection biopsy of the neoplasm confirmed high-grade papillary UC (WHO grade III). The TNM stage was rT1N0M1 stage IV. The patient received six cycles of gemcitabine and cisplatin (GP) as first-line chemotherapy from July 7, 2018 to January 19, 2019. In March 2020, the patient presented to our department complaining of bloody sputum for 2 wk.

**History of past illness**
In May 2006, the patient presented with intermittent hematuria for 6 mo. On June 18, 2006, he received transurethral resection of bladder tumor in local hospital, and the immunohistochemistry results revealed invasive urothelial cancer (grade 3). Due to repeated local recurrence, the patient received repeated (10 times) of transurethral resection of bladder tumor from June 2006 to July 2017. On July 5, 2017, the patients received laparoscopic total cystectomy and ileal neobladder, the postoperative pathology showed high-grade papillary urothelial carcinoma (WHO grade III) with muscularis invasion (rpT1N0M0, stage II). Pathology confirmed that the surgical margin was negative. In July 2018, the patient presented to local hospital for intermittent hematuria for 1 mo. The cystoscope showed neoplasm on urethra. The resection biopsy of the neoplasm confirmed high-grade papillary urothelial carcinoma (WHO grade III). The TNM stage was rT0N0M1 stage IV. The patient received six cycles of GP (gemcitabine and cisplatin) as first-line chemotherapy from July 7, 2018 to January 19, 2019. On March 2020, the patient presented at our department complaining of bloody sputum for half a month.

**Personal and family history**
The patient’s previous medical history was hypertension, without a family history of cancer.

**Physical examination**
The Eastern Cooperative Oncology Group score was 0 to 1, and the numeric pain intensity scale score was 0. There was an old surgical scar of about 11 cm in the lower abdomen.

**Laboratory examinations**
Routine blood examination, blood biochemistry and urinalysis were normal. Serum tumor markers including -fetoprotein, carcinoembryonic antigen, cancer antigen (CA)125, CA 19-9, and ferritin were routinely monitored, and all were normal.

**Imaging examinations**
Electrocardiography was normal. Chest computed tomography (CT) showed multiple lung metastases ([Figure 1A](#)). Enhanced abdominal CT showed postoperative changes of bladder cancer. Next-generation sequencing (NGS) showed PD-ligand 1 (PD-L1) < 1%, TMB 3.4/Mb, in-frame insertion of ERBB2 [c.2313-2323dup ATACGTAGTGGC (p.Y772-A775dup), 21.6%] and ERBB3 amplification (2.5 times).

**FINAL DIAGNOSIS**
mUC (cT0N0M1, stage IV).

**TREATMENT**
The patient refused CT-guided percutaneous lung biopsy. Since March 19, 2020, the patient received six cycles of paclitaxel 300 mg plus sindilimab 200 mg once every 3 wk as second-line therapy and subsequently received sindilimab 200 mg once every 3 wk as maintenance treatment.

**OUTCOME AND FOLLOW-UP**
After two cycles of treatment, chest CT revealed that the lung metastases were markedly reduced in size ([Figure 1C and D](#)). After six cycles, chest CT revealed further reduction of the lung metastases ([Figure 1E and F](#)). The patient received review irregularly in a local hospital or in our central hospital. At the time of the last follow-up on July 5, 2021, the patient exhibited a durable partial response ([Figure 1G and H](#)) and progression-free survival (PFS) was 19 mo. No obvious side effects were observed and the patient was satisfied with the treatment.
DISCUSSION

ICls have revolutionized the treatment of a range of solid tumors, including lung cancer, melanoma, esophageal cancer, and colorectal cancer with MSI-H for their durable clinical benefit and lower toxic effects[14,15]. Since 2016, US Food and Drug Administration has approved five ICls (atezolizumab, nivolumab, pembrolizumab, avelumab and durvalumab) the for the treatment of mUC (Table 1). Although ICls are effective at treating metastatic urothelial bladder cancer, only a small proportion of patients receive a definite benefit. Currently, no single biomarker can clearly predict treatment response. To better predict the patients who are the mostly likely to benefit from ICls, several ongoing trials have been conducted to identify effective biomarkers. With the wide application of NGS, an increasing number of new biomarkers are being discovered.

The epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases consists of four members: EGFR1/ERBB1/HER1, ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4[16]. Signaling through these receptors regulates many key cellular activities, including cell division, migration, adhesion, differentiation and apoptosis[17]. ERBB2/3 mutations (including point mutations and amplification) are observed in many types of solid tumors (e.g., breast cancer, gastric cancer, lung cancer and UC). An ERBB2 in-frame insertion into exon 20 has been associated with tyrosine kinase inhibitor resistance in lung adenocarcinoma[18]. Moreover, ERBB3 overexpression has been associated with resistance to a large number of therapies in some cancers[19,20]. ERBB2/3 mutations are associated with the treatment efficacy of PD-L1 monoclonal antibodies for gallbladder carcinoma[13]. ICI monotherapy after the failure of first-line treatment is another reason for the low response rate associated with ICls.
May 18, 2017: As second-line monotherapy for patients with locally advanced or metastatic UC who have disease progression within 12 mo of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Initial approval April 2017 and modified June 19, 2018 (restricted to PD-L1+): as first-line monotherapy for patients with locally advanced or metastatic UC (who: 1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells covering ≥ 5% of the tumor area), as determined by an FDA-approved test, or 2) are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

May 1, 2017: As second-line monotherapy for patients with locally advanced or metastatic UC whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

June 30, 2020: As maintenance treatment for patients with locally advanced or metastatic UC that has not progressed with first-line platinum-containing chemotherapy.

May 1, 2017: As second-line monotherapy for patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 mo of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

NCT01693562

Table 1 United States Food and Drug Administration approval of immune checkpoint inhibitors in urothelial carcinoma

<table>
<thead>
<tr>
<th>Anti-PD-L1 antibodies</th>
<th>Approvals of FDA</th>
<th>Clinical trials</th>
</tr>
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<tbody>
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<td><strong>US FDA approval of anti-PD-L1 antibodies in UC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>May 18, 2016: As second-line monotherapy for patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 mo of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.</td>
<td>IMvigor 210</td>
</tr>
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<td></td>
<td>Initial approval April 2017 and modified June 19, 2018 (restricted to PD-L1+): as first-line monotherapy for patients with locally advanced or metastatic UC (who: 1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells covering ≥ 5% of the tumor area), as determined by an FDA-approved test, or 2) are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.</td>
<td>IMvigor 210, IMvigor130</td>
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<tr>
<td>Avelumab</td>
<td>May 9, 2017: As second-line monotherapy for patients with locally advanced or metastatic UC whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.</td>
<td>JAVELIN11b</td>
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<tr>
<td></td>
<td>June 30, 2020: As maintenance treatment for patients with locally advanced or metastatic UC that has not progressed with first-line platinum-containing chemotherapy.</td>
<td>JAVELIN Bladder 100</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>May 1, 2017: As second-line monotherapy for patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 mo of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.</td>
<td>NCT01693562</td>
</tr>
<tr>
<td><strong>US FDA approval of anti-PD-1 antibodies in UC</strong></td>
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<tr>
<td>Anti-PD-1 antibodies</td>
<td>Approvals of FDA</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>February 2, 2017: As second-line monotherapy for patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 mo of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy.</td>
<td>Checkmate 275</td>
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<td>Pembrolizumab</td>
<td>May 18, 2017: As second-line monotherapy for patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or within 12 mo of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.</td>
<td>Keynote-045</td>
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<td></td>
<td>May 18, 2017: As first-line monotherapy for patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy.</td>
<td>Keynote-052</td>
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Ongoing trials are investigating the regimens of ICIs combined with chemotherapy. The rationale is chemotherapy induces immunogenic cell death resulting in tumor antigens releasing and increasing MHC-I-mediated tumor antigen presentation which may enhance the effects of the immune response within the tumor. Another mechanism is directly modulating the activity and/or quantity of immunosuppressive cellular subsets[21,22]. Several trials have explored the efficacy of ICIs in combination with chemotherapy for mUC. IMvigor-130 is a double blind, three-arm, multicenter, phase 3 trial investigating the use of atezolizumab as monotherapy or combined with platinum-based chemotherapy comparing with chemotherapy alone as first-line treatment for patients with locally advanced or metastatic bladder carcinoma[23]. The addition of atezolizumab to platinum-based chemotherapy as a first-line treatment prolonged PFS in patients with mUC (mPFS 8.2 mo (95%CI: 6.5-8.3) in the atezolizumab plus platinum-based chemotherapy group and 6.3 (6.2-7.0) mo in the placebo plus platinum-based chemotherapy group (stratified hazard ratio: 0.82, 95%CI: 0.70-0.96; one-sided P = 0.007). In addition, the median overall survival was 16.0 (13.9–18.9) mo in the atezolizumab plus platinum-based chemotherapy group and 13.4 (12.0–15.2) mo in the placebo plus platinum-based chemotherapy group (0.83, 0.69–1.0; one-sided P = 0.027). A similar three-arm, multicenter, phase 3 clinical trial (KEYNOTE-036) was established to investigate pembrolizumab as a monotherapy or combined with platinum-based chemotherapy against standard chemotherapy plus placebo as first-line treatment. A phase 2 study also investigated cisplatin combined with gemcitabine plus ipilimumab compared with chemotherapy alone for patients with mUC. The objective response rate was as high as 69% and the completed response rate was 17%[2].

We first reported metastatic bladder UC harboring an ERBB2 in-frame insertion in an exon 20 mutation and ERBB3 amplification treated with paclitaxel plus sindilimab as second-line treatment. Although PD-L1 expression was negative and the TMB was low, the patient still achieved a durable response, with lung metastases being significantly reduced. At the last follow-up, the PFS was 19 mo. We will continue to focus on the follow-up treatment of this patient. However, we only included one case in this report, further studies and cases are required to confirm the relationship between ERBB2/3 mutations and response to ICIs in mUC.
CONCLUSION

This case indicates that mUC patients with ERBB2/3 mutations may benefit from ICIs. Further studies and cases are required to explore the ability of ERBB2/3 mutations to predict the efficacy of ICIs.

FOOTNOTES

Author contributions: Yan FF, Jiang Q, and Zhang XC were the patient’s oncologists, reviewed the literature, and contributed to manuscript drafting; Ru B and Fei XJ analyzed and interpreted the imaging findings; Ruan J and Zhang XC reviewed and edited the manuscript; Yan FF and Jiang Q contributed equally to this work; all authors read and approved the final manuscript.

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Retroperitoneal congenital epidermoid cyst misdiagnosed as a solid pseudopapillary tumor of the pancreas: A case report

Jun Ma, Ya-Ming Zhang, Chao-Ping Zhou, Lei Zhu

Abstract

BACKGROUND
Retroperitoneal cysts are rare and usually asymptomatic abdominal lesions. Epidermoid cysts are frequent benign cutaneous tumors, but retroperitoneal localization of these cysts does not occur very often.

CASE SUMMARY
We report a case report of a 25-year-old woman with a giant mass in the abdominal cavity. Because imaging examination indicated that the mass probably originated from the pancreas, the mass was considered a solid pseudopapillary tumor of the pancreas (SPTP). However, surgery revealed a retroperitoneal epidermoid cyst located behind the pancreas neck and the root of the superior mesenteric artery (SMA). We performed complete resection of the tumor. Postoperative pathology showed an epidermoid cyst. The patient fared well after two months of follow-up.

CONCLUSION
Surgery is the gold standard for the diagnosis and treatment of retroperitoneal epidermoid cysts. Retroperitoneal epidermoid cysts around the pancreas are easily misdiagnosed as cystic SPTPs. Surgeons should pay particular attention to preoperative diagnosis to reduce severe surgical complications and improve the quality of life of patients.

Key Words: Epidermoid cysts; Retroperitoneal tumor; Solid pseudopapillary tumor of pancreas; Surgery; Case report

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Core Tip: Retroperitoneal cysts are rare and usually asymptomatic abdominal lesions. Epidermoid cysts are frequent benign cutaneous tumors, but retroperitoneal localization of these cysts does not occur very often. Surgery is the gold standard for the diagnosis and treatment of retroperitoneal epidermoid cysts. Epidermoid cysts around the pancreas are easily misdiagnosed as cystic solid pseudopapillary tumors of the pancreas (SPTPs). Because of the different biological characteristics of retroperitoneal epidermoid cysts and SPTPs and the different surgical methods used for their treatment, surgeons should pay particular attention to preoperative diagnosis to reduce severe surgical complications and improve the quality of life of patients.

INTRODUCTION

Epidermoid cysts are tumor-like benign lesions that can be divided into congenital and acquired lesions. Congenital tumors often occur in the central nervous system and reproductive system and originate from the ectoderm of the skin at an early stage of the embryo. Acquired tumors are mostly caused by trauma and surgery wherein the epidermis is introduced into deep tissue. Epidermoid cysts are commonly found in the brain, trunk and neck and less commonly reported in the testis, penis, spleen and kidney[1,2]. The incidence of retroperitoneal epidermoid cysts is less than 1/40000, and most of them grow in the presacral region[3]. Retroperitoneal epidermoid cysts are less common at the back of the pancreatic neck or the root of mesenteric vessels. Because of the atypical location in this case, the cyst was misdiagnosed as a solid pseudopapillary tumor of the pancreas (SPTP) before laparotomy.

CASE PRESENTATION

Chief complaints
A 25-year-old Chinese woman experienced a one-month history of upper abdominal pain, abdominal distension and vomiting.

History of present illness
The patient developed epigastric pain without obvious cause one month prior, and she had symptoms of nausea and vomiting. She experienced no hematemesis or bloody stool, no chills or fever, and no significant weight loss.

History of past illness
The patient had no previous history of pancreatitis, trauma, surgery or a malignant tumor.

Personal and family history
The patient had her menarche at the age of 14, and her menstrual cycle was regular. Her parents had no related diseases.

Physical examination
The physical examination revealed a firm abdominal mass reaching the navel, and the rest of the examination revealed no abnormalities.

Laboratory examinations
Laboratory tests were normal.

Imaging examinations
Computed tomography (CT) detected a 98 mm × 63 mm × 54 mm subcircular mass in the uncinate process of the pancreas; the boundary was clear, and the adjacent tissue was pressed upon, with multiple spots and granular dense shadows observed. The dual-phase CT values were approximately 30 to 36 HU, and the density of the mass (which was considered to be an SPTP) was inhomogeneous (Figure 1A).
Magnetic resonance imaging (MRI) detected one 91 mm × 72 mm × 63 mm mass below the pancreas, which appeared hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging, T2-weighted fat suppression imaging, and diffusion-weighted imaging (DWI; b1200). The wall of the mass showed progressive enhancement. The tumor was adjacent to the pancreas, and the uncinate process was suspected to be the initial site of the tumor (which was considered to be an SPTP) (Figure 1B).

**FINAL DIAGNOSIS**

Postoperative pathology showed an epidermoid cyst.

**TREATMENT**

The patient underwent a median incision of the upper abdomen under general anesthesia. When the transverse colon was lifted upward, we observed a large cystic mass of approximately 100 mm × 70 mm × 60 mm with an intact wall. The lesion was located behind the pancreas neck, with the superior mesenteric artery (SMA) and horizontal part of the duodenum under compression; the right margin adhered closely to the superior mesenteric vein (SMV), and the left margin was close to the inferior mesenteric vein (IMV), caudally extending to separate the SMV and SMA (Figure 2A). We performed complete resection of the tumor. The cyst was excised after mobilization of the SMV and splenic vein (SV), which were found on the right side and cephalic side, respectively, of the tumor. During surgery, special attention was given to the connection between the lesion and the pancreas. The incidence of recurrence for retroperitoneal cysts is higher than that of other forms of cysts, as their proximity to major blood vessels and vital structures can make retroperitoneal cysts difficult to completely excise. Grossly, the cyst was approximately 10 cm in the largest dimension (Figure 2B).

**OUTCOME AND FOLLOW-UP**

The patient recovered well and was discharged one week after the operation. Postoperative pathology
showed an epidermoid cyst (Figure 3A). Two months later, enhanced CT revealed a normal shape of the SMV and SMA, no intravascular thrombus, no pseudoaneurysm, no obvious peripancreatic effusion, and no tumor recurrence or metastasis (Figure 3B).

DISCUSSION

The case was diagnosed as a retroperitoneal congenital epidermoid cyst for several reasons. First, the tumor was located at the back of the neck of the pancreas and the root of the SMA; second, the patient had no history of trauma or surgery.

The wall of the epidermoid cyst was composed of stratified squamous cells. The keratin and cholesterol that filled the cyst were gray–white, caseous, keratinized substances mixed with shed, broken epidermal cells. Epidermoid cysts are slow-growing benign tumors composed of epithelial cells [4].

The incidence of retroperitoneal congenital cysts is approximately 1/40000-1/63000. The main types of these cysts are epidermoid cysts, dermoid cysts, cystic hamartomas, teratomas and malignant teratomas [5].

Patients with retroperitoneal epidermoid cysts may have related symptoms, such as abdominal distension, abdominal pain, vomiting and constipation, depending on the location and volume of the tumor. Female patients are easily misdiagnosed with gynecological diseases. Some patients without clinical symptoms are diagnosed as a result of imaging examination.

CT features of epidermoid cysts include discrete lesions, thin and smooth cystic walls and homogeneous liquid density shadows [6]. On MRI, these cysts appear hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging. However, some scattered low-density foci can be observed on T2-weighted imaging, which may be related to keratin in the cyst [6]. Because there are no vessels in the cysts, the masses are not enhanced by contrast medium. Retroperitoneal epidermoid cysts are rare and lack imaging specificity; therefore, it is difficult to distinguish them from other cystic tumors.

The first report of SPTP was by Frantz in 1959. SPTPs are mostly benign or low-grade malignant tumors and often occur in women, mainly between the ages of 20 and 30 years [7,8]. SPTPs can be circular or subcircular and can be located in any position on the pancreas [9]. SPTPs can be divided into three types: Solid, cystic-solid and cystic. On CT, the cystic type appears as an area of low density and is not enhanced by contrast medium. On MRI, the cystic type is hypointense on T1-weighted imaging, hyperintense on T2-weighted imaging, somewhat hyperintense on DWI imaging, and marginally strengthened on enhanced imaging.

There were several reasons for the mass to have been misdiagnosed as an SPTP. First, the patient was a young woman. Second, the mass was mainly located on the left side of the pancreatic head and behind the pancreatic neck, which led us to believe that the cyst may have originated from the pancreas. Third, preoperative images of retroperitoneal epidermoid cysts are similar to those of SPTPs.

Surgery is the main method of treatment for retroperitoneal epidermoid cysts. Because this disease is rare, it is easily confused with other types of tumors of the abdominal cavity. Misdiagnosis can lead to inappropriate surgery, increasing the risks of postoperative complications and mortality and thereby leading to significantly worse quality of life of patients. In the present case, careful exploration during the operation revealed that the tumor originated from the root of the SMA and failed to invade the pancreas; thus, fortunately, the woman avoided pancreaticoduodenectomy or middle pancreatectomy.
In addition, with the continuous growth of lesions, inflammatory adhesion occurs around vital vessels and organs, which makes the lesions difficult to completely excise.

CONCLUSION

In summary, retroperitoneal epidermoid cysts around the pancreas are easily misdiagnosed as a cystic SPTP. Because of their different biological characteristics and surgical methods used for retroperitoneal epidermoid cysts and SPTP, surgeons should pay more attention to preoperative diagnosis to reduce severe surgical complications and improve the quality of life of patients.

FOOTNOTES

Author contributions: Ma J wrote and edited the original draft; Zhu L contributed to data collection and analysis; Zhou CP reviewed the literature, Zhang YM reviewed and approved the final manuscript; all authors have read and approve the final manuscript.

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CASE REPORT

Immunoglobulin G4-related kidney disease involving the renal pelvis and perirenal fat: A case report

Jun-Wei He, Qian-Ming Zou, Jun Pan, Shu-Sheng Wang, Song-Tao Xiang

Abstract

BACKGROUND
Immunoglobulin (Ig) G4-related disease (IgG4-RD) is an autoimmune disease associated with chronic and progressive inflammation and fibrosis. It is difficult to differentiate IgG4-RD involving the kidney from infectious diseases and malignancy on imaging.

CASE SUMMARY
We report the case of a 51-year-old Chinese man whose abdominal computed tomography scan showed diffuse bilateral enlargement of the kidneys and perirenal fat, thickening of the renal pelvic walls, and hydronephrosis of the right kidney. Relevant laboratory test results showed a serum creatinine level of 464 μmol/L. The patient was diagnosed with acute renal failure and was started on intermittent hemodialysis. Further tests revealed high serum IgG4 levels (20.8 g/L) and an enlarged right submaxillary lymph node. Biopsy and histopathological examination of the enlarged node led to the diagnosis of IgG4-RD. After corticosteroid therapy, his serum creatinine level quickly decreased to near normal levels.

CONCLUSION
IgG4-RD affecting the renal pelvis or perirenal fat is rare, with atypical imaging features. Multidisciplinary consultation is critical for accurate diagnosis and treatment of this disease. Suspected cases should undergo biopsy to avoid misdiagnosis.

Key Words: Immunoglobulin G4-related disease; Renal pelvic; Perirenal fat; Case report
Core Tip: In this case, computed tomography showed diffuse bilateral enlargement of the kidneys and perirenal fat, thickening of the renal pelvic walls, and hydronephrosis of the right kidney which was similar to those of infectious diseases and malignancy. Histological examination confirmed the diagnosis of IgG4-RD.

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INTRODUCTION
Immunoglobulin (Ig) G4-related disease (IgG4-RD) is an autoimmune disease associated with chronic and progressive inflammation and fibrosis, characterized by heavy IgG4-positive plasma cell infiltration and fibrosis in the affected tissues[1]. It is also known as IgG4-related kidney disease (IgG4-RKD), as it usually involves the renal parenchyma, perirenal fat, renal pelvis, and ureter. The disease manifests on computed tomography (CT) scans as a diffuse enlarged kidney, swollen perirenal fat, and thickened renal pelvis and ureter, which makes it difficult to differentiate from an infectious disease or tumor. Recently, we encountered a 51-year-old Chinese man who was finally diagnosed with IgG4-RD after pathological examination. We report this rare case of IgG4-RD, which is easily misdiagnosed as either a malignant tumor or an infectious disease, along with a summary of relevant literature.

CASE PRESENTATION
Chief complaints
On January 11, 2020, a 51-year-old man was admitted to our hospital with the complaint of chest oppression.

History of present illness
The patient had symptoms of chest oppression for 10 d, with no obvious cause, along with edema of both lower extremities. The patient denied having pain upon urination, low back pain, fever, or any other clinical manifestations.

History of past illness
The patient had no previous medical history.

Personal and family history
The patient had no specific personal and family history.

Physical examination
Physical examination of the heart and lungs was unremarkable, but both lower extremities had moderate edema. Blood pressure was normal without significant fluctuations. The patient also had an enlarged right submaxillary lymph node.

Laboratory examinations
Laboratory tests revealed a serum creatinine (Cr) level of 464 μmol/L, potassium concentration of 5.52 mmol/L, brain natriuretic peptide level of 376.2 pg/mL, and high-sensitivity C-reactive protein level of 20.4 mg/L (normal reference range: 0 to 6.0 mg/L). A routine urine test revealed a red blood cell count of 67.3/μL (normal reference range, 0 to 4/μL) and a white blood cell count of 731/μL (normal reference range, 0 to 5/μL). Serum IgG4 level was found to be high at 20.8 g/L (normal reference range, 0.03 to 2 g/L). Hepatitis B surface antigen, antineutrophil cytoplasmic antibody, and rheumatoid factor were negative, and other test results were within the normal limits.

Imaging examinations
Abdominal CT showed diffuse bilateral enlargement of the kidneys and perirenal fat, thickening of the renal pelvic walls, and hydronephrosis of the right kidney (Figure 1A). On magnetic resonance imaging (MRI) scans, the wall of the renal pelvis and ureter was thickened on contrast-enhanced images (Figure 1B). An ultrasound of the neck revealed an enlarged right submaxillary lymph node measuring
Pathology and immunohistochemical examination

Biopsy of the submaxillary node was performed for histopathological examination, which revealed a dense infiltrate of lymphoplasmacytic cells along with fibrosis. The IgG4+/IgG ratio determined by immunohistochemical staining was 60% in the specimens, and the average IgG4 plasma cell count was 100/high-power field (HPF) (Figure 2).

FINAL DIAGNOSIS

According to the comprehensive diagnostic criteria for IgG4-RD, the patient was finally diagnosed with IgG4-RD.

TREATMENT

The patient first presented with chest oppression to the Cardiovascular Department. However, coronary heart disease was ruled out by the cardiologist according to the laboratory tests. The patient was hospitalized and maintained on intermittent hemodialysis due to acute renal failure. The level of urinary protein excretion was 2129.6 mg/d. Laboratory tests revealed a serum IgG level of 21.15 g/L, and serum complement 4 level of 0.52 g/L. Further tests were conducted to determine the cause of diffuse bilateral enlargement of the kidneys and perirenal and thickening of the renal pelvic walls. Serum IgG4 level was found to be high at 20.8 g/L (normal reference range, 0.03 to 2 g/L), and an enlarged lymph node was found in the right submaxillary area. Ultrasound indicated that the right submaxillary lymph node was enlarged, and was approximately 29 mm × 19 mm in size. Pathological biopsy of the submaxillary mass was performed. Dense lymphoplasmacytic cells with fibrotic changes were found on histopathology. Based on these findings, the patient was diagnosed with IgG4-RD. He was initially started on intravenous methylprednisolone sodium succinate 40 mg/d for 2 wk. Two weeks later, his Cr level decreased to 117 μmol/L; thus, treatment was changed to oral prednisone at 40 mg once a day, and then the dosage was reduced by 10 mg biweekly.

OUTCOME AND FOLLOW-UP

During the follow-up period, urinary tract ultrasound was performed every 6 mo, and the serum Cr level was examined every 2 mo. To date, no recurrence has been identified, and serum Cr level is normal.

DISCUSSION

IgG4-RD is a new disease recognized in the twenty-first century. Kamisawa proposed the concept of
IgG4 systemic disease for the first time in 2003 and named the disease IgG4-RD in 2010[2,3]. IgG4-RD is a systemic disease characterized by diffuse enlargement of single or multiple organs and elevated IgG4 serum levels, with infiltration of lymphocytes and IgG4-positive plasma cells, as well as fibrosis, typically seen on histopathology. Two IgG4-RD study groups, the Umehara and Okazaki teams, organized by the Ministry of Health, Labour and Welfare in Japan, established the definitive diagnostic criteria for IgG4-RD in 2011 as follows: (1) Clinical examination showing characteristic diffuse/localized swelling or masses in a single organ or multiple organs; (2) Hematological examination showing elevated serum IgG4 concentrations (≥ 135 mg/dL); and (3) Histopathologic examination showing: (a) Marked lymphocyte and plasmacyte infiltration and fibrosis; and (b) Infiltration of IgG4+ plasma cells with a ratio of IgG4+/IgG+ cells >40% and >10 IgG4+ plasma cells/HPF[4]. Corticosteroid therapy has been found to be effective for IgG4-RD. All three criteria were met, and a good outcome was achieved after corticosteroid therapy in our case.

IgG4-RD that involves the kidney, also known as IgG4-RKD, is difficult to differentiate from infectious diseases and malignancy on imaging. The characteristic radiological features of IgG4-RKD are as follows: (1) Multiple low-density areas on contrast CT, (2) Diffuse bilateral enlargement of the kidneys in patients with decreased renal function in whom the administration of contrast medium is inadvisable, and (3) Diffuse thickening of the renal pelvic walls with a smooth luminal surface[5]. Kim et al[6] proposed that the characteristic MRI findings of IgG4-RKD were bilateral, multiple, renal parenchymal nodules with T2 hypointensity, diffusion restriction, and a progressive enhancement pattern.

IgG4-RKD usually involves the renal parenchyma. However, renal pelvis and ureter involvement are rare, and perirenal fat involvement is even rarer. Renal pelvis involvement in IgG4-RKD is usually characterized by thickening of the pelvic wall, which is easily misdiagnosed as carcinoma of the renal pelvis and removed surgically. Naoto et al, in 2009, reported the first case of IgG4 systemic disease involving the renal pelvis. The patient was misdiagnosed on imaging with a renal pelvis tumor and underwent nephroureterectomy; however, histopathological examination prompted the diagnosis of IgG4-related disease of the renal pelvis. This was the first case of pathology-confirmed IgG4 systemic disease involving the renal pelvis[7]. We searched the literature for articles published in the English language between January 2000 and June 2020 concerning manifestations of IgG4-RKD affecting the renal pelvis or perirenal fat. We identified and reviewed 13 articles that reported cases of IgG4-RKD affecting the renal pelvis or perirenal fat[8-12]. Among the cases of IgG4-RD affecting the renal pelvis or perirenal fat reported in the literature, 53.8% (7/13) underwent nephrectomy or nephroureterectomy, and the pathological diagnosis was IgG4-RKD[13-17]. From our literature review, we found that the misdiagnosis rate of IgG4-RD involving the renal pelvis was very high, suggesting that currently, urologists generally lack understanding of this disease[18,19]. This causes a certain delay in the diagnosis and treatment stages. Fortunately, renal function was restored after treatment, and further unnecessary surgery was avoided. The manifestations of this disease on imaging are atypical, involving the renal parenchyma, renal pelvis, ureter, and perirenal fat at the same time. The literature review showed that only two cases of IgG4-RD involving the perirenal fat have been reported globally, which are extremely rare cases[17].

There has been little attention to urinary system involvement besides renal parenchyma. According to the study by Zhang et al[12], elevated serum IgG and IgG4 were found in all patients with IgG4-RKD, but no hypocomplementemia was found. Teng et al[20] reported that all patients with IgG4-related urinary disease had marked elevations in serum IgG4 levels, and 76.9% had hyperglobulinemia at diagnosis. The study also showed that 20% of patients with IgG4-related urinary disease had nephritis.
confirmed by urine tubular injury markers accompanied by acute renal dysfunction and required emergency medical intervention. More than 90% of IgG4-RKD patients have a history of extrarenal lesions, which is an important basis for differential diagnosis. A satisfactory response to corticosteroid therapy is a characteristic feature of IgG4-RD.

CONCLUSION

IgG4-RD is a recently identified disease, which rarely affects the renal pelvis or perirenal fat and has atypical imaging features that make it difficult to differentiate from infectious diseases and malignancy. Therefore, urological surgeons must improve their understanding of these diseases, so they can identify the nonspecific clinical symptoms and the bilateral, multiple, atypical organ lesions on imaging, and confirm the diagnosis with serological examination. There were several characteristic clinical features of IgG4-RKD in our case, including the involvement of multiple organs, high levels of serum IgG and IgG4, and a rapid initial response to corticosteroids. Multidisciplinary consultation is critical for the accurate diagnosis and treatment of this disease. Suspected cases should undergo biopsy to avoid misdiagnosis.

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FOOTNOTES

Author contributions: He JW drafted the manuscript and designed the figures and table; Zou QM and Wang SS analyzed and interpreted the data regarding computed tomography and magnetic resonance imaging; Pan J searched and reviewed the literature; Xiang ST participated in the final diagnosis and reviewed the final version of this work.

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Fluoroscopic removal of fractured, retained, embedded Z self-expanding metal stent using a guidewire lasso technique: A case report

Yong-Hua Bi, Jian-Zhuang Ren, Jin-Dong Li, Xin-Wei Han

BACKGROUND
There are few reports of a fractured esophageal self-expanding metallic stent (SEMS) and the lasso retrieval technique, forming a guidewire loop by directing the guidewire back up the external stent for retrieval.

CASE SUMMARY
A 74-year-old man complained of dysphagia approximately 6 mo after radical resection of esophageal cancer. Benign anastomotic stenosis was diagnosed, and a 20 mm in diameter and 60 mm in length esophageal covered SEMS was inserted after repeated balloon dilatation. About 13.5 mo after stenting, dysphagia recurred and esophagography showed severe stenosis above the proximal stent and stent removal was performed. One-third of the stent was removed and the fractured stent remained in the proximal esophagus. A suction tube was introduced through the guidewire and then the guidewire was grabbed, acting like a “lasso” on tightening. The remaining fractured stent was successfully removed by slowly pulling back the guidewire, with no fragments of stent wires retained.

CONCLUSION
The guidewire lasso technique is a simple, effective method of removing esophageal SEMS in rare cases of stent fracture.

Key Words: Self-expanding metallic stent; Stenosis; Guidewire lasso technique; Stent removal; Esophagus; Case report
Core Tip: We present a case in which the guidewire lasso technique was used to remove a fractured esophageal Z-stent. A 74-year-old man developed dysphagia approximately 6 mo after resection for esophageal cancer and a Z stent was inserted. After 13.5 mo, esophagography showed severe stenosis above the proximal stent. One-third of the stent was removed and the fractured stent remained in the proximal esophagus. A suction tube was introduced through the guidewire and then the guidewire was grabbed, acting like a “lasso” on tightening. The fractured stent was successfully removed by slowly pulling back the guidewire, with no fragments of stent wires retained.

INTRODUCTION

Covered esophageal stents are mainly reserved for malignant indications, such as esophageal stricture or fistula caused by esophageal cancer. Self-expanding metallic stent (SEMSs) have not been widely used in patients with benign dysphagia due to their expected long-term complications[1,2]. SEMSs may serve as a routine option for the management of refractory benign stenosis if they can be timely and safely retrieved within 2 to 3 mo[3] or before excessive epithelial hyperplasia develops[1]. There are few reports of a fractured esophageal SEMS and the lasso retrieval technique, in which a guidewire loop is formed by directing the guidewire back up the external stent for retrieval. We present a case in which this technique was used to remove a fractured esophageal Z-stent.

CASE PRESENTATION

Chief complaints
A 74-year-old man developed aggravation of dysphagia approximately 13.5 mo after stent insertion following resection of esophageal cancer 6 mo previously.

History of present illness
The patient gradually developed dysphagia 21 mo ago. Esophagography and a chest contrast-enhanced computed tomography (CT) scan showed a tumor located in the middle and lower part of the esophagus (Figure 1A and B). Esophageal gastroscopy examination was performed and biopsy pathology confirmed esophageal squamous cell carcinoma (Figure 1C). Radical resection of esophageal cancer was performed 19.5 mo ago under general anesthesia. The patient complained again of dysphagia about 13.5 mo ago and benign anastomotic stenosis was diagnosed. A 20 mm in diameter and 60 mm in length esophageal covered SEMS was inserted after repeated balloon dilatation. The retrievable Z-stents are made of stainless steel and coated with silicon (Sigma Medical Industry Co., Ltd., Huaiian, Jiangsu Province, China). Two weeks ago, the symptoms of dysphagia were significantly aggravated and esophagography showed severe stenosis above the proximal stent.

History of past illness
The patient had mild coronary heart disease for 15 years, but did not take medication.

Personal and family history
The patient had no history of smoking, drinking, or familial cancers.

Physical examination
Vital signs were as follows: Body temperature 36 °C, pulse 88 bpm, respiration 22 breaths/min, blood pressure 99/69 mmHg, height 169 cm, and body weight 50.0 kg. Oxygen saturation in room air was 99%.

Laboratory examinations
Routine blood tests showed the following: Leukocyte count 4.73 × 10⁹/L, erythrocyte count 3.80↓ × 10¹²
Bi YH et al. Guidewire lasso for esophageal stent

Figure 1 Examination before esophagectomy 21 mo ago. A: Esophagography showed that the tumor was located in the middle and lower part of the esophagus; B: A chest contrast-enhanced computed tomography scan showed thickened esophageal wall; C: Esophageal gastroscopy examination was performed and biopsy pathology confirmed esophageal squamous cell carcinoma.

/L, hemoglobin 117.0 g/L↓↓, Platelet count 202 × 10⁹/L, neutrophil percentage 75.6%↑, and lymphocyte percentage 15.7%.

Imaging examinations
Severe stenosis above the proximal stent was diagnosed by esophagography (Figure 2A). Removal of the stent was decided due to aggravated dysphagia after repeated balloon dilation.

FINAL DIAGNOSIS
The final diagnosis of the case presented was severe benign anastomotic stenosis above the proximal stent.

TREATMENT
Two days after admission, esophageal balloon dilatation and stent removal was performed under fluoroscopy. The procedure was as follows: The patient lay supine on the operating table; 10 mL of iodine contrast agent was administered orally. After local mucosal anesthesia, an opener was placed in the mouth. A 5F single curved catheter and 0.035-inch guidewire was introduced and passed through the esophageal stent. An AMPLAZ stiff guidewire was exchanged and a 20 mm in diameter and 40 mm in length balloon catheter (Cook Medical, Bloomington, IN, United States) was introduced to dilate the stenotic segment (Figure 2B). After withdrawing the catheter, the stent removal sheath was introduced and then the removal hook was placed in the lower part of the stent in order to remove the whole stent (Figure 2C).

Because the stent was embedded in proliferative tissue, it fractured during the removal process. After the application of considerable traction to the distal end of the stent, only one-third of the stent was removed and the fractured stent remained in the proximal esophagus. We failed to remove the retained stent using the same method again.

A 0.035-inch guidewire was introduced and passed over the retained stent and looped back from the stent to the mouth (Figure 2D). A suction tube was introduced through the guidewire and then the guidewire was grabbed, acting like a “lasso” on tightening (Figure 2E). Under fluoroscopy, the fractured
Bi YH et al. Guidewire lasso for esophageal stent

Figure 2 Balloon dilation and stent removal performed 13.5 mo after stenting. A: Esophagography showed severe stenosis (arrow) above the proximal stent; B: A 20 mm in diameter and 40 mm in length balloon catheter was introduced to dilate the stenotic segment; C: A stent removal sheath was introduced and then a removal hook (arrow) was placed in the lower part of the stent, stent fracture occurred and only one-third of the stent was retrieved; D: A 0.035-inch guidewire was introduced and passed over the remaining fractured stent and looped back from the stent to the mouth (arrow); E: A suction tube was introduced through the guidewire and then the guidewire was grabbed, acting like a “lasso” on tightening; F: The fractured stent was successfully removed and the strut was deformed (arrow).

stent was successfully removed by slowly pulling back the guidewire, with no fragments of stent wires retained. Proliferative tissue could be seen in the removed stent and the strut was deformed (Figure 2F). Mild bleeding occurred during the procedure, and epinephrine was administered orally for hemostasis.

OUTCOME AND FOLLOW-UP

Reexamination showed that stenosis was no longer present and there was no overflow of contrast agent. The patient complained of mild postoperative pharyngeal pain which did not require treatment, and dysphagia symptoms disappeared so that he could eat. After a total of 4-d of hospitalization the patient was discharged.

The patient complained of dysphagia again about 40 d later. A chest contrast-enhanced CT examination and esophagography showed severe stenosis in the proximal part of the esophagus (Figure 3A and B). A 28 mm in diameter and 40 mm in length big balloon catheter (Cook) was used to dilate the stenotic section (Figure 3C). Esophagography showed that the stenosis disappeared after dilation (Figure 3D) and the patient did not complain of dysphagia thereafter.

DISCUSSION

Covered esophageal stents are mainly reserved for malignant indications, such as esophageal stricture or fistula caused by esophageal cancer. The ability of SEMSs to relieve dysphagia effectively in patients with malignancy is accepted generally. SEMSs have not been widely used in patients with benign
Figure 3 Balloon dilation performed approximately 40 d after stent removal. A: Chest enhanced computed tomography examination showed obvious thickened esophageal wall (arrow); B: Esophagography showed severe stenosis (arrow) in the proximal part of the esophagus; C: A 28 mm in diameter and 40 mm in length big balloon catheter was used to dilate the stenotic section; D: Esophagography showed that the stenosis (arrow) disappeared after dilation.

Figure 3 Balloon dilation performed approximately 40 d after stent removal. A: Chest enhanced computed tomography examination showed obvious thickened esophageal wall (arrow); B: Esophagography showed severe stenosis (arrow) in the proximal part of the esophagus; C: A 28 mm in diameter and 40 mm in length big balloon catheter was used to dilate the stenotic section; D: Esophagography showed that the stenosis (arrow) disappeared after dilation.

dysphagia due to their expected long-term complications. Due to pressure necrosis caused by SEMS expansion, the bare ends are routinely incorporated into the esophageal mucosa and then covered by pseudomembrane[1]. Benign granulation tissue hyperplasia may extend into the deeper layers of the esophageal wall and increase the possibility of formation of secondary obstruction formation[1,2]. Esophageal resection may be required due to severe stricture after stent placement in benign disease[3]. Additional stent placement or laser ablation are routine management options if granulation tissue overgrowth occurs in patients with malignancy. However, other options can be used in patients with benign disease[4].

A SEMS may serve as a routine option for the management of refractory benign stenosis if the retrievable stents can be safely retrieved within 2 to 3 mo[4] or before excessive epithelial hyperplasia develops[1]. Esophageal stent removal methods should be varied according to the different types of SEMS, including the endoscopic removal technique of multiple SEMS in certain cases, such as both Z-stents and Ultraflex stents. Previous studies have reported the removal of SEMSs for inappropriate insertion or stent migration. For example, Mallery and Freeman[5] removed an Ultraflex stent with distal-to-proximal invagination into an overtube. However, this method was unable to extract a similar stent one month after deployment. The Ultraflex stent is more flexible than other brands including the Gianturco and Wallstent stents; thus, this removal technique may not be applicable for various types of SEMSs.

Fragments of stent wires are commonly retrieved endoscopically with grasping forceps. There are few reports of a fractured esophageal SEMS and the lasso retrieval technique in which a guidewire loop is formed by directing the guidewire back up the external stent for retrieval. This technique has been used successfully to extract a migrated colonic stent[6], as well as an esophageal SEMS that had migrated into the stomach[7]. The Z stents may be best removed by polyp snare rather than invagination removal from distal to proximal ends. Our report describes a stent retrieval method that can be performed in selected cases of benign disease in which stent fracture has occurred.
CONCLUSION

This case validates that the guidewire lasso technique is a simple and effective method of removing esophageal SEMSs in rare cases in which stent fracture occurs. The ability to retrieve fractured and retained Z-stents may facilitate broader stent applications.

FOOTNOTES

Author contributions: Bi YH, Li JD, Han XW, and Ren JZ designed the study; Bi YH and Ren JZ performed the study; Ren JZ collected and analyzed data; all authors wrote the paper and finally approved the version to be published.

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REFERENCES

Treatment and five-year follow-up of type A insulin resistance syndrome: A case report

Yong-Hua Chen, Qing-Qing Chen, Chun-Lin Wang

BACKGROUND
Type A insulin resistance syndrome (TAIRS) is a rare disorder characterized by severe insulin resistance due to defects in insulin receptor signaling. No specific drugs are available for the treatment of TAIRS. We report a case of TAIRS successfully treated with pioglitazone and flutamide for 5 years.

CASE SUMMARY
We present the rare case of a female patient aged 11 years and 9 mo with type A insulin resistance and an INSR heterozygous mutation (c.3614C>T), who was treated with a combination of pioglitazone and flutamide. This treatment regimen reduced hemoglobin A1c, fasting insulin and androgen levels.

CONCLUSION
Pioglitazone attenuated insulin resistance in this patient with TAIRS, and flutamide ameliorated masculinization.

Key Words: Type A insulin resistance syndrome; Treatment; Pioglitazone; Flutamide; Case report

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Core Tip: Type A insulin resistance syndrome (TAIRS) is a rare disorder characterized by severe insulin resistance due to defects in signaling through the insulin receptor. We present the rare case of a female patient aged 11 years and 9 mo who had type A insulin resistance with an INSR heterozygous mutation (c.3614C>T). This is the first case report describing the use of pioglitazone and flutamide used in combination in a child with TAIRS. This protocol for TAIRS is inexpensive, effective, and free of side effects.

INTRODUCTION
Insulin resistance (IR) is a condition that cells, tissues or organs can't respond properly to a given dose of insulin.[1]. Type A insulin resistance syndrome (TAIRS) is an autosomal recessive or dominant genetic disease[2]. Insulin receptor gene mutation affects insulin and insulin receptors, leading to insulin dysfunction[3]. Teenage females are more commonly affected and mainly develop severe IR, hyperandrogenism and acanthosis nigricans, which may be accompanied by polycystic ovary syndrome.

In this report, a female patient aged 11 years and 9 mo was diagnosed with severe IR and hyperandrogenism after comprehensive physical examination and related examinations. She was given oral medication, was followed up to observe changes in clinical symptoms and signs, and underwent monitoring of metabolism, IR and androgen levels. This study aimed to observe and analyze the curative effect of drugs in this patient, improve the understanding of the etiology and mechanism of TAIRS and explore effective treatment schemes.

CASE PRESENTATION
Chief complaints
The female patient aged 11 years and 9 mo was admitted to our outpatient clinic due to hairiness and melanosis of the skin and hoarseness.

History of present illness
On October 30, 2015, the girl was admitted to our outpatient clinic due to hairiness and melanosis of the skin and hoarseness. Pigmentation started soon after birth without an obvious cause, and the child had noticeably more hair on her body than children of the same age. In addition, the degree of severity gradually increased with age. Pubic hair appeared 8 mo prior to presentation and was noted to be increasing rapidly; the patient’s voice became hoarse 4 mo prior to presentation. She denied complaints of headache, dizziness, fatigue, abdominal pain and other discomfort.

The patient was born with a birth weight of 2650 g. After birth, she was noted to have excessive hair on her body and excessive skin pigmentation.

History of past illness
The growth and development of the patients are similar to those of their peers, and there is no long-term medication history.

Personal and family history
Family history was significant for diabetes in her father, grandfather and aunt.

Physical examination
Physical examination showed as follows: height 149 cm, weight 36 kg, BMI 16.21 kg/m², hirsutism, dense pubic hair, and perineal pubic hair distributed in diamond shape. The skin showed acanthosis-like changes (Figure 1). There was no acne or thyroid enlargement. Her pubertal development was Tanner grade IV.

Laboratory examinations
Routine blood tests, blood gas analysis, thyroid function, liver and kidney function tests showed that 17-
hydroxyprogesterone, alpha fetoprotein and human chorionic gonadotropin were normal. Cortisol rhythm was also normal (5.48 µg/dL at 8 am; 5.12 µg/dL at 4 pm; and 12.8 pg/mL of adrenocorticotropic hormone at 8 am). At 24 h, urine free cortisol was 95.37 µg (reference range 20.9-292.3 µg). The dehydroepiandrosterone sulfate level was 76.45 µg/mL (reference range 0.3-1.47 µg/mL). The androstenedione level was 5.03 ng/mL (reference range 0.50-4.70 ng/mL). The sex hormone levels were as follows: follicle stimulating hormone was 4.9 mIU/mL, luteinizing hormone was 4.65 mIU/mL, testosterone was 128.7 ng/dL, estradiol was 48.0 pg/mL, and prolactin was 4.5 ng/mL. A 75 g glucose tolerance test was performed, which showed that fasting blood glucose was 4.3 mmol/L and 2-h blood glucose was 13 mmol/L. Hemoglobin A1c (HbA1c) was 6.9%.

**Imaging examinations**
Transrectal color Doppler ultrasound of the uterine annex showed no polycystic changes in either ovary. Head MRI, abdominal B-ultrasound, cardiac B-ultrasound and adrenal B-ultrasound were normal.

**FINAL DIAGNOSIS**
The clinical manifestations and laboratory diagnosis of this patient indicated TAIRS. Therefore, after obtaining the consent of the patient and her family, genetic testing was performed. The results showed that INSR gene had a mutation. (c.3614C>T).

**TREATMENT**
We recommended that the patient work on strengthening exercises and adopt a controlled diet. Treatment with metformin 1.0 g/d was administered. However, the patient suffered fasting hypoglycemia many times; therefore, metformin was changed to pioglitazone 15 mg/d. In addition, hyperandrogenism was treated with flutamide.

**OUTCOME AND FOLLOW-UP**
Blood sampling was performed on admission and every 3 mo thereafter to evaluate the patient’s plasma glucose profile, HbA1C, plasma insulin, and sex hormone levels. Height and weight were measured on each admission. A 75 g glucose tolerance test was performed 15 mo after treatment. Following the administration of pioglitazone, plasma glucose, plasma insulin, and HbA1c normalized, as shown in Figure 2 and Figure 3. During treatment, the patient did not have any hypoglycemic attacks or abnormal routine laboratory data. Acanthosis nigricans also seemed to improve gradually. Hirsutism and serum testosterone concentration slowly improved after the administration of flutamide, as shown in Figure 4. Menstruation started 9 mo after initiation of treatment; however, it was noted to be irregular.
DISCUSSION

In this report, we described a child with hirsutism and acanthosis nigricans on examination. Blood lipid metabolism abnormalities were not observed on biochemical examination. Hormone level testing suggested the existence of hyperandrogenism and severe IR. Genetic testing showed INSR c.3614C>T; thus, TAIRS was diagnosed.

Insulin is an important regulator of sex hormone metabolism. High insulin leads to a decrease in sex hormone binding protein synthesis in the liver and stimulates androgen synthesis in the ovary and adrenal glands[4]. However, high androgen levels can inhibit the effect of insulin stimulating the uptake of glucose by tissues, thereby causing IR[5]. Therefore, hyperinsulinemia interacts with hyperandrogenism, causing a vicious cycle.

At present, there is no guideline or consensus statement to describe how to best treat patients with severe IR. The treatment of patients mainly aims to prevent long-term complications caused by diabetes and hyperandrogenism[6]. Maintaining body weight and BMI plays an important role in maintaining blood glucose homeostasis[7]. There is no definitive and effective drug treatment for type A IR, and the use of metformin, insulin sensitizer, and insulin-like growth factor-1 has been reported. Metformin, a biguanide derivative, has been demonstrated to have beneficial results in further decreasing BMI. The molecular mechanism of metformin is not completely clear. Many potential mechanisms of action have been proposed, such as inhibiting mitochondrial respiratory chain (complex I), activating AMP-activated protein kinase (AMPK), and inhibiting glucagon-induced increase of cyclic adenosine monophosphate (cAMP), while reducing the activation of protein kinase A (PKA), inhibition of mitochondrial glycerophosphate dehydrogenase, and an effect on gut microbiota[8,9]. Metformin inhibits the secretion of growth hormone, adrenocorticotropic hormone, follicle stimulating hormone and anterior melanocortin from the pituitary basal body, which partly explains its insulin sensitization effect through various actions on tissues, including liver, skeletal muscle, endothelium, adipose tissue and ovaries[10]. However, in this case, oral metformin was discontinued due to repeated fasting hypoglycemia, and the patient was given pioglitazone. Pioglitazone selectively stimulates nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and, to a lesser extent, PPAR-α[11]. Pioglitazone modulates transcription of the genes involved in the control of glucose and lipid metabolism in the muscle, adipose tissue, and liver. As a result, pioglitazone reduces IR in the liver and peripheral tissues, decreases gluconeogenesis in the liver, and reduces the quantities of glucose and glycated hemoglobin in the bloodstream[12]. After treatment, our patient showed a significant decrease in fasting insulin, and her glucose metabolism improved. Acanthosis nigricans also faded significantly.

Figure 2 Blood glucose, serum insulin and C-peptide, and oral glucose tolerance test before and after treatment.

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She had menarche when she was 13 years old, but her menstruation was irregular. Up to now, no adverse reactions have occurred.

Treating TAIRS is challenging. Recombinant human IGF-1 can activate IGF-1 receptor, and it can be an effective treatment for TAIRS, because IGF-1 receptor shares structural homology and downstream signal pathway with INSR.[13]. However, recombinant human IGF-1 therapy is expensive, and the drug is not available in China. Glucagon-like peptide 1 (GLP-1) receptor agonists stimulate GLP-1 receptors in the pancreas and thereby increase insulin release and inhibit glucagon secretion, but they are not approved by the FD[14]. SGLT2 inhibitor is a new type of antidiabetic drug, which can reduce blood sugar by inhibiting renal glucose reabsorption, and has nothing to do with insulin.[15]. A recent study showed that a sodium–glucose cotransporter 2 inhibitor had a good therapeutic effect in a patient with TAIRS[16]; however, further research is required. Patients who fail to take oral hypoglycemic drugs...
usually require a larger dose of insulin.

Patients with hirsutism, acne, and amenorrhea caused by hyperandrogenemia can be treated with anti-androgen drugs such as cyproterone acetate, flutamide, and spironolactone. Flutamide, as a selective antagonist of androgen receptor (AR), competes with androgens such as testosterone and dihydrotestosterone to bind AR in prostate and other tissues. Flutamide prevents their effects and prevents them from stimulating the growth of prostate cancer cells. Studies have shown that flutamide is effective in treating hirsutism[17]. Following flutamide application, hirsutism in this patient was obviously improved.

CONCLUSION

In conclusion, there is no definite treatment for TAIRS. Based on 5 years of follow-up, our protocol is inexpensive, effective, and was not associated with side effects in this patient with TAIRS.

FOOTNOTES

Author contributions: Wang CL conceived and designed the research; Chen YH and Chen QQ analyzed the data. Chen YH, Chen QQ, and Wang CL wrote the manuscript.

Informed consent statement: Informed written consent was obtained from the patient’s parents for publication of this report and any accompanying images.

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Effective response to crizotinib of concurrent KIF5B-MET and MET-CDR2-rearranged non-small cell lung cancer: A case report

Lian-Fang Liu, Jia-Ying Deng, Analyn Lizaso, Jing Lin, Si Sun

BACKGROUND
Due to the rarity of mesenchymal-epithelial transition factor (MET) fusions, the clinical efficacy of crizotinib has only been described in a few patients with MET fusions involving various fusion partners. Herein, we report the clinical response to crizotinib of a patient with advanced poorly differentiated non-small cell carcinoma (NSCLC) having concurrent MET fusions.

CASE SUMMARY
A 46-year-old woman was diagnosed with poorly differentiated NSCLC (T4N3M1). With no classic driver mutations, she was treated with two cycles of gemcitabine and cisplatin without clinical benefit. Targeted sequencing revealed the detection of two concurrent MET fusions, KIF5B-MET and novel MET-CDR2. Crizotinib was initiated at a dose of 250 mg twice daily. Within 4 wk of crizotinib therapy, repeat computed chromatography revealed a dramatic reduction in primary and metastatic lesions, assessed as partial response. She continued to benefit from crizotinib for 3 mo until disease progression and died within 1 mo despite receiving nivolumab therapy.
CONCLUSION
Crizotinib sensitivity was observed in an advanced poorly differentiated NSCLC patient with concurrent MET fusions KIF5B-MET and MET-CDR2. Crizotinib can serve as a therapeutic option for patients with MET fusions. In addition, our case also highlights the importance of comprehensive genomic profiling particularly in patients with no classic driver mutation for guiding alternative therapeutic decisions.

Key Words: Poorly differentiated; Non-small cell carcinoma; Mesenchymal-epithelial transition factor fusion; Crizotinib; Case report

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Core Tip: The most common mesenchymal-epithelial transition factor (MET) gene aberrations are gene amplifications and exon 14 splice variants found in approximately 2% to 10% of lung cancer patients. Chromosomal rearrangements resulting in gene fusions involving MET are generally rare but could account for MET-driven oncogenesis. The rarity and diversity of MET fusions in non-small cell lung cancer (NSCLC) limit the volume of evidence documenting the clinical efficacy of crizotinib in treating MET-rearranged NSCLC patients. Herein, we report the clinical response to crizotinib of a patient with advanced poorly differentiated NSCLC harboring concurrent MET-involving rearrangements, including a novel MET-CDR2 gene fusion.

INTRODUCTION
The mesenchymal-epithelial transition (MET) gene, located on chromosome 7q21-31, encodes a receptor tyrosine kinase and is activated by its ligand, hepatocyte growth factor[1,2]. The MET signaling pathway is often upregulated in various human malignancies, including non-small cell lung cancer (NSCLC)[2]. The most common MET gene aberrations are gene amplifications and exon 14 splice variants found de novo in approximately 2% to 10% of lung cancer patients[3]. Chromosomal rearrangements resulting in gene fusions involving MET are generally rare but could account for MET-driven oncogenesis[4]. Currently, a total of five MET fusion partner genes have been reported in NSCLC, including KIF5B[5,6], STARD3NL[5], HLA-DRB1[7,8], UBE2H[9], and ATXN7L1[10] (Table 1). Crizotinib, an FDA-approved tyrosine kinase inhibitor for ALK-rearranged and ROS1-rearranged NSCLC, has been originally designed to target MET amplifications and mutations[11]. Several cases and clinical studies have reported the efficacy of crizotinib in MET-altered NSCLC patients. A recent meta-analysis analyzed six clinical trials (cohort size range: 8-69) on MET-altered NSCLC revealed an objective response rate of 40.6% (95%CI: 28.3%–53.0%) and disease control rate of 78.9% (95%CI: 70.3%–87.4%) for crizotinib, with a median progression-free survival and overall survival of 5.2 and 12.7 mo, respectively[15]. Most of these studies enrolled few MET fusion-positive patients, because they are exceedingly rare. Current knowledge regarding MET fusions is mostly derived from two cohort studies in Chinese lung cancer patients, which identified one (0.04%, 1/2410) fusion[16] and fifteen (0.26%, 15/5695) fusions involving the MET kinase domain[17], respectively.

Herein, we report the clinical efficacy of crizotinib in a patient with poorly differentiated NSCLC with KIF5B-MET and a concurrent novel MET-CDR2 fusion.

CASE PRESENTATION
Chief complaints
In November 2018, a 46-year-old female never-smoker presented in our clinic with a complaint of persistent dry cough.
**Table 1 Summary of case reports of crizotinib (250 mg/b.i.d. orally) in treating MET-rearranged non-small cell carcinoma**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Age</th>
<th>Sex</th>
<th>Smoker</th>
<th>Stage</th>
<th>Histology</th>
<th>MET fusion</th>
<th>Best overall response</th>
<th>PFS (mo)</th>
<th>Grade ≥ 3 AEs</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>[5]</td>
<td>33</td>
<td>F</td>
<td>Yes</td>
<td>IV</td>
<td>ADC</td>
<td>KIF5B-MET</td>
<td>PR</td>
<td>8</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>[5]</td>
<td>62</td>
<td>F</td>
<td>No</td>
<td>IV</td>
<td>ADC</td>
<td>STARD3NL-MET</td>
<td>PR</td>
<td>14</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>[6]</td>
<td>51</td>
<td>F</td>
<td>No</td>
<td>IV</td>
<td>ADC</td>
<td>KIF5B-MET</td>
<td>PR</td>
<td>10</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>[7]</td>
<td>74</td>
<td>F</td>
<td>No</td>
<td>Recurrent</td>
<td>ADC</td>
<td>HLA-DRB1-MET</td>
<td>Complete resolution of nodules while pleural effusion persisted</td>
<td>8</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>[8]</td>
<td>59</td>
<td>F</td>
<td>No</td>
<td>Recurrent</td>
<td>ADC</td>
<td>HLA-DRB1-MET</td>
<td>Complete radiographic response</td>
<td>/</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>[9]</td>
<td>43</td>
<td>F</td>
<td>No</td>
<td>IV</td>
<td>ADC</td>
<td>MET-UBE2H</td>
<td>PR</td>
<td>6.5</td>
<td>NR</td>
<td>MET fusion was acquired on EGFR-targeted therapy</td>
</tr>
<tr>
<td>[10]</td>
<td>56</td>
<td>F</td>
<td>No</td>
<td>IV</td>
<td>ADC</td>
<td>MET–ATXN7L1</td>
<td>PR</td>
<td>4</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

ADC: Adenocarcinoma; AE: Adverse event; NR: Not reported; PR: Partial response.

**History of present illness**
The cough had been lasted for over a week.

**History of past illness**
Past medical history was not remarkable for this patient.

**Laboratory examinations**
Histopathological analysis of tissue biopsy samples collected from the right lung revealed poorly differentiated NSCLC (Figure 1) with the immunohistochemistry results of AE1/AE3 (+), SMACA4 BRG1 (+), CK18 (+), INI-1 (+), CD56 (-), chromogranin A (-), synaptophysin (-), CK7 (-), ERG (-), GATA3 (-), CD34 (-), CDX2 (-), P40 (-), SALL4 (-), TTF-1 (-), Desmin (-), and S-100 (-). In addition, PD-L1 expression analysis revealed a tumor proportion score of 80%. Molecular analysis of the biopsies detected no driver alterations in EGFR, ALK, or ROS1.

**Imaging examinations**
Computed tomography (CT) and magnetic resonance imaging revealed a tumor in the lower lobe of the right lung, right hilar and mediastinal lymph node involvement, and multi-organ metastasis including the left pleura, liver, pericardium, and bone.

**FINAL DIAGNOSIS**
The final diagnosis of the patient was NSCLC stage IV (T4N3M1).

**TREATMENT**
Based on the findings presented above, the patient was then treated with two cycles of gemcitabine (1.0 g/m² on days 1 and 8) plus cisplatin (75 mg/m² on day 1) with no clinical benefit.

**OUTCOME AND FOLLOW-UP**
In January 2019, an abdominal CT scan revealed the enlargement of the lung primary and liver metastases. To explore potentially actionable mutations, tumor biopsy samples were submitted for capture-based targeted sequencing using a panel with 520 cancer-related genes (OncoScreen Plus, Burning Rock, China). As shown in Figure 2, the analysis revealed the detection of two concurrent MET fusions with respective partner genes KIF5B (K24:M15) and CDR2 (M15:C3). No other classic lung cancer driver mutations were detected apart from TP53 C277X. Due to economic and insurance conditions and out of concern over evidence suggesting reduced efficacy of immunotherapy in non-
small cell lung cancer patients carrying oncogenic driver alterations[18], crizotinib (250 mg, p.o. bid) was started as the second line treatment in February 2019. After 4 wk of therapy, review of chest CT revealed a dramatic reduction of the lesions in the left and right lobes of the lungs with no new lesions, which was evaluated as partial response with Response Evaluation Criteria in Solid Tumors v.1.1 (RECIST 1.1) (Figure 3A and B). At approximately 3 mo from the start of targeted therapy, the patient continued to benefit from crizotinib without side effects. However, the disease progressed afterwards in May, 2019 as per RECIST 1.1. Specifically, compared with the previous evaluation (Figure 3B), new lesions emerged mostly in the right lung, accompanied by growth of the previously reduced tumor (Figure 3C and D).

After crizotinib failure, we chose nivolumab (a human IgG4 PD-1 antibody) as a salvage therapy because of the high PD-L1 expression. However, the patient did not benefit from nivolumab and her condition was declining significantly. She was hospitalized for worsening respiratory function and died shortly thereafter with an overall survival (OS) of 7 mo from diagnosis.

DISCUSSION

Gene alterations in MET are emerging as clinically relevant biomarker for predicting the response to MET inhibitors[2]. However, due to the rarity of MET fusions, treatment responses have only been clinically evaluated for MET amplification and exon 14 skipping[12-14] and only a few case reports have reported the efficacy of crizotinib in patients with MET fusions with various partners[5-7]. In our report, we describe the detection of KIF5B-MET co-occurring with a novel gene fusion involving MET and CDR2 and provided the clinical evidence of the efficacy of crizotinib in a KIF5B-MET and MET-CDR2-rearranged poorly differentiated NSCLC patient. KIF5B-MET K24:M15 has been reported in 0.5% (1/206) of adenocarcinoma and 4% (2/28) of sarcomatoid lung cancer patients in a recent study in Taiwanese patients[19]. In vitro and in vivo studies consistently demonstrated the oncogenic potential of KIF5B-MET fusion and sensitivity to crizotinib[19]. Consistently, several case reports have observed clinical efficacy of crizotinib in K24:M14[6] and K24:M15[5] KIF5B-MET-rearranged NSCLC[5,6]. The dramatic response to crizotinib observed in our patient highly suggests that the fusions acting either solely or in synergy served as oncogenic driver/s in the patient’s tumor which confers sensitivity to crizotinib. The oncogenic potential and sensitivity to crizotinib or other MET inhibitors of the novel gene fusion MET-CDR2 as well as the presence of two concurrent MET fusions require further investigations.

The negative results for histopathologic markers TTF-1, CK7, P40, and CDX2 and classic driver mutations in EGFR, ALK, and ROS1 provided neither clear indication of the cell differentiation nor any therapeutic targets. With a poor response to the first-line chemotherapy regimen, our patient had a very poor prognosis. Comprehensive genomic profiling allowed us to understand the mutation landscape of the tumor and explore alternative therapeutic targets that provided benefit to our patient. The detection of the potentially targetable MET fusions in our patient with poorly differentiated NSCLC highlights the importance of comprehensive genomic profiling regardless of tumor histology, particularly in patients with no known driver mutations to guide therapeutic decisions.

After the failure of crizotinib, we chose an immune checkpoint inhibitor (ICI) as a salvage therapy. Although with high PD-L1 expression, the patient did not benefit from the ICI. This is similar with the finding of previous studies that ICIs are less effective in NSCLC with EGFR mutation or EML4-ALK fusion[18,20].
Liu L et al. Crizotinib effective in a novel MET fusion

Figure 2 Next-generation sequencing revealed two concurrent MET fusions with different fusion partners, MET-CDR2 and KIF5B-MET. A: Images from the Integrative Genomics Viewer demonstrating the chromosomal rearrangement involving MET (chromosome 7, sequencing reads with gray background) and CDR2 (chromosome 16, sequencing reads with blue background); B: KIF5B (chromosome 10, sequencing reads with blue background). Illustrations below demonstrate the protein structure resulting from the gene fusions indicating the breakpoints of the nearby exons.

Attention should be paid to managing toxicities associated with crizotinib monotherapy. In a study of 2028 Japanese ALK-rearranged patients receiving crizotinib, adverse drug reactions occurred in 91.6% of patients, the most common (incidence ≥ 15%) of which were nausea (32.2%), diarrhea (24.3%), photopsia (18.9%), vomiting (17.5%), and dysgeusia (16.8%). A considerable proportion of patients (623, 30.7%) discontinued treatment within 12 wk after therapy initiation due to adverse events. Only 68.2% of patients remained on crizotinib after 3 mo, 55.2% after 6 mo, and 36.1% after 12 mo, with a median duration of 7.9 mo[10]. Therefore, it is advised to monitor patients for these adverse reactions during the...
CONCLUSION
The efficacy of crizotinib in an advanced poorly differentiated NSCLC patient with concurrent KIF5B-MET and MET-CDR2 gene fusions suggests that crizotinib can serve as a therapeutic option in patients with MET fusions. Further clinical studies are required to confirm the clinical value of crizotinib or other MET inhibitors in patients with MET fusion.

ACKNOWLEDGEMENTS
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FOOTNOTES
Author contributions: Liu LF and Deng JY contributed to the study concept and design and performed the statistical analysis; Liu LF, Deng JY, and Lin J contributed to the acquisition, analysis, and interpretation of the data; Liu L, Deng J, and Lizaso A contributed to the drafting of the manuscript; Sun S contributed to the critical revision of the manuscript for important intellectual content.

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CASE REPORT

Idarucizumab reverses dabigatran-induced anticoagulation in treatment of gastric bleeding: A case report

Yu Jia, Shao-Hua Wang, Na-Juan Cui, Quan-Xi Liu, Wei Wang, Xue Li, Ya-Mei Gu, Yan Zhu

Abstract

BACKGROUND
The drug instructions for dabigatran recommend adjusting the dosage to 110 mg twice daily for patients with bleeding risk, and performing at least one renal function test per year for patients with moderate renal impairment. However, owing to chronic insidiously worsening renal insufficiency, dabigatran can still accumulate abnormally, necessitating therapy with idarucizumab to reverse the anticoagulation due to severe erosive gastritis with widespread stomach mucosal bleeding.

CASE SUMMARY
A 76-year-old woman with a history of atrial fibrillation who took dabigatran 110 mg twice daily as directed to lessen the chance of stroke, was transported to the hospital with hematemesys and melena. Laboratory findings revealed severe life-threatening, blood-loss-induced anemia with a hemoglobin (Hb) level of 41.0 g/L and marked coagulation abnormalities with thrombin time (TT) > 180 s, most likely caused by dabigatran-induced metabolic disorder. Aggressive acid suppressive, hemostatic, and blood transfusion therapy resulted in the misconception that the bleeding was controlled, with subsequent rebleeding. Idarucizumab was administered in a timely manner to counteract dabigatran's anticoagulant impact, and 12 h later, TT was determined to be 17.4 s, which was within the normal range. Finally, the patient had no active bleeding signs and laboratory findings showed an Hb level of 104 g/L and TT of 17.7 s.

CONCLUSION
Renal function, coagulation function, and dabigatran concentration should be regularly monitored in older patients. Proton pump inhibitor and dabigatran coadministration is still controversial in preventing upper gastrointestinal tract bleeding.
INTRODUCTION
Dabigatran is an oral direct-acting thrombin inhibitor that was initially approved by the US Food and Drug Administration for the prevention of stroke and systemic embolism caused by nonvalvular atrial fibrillation (AF)[1,2]. It is considered safer and more effective than warfarin and does not require regular coagulation monitoring or dose adjustment, except for those with renal insufficiency (RI), advanced age, and low body weight[3].

However, even long-term dose-adjusted dabigatran therapy in older patients may also increase the risk of major bleeding such as the gastrointestinal (GI) hemorrhage described in this report or cerebral hemorrhage. Idarucizumab was introduced as a dabigatran antidote in December 2015, and its safety and efficacy have been proven in various studies[4]; however, clinical data are still limited, especially in Asians. Here, we report a case of an older Asian woman whose coagulation function was timely and successfully restored by idarucizumab to rescue her from this life-threatening GI bleeding.

CASE PRESENTATION

Chief complaints
On January 26, 2021, a 76-year-old Asian woman was admitted to our hospital with hematemesis and melena, which she had never experienced before and began the previous day.

History of present illness
Four days prior to this reported incident, the patient experienced upper abdominal discomfort and appetite loss without any recognizable precipitating factors.

History of past illness
The patient had a history of AF since 2019, and had been taking dabigatran (110 mg twice daily) to reduce her stroke risk. She had stopped taking dabigatran for at least 4 d before presenting to the hospital. In addition, she had a history of hypertension and coronary atherosclerotic heart disease for > 20 years, type 2 diabetes for > 5 years, and chronic RI (creatinine clearance 30-50 mL/min per 1.73 m²) for 1 year. The present event occurred > 12 years after she underwent surgery for bladder cancer and 7 years after thyroid nodule surgery.

Personal and family history
The patient had no other disease history and relevant family disease history.

Physical examination
On arrival at the ward, the temperature, heart rate, respiratory rate, and blood pressure of the patient
were 36.3 °C, 90 bpm, 18 breaths/min, and 105/80 mmHg, respectively. Her palpebral conjunctiva and complexion were pale, abdomen was soft, and middle and upper abdomen showed slight tenderness. In addition, the bowel sounds of the patient were 6/min.

**Laboratory examinations**
The routine blood tests of the patient showed a white blood cell count of 6890/μL and hemoglobin (Hb) level of 41 g/dL. The coagulation function test showed the following results: thrombin time (TT) > 180 s; activated partial thromboplastin time, 36.2 s; and international normalized ratio (INR), 1.20. The biochemical parameters of the patient were as follows: albumin, 34.6 g/L; blood urea nitrogen, 26.96 mmol/L; and serum creatinine, 251.0 μmol/L (Table 1). The tumor markers -fetoprotein, carcinoembryonic antigen, cancer antigen (CA)199, and CA125 were all within the normal range. The 13C urea breath test for detection of *Helicobacter pylori* (*H.* pylori) was negative.

**Imaging examinations**
Computed tomography of the entire abdomen showed no obvious abnormalities and electrocardiography showed normal sinus rhythm and abnormal ST-T changes. The electronic gastroscopy showed acute erosive gastritis with extensive gastric mucosal bleeding (Figure 1).

**FINAL DIAGNOSIS**
Acute erosive gastritis with extensive gastric mucosal bleeding was diagnosed using an electronic gastroscope.

**TREATMENT**
The patient was administered 2 U 400 mL packed red blood cells (PRBCs), a proton-pump inhibitor (PPI), and octreotide intravenously. On day 2, Hb level increased to 67 g/L and the chief complaints were nausea and retching, which appeared to be well controlled; the remaining concern was abnormal coagulation. On the next day, the patient defecated approximately 400 mL black stools with an Hb level, TT, PT and INR of 44 g/L, 121.20 s, 14.2 s, and 1.25, respectively and was immediately administered 2 U PRBCs.

Single doses of idarucizumab (2.5 g) were administered twice via intravenous infusion to reverse the effect of dabigatran, and the related commonly encountered adverse reactions such as fever, headache, hypokalemia, and delirium were not observed. Twelve hours later, the TT of the patient was 17.4 s, which was within the normal range. On day 4, she was administered an additional 2 U PRBCs for the third time, without symptoms of hematemesis and melena on the following days.

**OUTCOME AND FOLLOW-UP**
The patient had no recurrence of AF during hospitalization and her routine stool and occult blood test results were normal. Finally, she was discharged on hospitalization day 14, with Hb level of 104 g/L and TT of 17.7 s.

**DISCUSSION**
In this study, we presented the case of an older Asian woman whose coagulation function was effectively restored using idarucizumab to reverse the life-threatening GI bleeding experienced following administration of dabigatran. The prodrug of dabigatran, dabigatran etexilate, is rapidly converted to its active form following oral administration. It is an oral non-vitamin K antagonist anticoagulant that acts as a direct reversible and competitive inhibitor of both free and platelet-bound thrombin, thereby affecting the final step of blood clotting[5]. Because of properties such as a short half-life, rapid onset of action, fewer effects on food and drugs, and no INR monitoring requirement[6], dabigatran is deemed a safer and more effective medicine for preventing stroke than some other available agents.

Nevertheless, the elimination of dabigatran is highly dependent on the kidney, through which approximately 85% of plasma dabigatran is excreted, and the process can be prolonged with RI[7]. The RE-LY study demonstrated that dabigatran could reduce all-cause mortality and intracranial hemorrhage, but increased GI bleeding compared with warfarin. The risk of dabigatran-related GI bleeding seems to be evenly distributed between the upper and lower canals (53% vs 47%), whereas...
Table 1 Laboratory values during hospitalization

<table>
<thead>
<tr>
<th>Hospital day</th>
<th>Hb (g/L)</th>
<th>TT (s)</th>
<th>PT (s)</th>
<th>APTT (s)</th>
<th>INR</th>
<th>SCr (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>41</td>
<td>&gt; 180</td>
<td>13.7</td>
<td>36.2</td>
<td>1.20</td>
<td>251</td>
</tr>
<tr>
<td>Day 2</td>
<td>67</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Day 3</td>
<td>44</td>
<td>121.20</td>
<td>14.2</td>
<td>36.3</td>
<td>1.25</td>
<td>229</td>
</tr>
<tr>
<td>Day 4</td>
<td>56</td>
<td>17.40</td>
<td>13.1</td>
<td>25.9</td>
<td>1.15</td>
<td>213</td>
</tr>
<tr>
<td>Day 5</td>
<td>57</td>
<td>18</td>
<td>12.6</td>
<td>26.0</td>
<td>1.10</td>
<td>202</td>
</tr>
<tr>
<td>Day 6</td>
<td>76</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>182</td>
</tr>
<tr>
<td>Day 8</td>
<td>78</td>
<td>20.90</td>
<td>12.0</td>
<td>28.0</td>
<td>1.04</td>
<td>N/A</td>
</tr>
<tr>
<td>Day 10</td>
<td>85</td>
<td>17.70</td>
<td>12.7</td>
<td>29.6</td>
<td>1.11</td>
<td>N/A</td>
</tr>
<tr>
<td>Day 14</td>
<td>104</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>216</td>
</tr>
</tbody>
</table>

Hb: Hemoglobin (normal concentration: 110-150 g/L); TT: Thrombin time (normal: 14-21 s); PT: Prothrombin time (normal: 9.8-12.7 s); APTT: Activated partial thromboplastin time (normal: 21.1–36.5 s); INR: International normalized ratio (normal: 0.85-1.15); SCr: Serum creatinine (normal: 44-133 μmol/L); N/A: Not available.

Figure 1 Images of esophagogastroduodenoscopy captured on February 4, 2021 showing erosive and contact bleeding of gastric body mucosal surface.

The mechanism by which bleeding is induced remains unclear. One possible theory suggests that the local metabolism of dabigatran etexilate increases the concentration of active dabigatran during transit through the GI tract. Dabigatran-induced GI hemorrhage is also related to age and primarily occurs in patients aged ≥ 75 years. H. pylori infection, liver cirrhosis, malignant tumors, genetic factors, history of major bleeding, peptic ulcers, and GI injury such as diverticulosis and intestinal vascular dysplasia can also increase the risk of bleeding.

In this case report, the patient was a 76-year-old Asian woman with a history of AF and concealed progressive RI. She had undergone long-term dabigatran therapy with dose adjustments for 1 year, regular blood coagulation function monitoring, and oral administration of a PPI. The massive hemorrhage from the gastric mucosa was likely induced by prolonged dabigatran excretion because of RI.

Idarucizumab is a humanized monoclonal antibody that specifically and efficiently inhibits the biological activity of dabigatran etexilate. After antibody-antigen binding, it irreversibly neutralizes the anticoagulant effect. The binding affinity of idarucizumab to dabigatran is 350 times higher than that of dabigatran to thrombin, and the reversal effect shows rapid onset and lasts 12 h, which is suitable for life-threatening bleeding, uncontrolled hemorrhage, or emergency surgery in patients administered dabigatran. A single dose of 5 g idarucizumab is reported to be sufficient to reverse the effect of dabigatran etexilate in 98% of patients, and the effect is maintained in most patients for 24 h.

Considering the extensive gastric mucosal bleeding experienced by this patient, endoscopic hemostasis was less efficient. The conventional therapeutic regimen of acid suppression, hemostasis,
and blood transfusion did not achieve hemostasis in this patient and idarucizumab was administered to reverse the effect of dabigatran to rescue her from the second episode of life-threatening bleeding. Subsequently, the patient, whose coagulation function was normalized during hospitalization, was relieved of the symptoms of hematemesis and melena, and her Hb level increased to 104 g/L on day 14. Finally, the patient was discharged in stable conditions.

This study had the following limitations and shortcomings that are worth mentioning. (1) The serum level of dabigatran was not measured because of restricted laboratory conditions; (2) Colonoscopy was not performed because we could not obtain informed consent from the patient; and (3) We were unable to detect any possible intracardiac thrombus caused by AF because the transesophageal echocardiography technique was unavailable.

CONCLUSION

We report a case of safe and successful reversal of dabigatran-induced abnormal coagulation function by idarucizumab. In addition, we provide evidence to support recommendations for regular renal and coagulation function tests and dabigatran concentration monitoring for older patients where clinical conditions permit. This is to ensure that proper dose adjustments of dabigatran are instituted or the drug discontinuation is timely if unpredictable blood loss occurs. As mentioned in the discussion regarding dabigatran-induced GI-bleeding-related factors, especially H. pylori infection, there is currently no consensus on the benefits of coadministration of PPIs with dabigatran, which warrants further investigation.

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FOOTNOTES

**Author contributions:** Jia Y and Zhu Y wrote and modified the manuscript; Wang SH performed the gastroscopy, confirmed the report, and provided the figures; Wang W and Li X collected the data; Cui N participated in the patient treatment; Zhu Y and Liu QX connected us to the pharmaceutical factory and purchased the idarucizumab; Gu YM and Wang SH reviewed the paper and provided suggestions for the revision; all authors have read and approved the final manuscript.

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Immunoglobulin G4-related disease involving multiple systems: A case report

Yu-Qiong An, Ning Ma, Yong Liu

**Abstract**

**BACKGROUND**

IgG4-related disease (IgG4-RD), an immune-mediated chronic progressive fibroinflammatory disease, can affect the functions of several organs. Some common characteristics can be observed in different IgG4-RDs, such as higher prevalence in middle-aged and elderly male patients, raised serum IgG4 levels, abundant infiltration of IgG4-positive cells and fibrosis, diffuse or localized swelling of the affected organs, and good response to glucocorticoids treatment.

**CASE SUMMARY**

A 72-year-old man complained of left upper abdominal pain 3 mo ago, and he was diagnosed with acute onset of chronic cholecystitis and acute pancreatitis in the local hospital. Pain improved after relevant treatment. Several days ago, his abdominal pain worsened, and he was admitted to our hospital for further treatment. Doppler ultrasound showed that the pancreas presented with sausage-like swelling and the parenchymal echo was diffusely reduced. Gallbladder volume was increased, while the wall was rough and thickened with bilateral signs. Furthermore, the left submandibular gland was enlarged, accompanied with significantly increased blood flow signals. Finally, we found that the adventitia of the abdominal aorta and right iliac artery was thickened locally. Serum IgG4 was elevated to 12600 mg/L. Therefore, the patient was diagnosed with IgG4-RD. After treatment with methylprednisolone, he had an uneventful course and was discharged in good condition.

**CONCLUSION**

IgG4-RD can involve almost any organs. Ultrasound has a significant role in timely and accurately diagnosis.
KEY WORDS: Immunoglobulin G4; Autoimmune pancreatitis; Cholecystitis; Arteritis; Ultrasound; Case report

Core Tip: Immunoglobulin G4-related disease (IgG4-RD) can involve multiple organs and sites, such as the glands and ductal tissues. However, it is rare that a patient with more than three organs are involved at the same time, as well as the arterial lesions. In our case, we report a patient with the autoimmune inflammation, his four organs and tissues are involved, they are the aorta, pancreas, gallbladder, and submandibular gland. Meanwhile, the involved abdominal aorta and iliac artery presented as IgG4-related periarteritis. Finally, we made a comprehensive diagnosis according to the clinical histology, imaging, serology, and the response to the therapy.

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INTRODUCTION

IgG4-related disease (IgG4-RD) is an immune-mediated chronic progressive fibroinflammatory disease, which can involve multiple organs or tissues, such as pancreas, biliary tract, salivary glands, lacrimal glands, lung, kidney, and retroperitoneum[1-4]. IgG4-RD has a higher prevalence in male patients with age over 50 years[5,6] and it is easily confused with malignant tumor, infection, and other autoimmune diseases. Histopathology plays a key role in the diagnosis of IgG4-RD, and the typical pathological manifestations include lymphoplasmacytic infiltration, storiform fibrosis, and obliterator phlebitis[7,8]. The affected organs present as localized or diffused swelling, while the serum IgG4 concentration is often significantly elevated[9]. A comprehensive diagnostic criterion was established by the Japan College of Rheumatology in 2011[9] and the corelative classification criteria for IgG4-RD was also developed by the American College of Rheumatology/European League Against in 2019[10]. Besides, most patients have a good response to the steroids or rituximab therapy within a short time, but it is common for this disease to recur.

Although IgG4-RD can involve multiple organs and sites, it is still rare that a patient with more than three organs are involved at the same time and most of the affected sites are glands and ductal tissues. Meanwhile, the arterial lesions are less common in IgG4-RD. In our case, the autoimmune inflammation involved four organs and tissues, including the aorta, pancreas, gallbladder, submandibular gland, and the abdominal aorta and iliac artery presented with IgG4-related periarteritis. Finally, a comprehensive diagnosis is made, according to the clinical histology, imaging, serology, the appearance of the affected organs, and response to therapy.

CASE PRESENTATION

Chief complaints
A 72-year-old man was admitted to the gastroenterology department with pain in the left upper quadrant for 3 mo.

History of present illness
The patient had left upper abdominal pain 3 mo ago, accompanying with symptoms of anorexia, yellow urine, chills, nausea, vomiting, abdominal distention, and diarrhea, but no cough, expectoration, hemoptysis and other lung symptoms. Thus, he was referred to the local hospital. After the relevant laboratory and imaging examinations, the patient was diagnosed with acute onset of chronic cholecystitis and acute pancreatitis. The pain symptom improved after liver protective and anti-infective treatment, resolving tetany, pain relief, and fluid rehydration. Three days ago, his abdominal pain worsened and he was admitted to the Department of Gastroenterology in our hospital for further treatment.

History of past illness
He has a history of chronic hepatitis B > 30 years and hypertension for 10 years treated with nifedipine.
He underwent excision of the right mandible mass 5 mo ago, and pathological results showed massive lymphocyte infiltration with fibrous tissue hyperplasia.

**Personal and family history**
His father and daughter are both carriers of hepatitis B virus.

**Physical examination**
There was tenderness in the upper abdomen, no rebound pain and muscle tension, and no mass was touched in the whole abdomen. A surgical scar of 3-4 cm was seen in his right mandible. The others showed no obvious abnormality.

**Laboratory examinations**
Biochemical examinations showed that ESR was 25 mm/h (normal range 0-15 mm/h). Tumor marker carbohydrate antigen 15-3 was 24.3 U/L. Hepatitis B surface antigen (HBsAg) was 1.06 IU/mL, hepatitis Be antigen (HBeAg) was 0.02 S/CO, hepatitis B core antibody (HBcAg) was 10.07 S/CO. Finally, serum IgG4 was elevated to 12600 mg/L. The routine urine tests and renal function tests were all normal.

**Imaging examinations**
Abdominal ultrasound revealed that the pancreas was diffusely enlarged and sausage-shaped, in which the anteroposterior diameters of the pancreatic head, body and tail were 3.1 cm, 2.7 cm and 2.2 cm, respectively. The pancreatic parenchyma echo was diffusely reduced and the boundary was not clear (Figure 1A). The gallbladder volume was enlarged, and the wall was rough and thickened with bilateral signs. Silt-like deposits were found in the gallbladder with a range of 5.6 cm × 2.0 cm (Figure 1B). Contrast-enhanced ultrasound (CEUS) revealed that the pancreatic lesions were uniformly enhanced in the arterial phase (Figure 1C). Computed tomography scan indicated that the pancreas was enlarged, and its head had spotty, high-density foci. The gallbladder was enlarged and the cyst wall was thickened (Figure 1D). Furthermore, there were no obvious abnormalities in the lung and kidneys. Thus, autoimmune pancreatitis with gallbladder involvement was considered.

Salivary gland ultrasound showed that the right submandibular gland was almost completely removed, and the left submandibular gland was enlarged with a size of 2.5 cm × 1.4 cm. We found that the parenchymal echo was not uniform, and companied with reticular separation and scattered flake-like hypoecho (Figure 2A). Color doppler flow imaging suggested that the blood flow signal was significantly increased (Figure 2B). There was no obvious abnormality in the bilateral parotid and sublingual glands.

Abdominal arterial ultrasound showed that the adventitia of the abdominal aorta and right iliac artery was locally thickened with a maximum up to 5.0 mm (Figure 3A and B). CEUS demonstrated that extensive new blood vessels were distributed in the adventitia, while the intensity of imaging was evaluated to grade III (Figure 3D). These results were similar to the inflammatory activity of periarteritis. Multiple strong echogenic plaques were seen on the arterial wall, suggesting atherosclerosis of the abdominal aorta and iliac artery. Additionally, ulceration was observed in the plaque of the posterior wall of the abdominal aorta (Figure 3C).

**FINAL DIAGNOSIS**
Combined with the clinical manifestations, pathological results, laboratory examinations, and imaging results, IgG4-RD simultaneously affects the pancreas (autoimmune pancreatitis), gallbladder (cholecystitis), salivary gland (submandibular adenitis), and aorta (pancreatitis).

**TREATMENT**
After excluding the relative contraindications for glucocorticoids, such as tumors and tuberculosis, the patient was injected intravenously with methylprednisolone and supplemented with antihypertensive and hypoglycemic treatment, gastric mucosa protection, liver protection and other treatments.

**OUTCOME AND FOLLOW-UP**
The patient had an uneventful course and was discharged in good general condition. The patient was instructed to take prednisolone on time and closely monitor blood pressure and blood glucose. One month later, there was no obvious abnormality when re-examined by the ultrasound and biochemical tests.
An YQ et al. A case report of IgG4-RD

DISCUSSION

IgG4-RD is a rare disease that can involve multiple organs at the same time[1,11,12], which is similar to many malignant, infectious, and inflammatory diseases[13]. The epidemiological data of IgG4-RD have not been completely established due to rarity and misdiagnosis[14,15]. The clinical manifestations of IgG4-RD mainly depend on the affected organs and lack specificity, which is challenging for making correct diagnosis[16]. According to the comprehensive diagnostic criteria published in 2012[9], IgG4-RD patients must have (1) A compatible clinical presentation (swelling or masses in single/multiple organs); (2) Serum IgG4 concentration > 135 mg/dL; and (3) Histopathological evidence of marked lymphocytic and plasmocytic infiltration (IgG4-plasma cells/high-power field > 10 with IgG4/IgG-positive cell ratio > 40%). The patient in our case initially presented with epigastric pain similar to pancreatitis and was misdiagnosed with acute pancreatitis in another hospital. However, it was later

Figure 1 The ultrasound and computed tomography images of pancreas and gallbladder. A: The pancreas is diffusely enlarged with unclear boundary and the parenchyma echo is reduced; B: The gallbladder volume is enlarged and the wall is rough, accompanying with the silt-like deposits; C: The pancreatic lesions area is uniformly enhanced in arterial phase after the intravenous ultrasound contrast-enhanced; D: Contrast-enhanced computed tomography image revealing that both the pancreas and gallbladder are enlarged and the gallbladder wall is thickened, which are consistent with the ultrasound results.

Figure 2 The ultrasound image of the left submandibular gland. A: The submandibular gland is enlarged and its parenchyma echo is not uniform; B: Color doppler flow imaging suggesting that the blood flow signal is significantly increased.
found that the lesions involved multiple sites, and the volume of the affected organs, such as the pancreas, gallbladder, and submandibular gland increased significantly, and serum IgG4 increased to 12600 mg/L (> 1.35 g/L). The pathological results of the previous operation on the submandibular gland suggested that lymphocyte infiltration was accompanied by fibrous tissue hyperplasia. Our case fulfilled all the comprehensive diagnostic criteria, so we made the diagnosis of multisystem IgG4-RD.

If patients present with any typical clinical, serological or radiographic results, the clinical diagnosis sometimes can be made without pathological biopsy examinations[17]. If the patient has typical imaging findings of IgG4-RD, such as sausage-shaped pancreas[3,18] and periarteritis affecting the aorta below the renal artery, combined with relevant clinical manifestations and serological data, clinical diagnosis of IgG4-RD should be considered[10]. For our patient, most of the characteristic manifestations of IgG4-RD were found (such as the lesion involved the pancreas and salivary gland), along with typical imaging findings (such as sausage-shaped swollen pancreas). In addition, periarteritis affecting the abdominal aorta and iliac artery, with inflammatory thickening of the arterial wall, supported the diagnosis of IgG4-RD[19].

The 72-year-old patient presented with multiple sclerotic plaques in the abdominal aorta and iliac artery. There was ulceration on the surface of the sclerotic plaque. At that time, we suspected that the autoimmune inflammation stimulated the arterial wall for a long time and IgG4-RD caused the sclerotic plaques to rupture and ulcerate. It has been shown that IgG4-RD retroperitoneal fibrosis usually occurs around the aorta, suggesting that the adventitia of the arterial vessels may also be a target of this disease[20]. Doppler ultrasound and CEUS revealed that the adventitia of the abdominal aorta and iliac artery were thickened with multiple neovascularization, which also suggested that IgG4-RD mainly involved the adventitia. It has also been reported that IgG4-RD arteritis can lead to aneurysm formation[20], suggesting that inflammation may stimulate diffuse thickening of the arterial wall, narrow the arterial lumen, and cause aneurysm formation[19]. Therefore, if the multisite lesion does not respond to conventional treatments, IgG4-RD should be considered. More attention should be paid to the lesions involving large vessels and aneurysm formation.

Glucocorticoid therapy is the best choice after diagnosis of IgG4-RD[21], while the surgery, radiotherapy and chemotherapy should be avoided as far as possible. Before using glucocorticoids, contraindications to corticosteroids (such as tuberculosis and tumor) should be excluded[22]. For patients with the arteritis, it is important to be aware of the risk of the artery wall becoming thinner or even rupturing during glucocorticoid therapy, which requires real-time monitoring and appropriate intervention.
CONCLUSION

In our case, IgG4-RD involved several anatomical sites and multiple tissues and organs. A comprehensive diagnosis of IgG4-RD, including clinical history, imaging results, and pathological features, should be made. Doppler ultrasound as a noninvasive and convenient method plays an important role in the diagnosis of IgG4-RD. Timely and effective diagnosis could prevent serious organ injury, tissue fibrosis, and even death.

FOOTNOTES

Author contributions: An YQ reviewed the literatures and contributed to manuscript drafting; Liu Y analyzed and interpreted the imaging findings; Liu Y and Ma N were responsible for the revision of the important intellectual contents; all authors issued the final approval for the submitted version.

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Daptomycin and linezolid for severe methicillin-resistant
*Staphylococcus aureus* psoas abscess and bacteremia: A case report and review of the literature

Xiao-Bing Hong, Ze-Lin Yu, Hong-Bo Fu, Ze-Hong Cai, Jie Chen

**Abstract**

**BACKGROUND**

Vancomycin remains a first-line treatment drug as per the treatment guidelines for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. However, a number of gram-positive cocci have developed resistance to several drugs, including glycopeptides. Therefore, there is an urgent need for effective and innovative antibacterial drugs to treat patients with infections caused by drug-resistant bacteria.

**CASE SUMMARY**

A 24-year-old male was admitted to hospital owing to lumbago, fever, and hematuria. Computed tomography (CT) results showed an abscess in the psoas major muscle of the patient. Repeated abscess drainage and blood culture suggested MRSA, and vancomycin was initiated. However, after day 10, CT scans showed abscesses in the lungs and legs of the patient. Therefore, treatment was switched to daptomycin. Linezolid was also added considering inflammation in the lungs. After 10 d of the dual-drug anti-MRSA treatment, culture of the abscess drainage turned negative for MRSA. On day 28, the patient was discharged without any complications.

**CONCLUSION**

This case indicates that daptomycin combined with linezolid is an effective remedy for bacteremia caused by MRSA with pulmonary complications.
Key Words: Bacteremia; Daptomycin; Gram-positive cocci; Linezolid; Methicillin-resistant Staphylococcus aureus; Vancomycin; Case report

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Core Tip: We analyzed a case of severe methicillin-resistant Staphylococcus aureus (MRSA) bacteremia who failed to respond to first line treatment using vancomycin. We believe that our study makes a significant contribution to the literature because it indicates that daptomycin combined with linezolid is an effective remedy for bacteremia caused by MRSA with pulmonary complications.

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INTRODUCTION

Vancomycin is the first-line treatment drug as per the treatment guidelines for methicillin-resistant Staphylococcus aureus (MRSA) infections. However, daptomycin is considered to be at least as effective as vancomycin in treating MRSA bacteremia, and a high dose of daptomycin is recommended in combination with another drug (including gentamicin, rifampicin, or linezolid) as a salvage treatment plan for persistent MRSA bacteremia when vancomycin fails. In general, the basic principles of using combination therapy involve a wide antibacterial spectrum, synergistic effect, and low risk of development of drug-resistant strains[1]. Daptomycin is a cyclic lipopeptide antibacterial agent produced by Streptomyces roseosporus. This agent targets the bacterial cell membrane through calcium-dependent pathways, disrupting electrical potential, altering cell membrane permeability, opening ion channels, and eventually causing cell death[2]. The drug has been approved by the U.S. Food and Drug Administration for adult patients with MRSA infections, including MRSA blood flow infections, right-sided infective endocarditis, and complicated skin and soft tissue infections[3]. Several studies have shown that daptomycin exhibits very good efficacy against bacteremia caused by MRSA, even when the minimum inhibitory concentration (MIC) of vancomycin is high[4]. In general, the use of 6 mg/kg daptomycin is recommended each day for bacteremia caused by MRSA[2]. However, several studies have shown that up to 8 mg/kg daptomycin each day is required for patients with refractory MRSA infections[5,6]. In such clinical situations, the combination of daptomycin and other synergistic antibacterial agents may serve as an effective therapeutic strategy. In this report, a case of severe MRSA bacteremia observed in the clinical setting was analyzed to provide a reference for clinical treatment.

CASE PRESENTATION

Chief complaints
The patient (male, aged 24 years, height 175 cm, weight 72 kg, Han nationality, unmarried) was admitted to our hospital for bilateral lumbago without obvious inducement and fever accompanied by hematuria for 14 d. He complained of reduced urine volume and gross hematuria at the end of urination.

History of present illness
He visited another hospital, but experienced not significant pain relief, before visiting our hospital for treatment.

History of past illness
The patient did not have any past medical history.

Personal and family history
The patient did not have any personal and family history.
Physical examination
The highest body temperature was recorded to be 37.7 °C.

Laboratory examinations
Laboratory examination results upon admission were the following: white blood cell (WBC), $42.08 \times 10^9 /L$; neutrophil count (NEUT %), 0.89; C-reactive protein (CRP), 271.42 mg/L; procalcitonin (PCT), 46.97 ng/mL; creatinine, 199 μmol/L; Na, 123 mmol/L; alanine aminotransferase, 63 U/L; aspartate transaminase, 96 U/L; and total bilirubin, 177.3 μmol/L. Abscess drainage culture was positive, but blood culture was negative for MRSA [Sensitive to vancomycin (MIC 0.5 μg/mL), teicoplanin, linezolid, and daptomycin; Table 1].

Imaging examinations
The chest, abdominal, and pelvic computed tomography (CT) scans revealed the following: multiple lesions in the left psoas major, iliopsoas, iliacus, and piriformis, suggesting the possibility of inflammation and abscess formation accompanied by a small amount of local pneumatosis; multiple calculi in the left kidney; a calculus in the left upper ureter; and mild dilation and effusion in the left renal pelvis, calyx, and upper ureter.

Further diagnostic work-up
He was admitted to the emergency department (observation area) of our hospital on May 27, 2020, where treatment with vancomycin (1 g every 12 h) was initiated. His condition did not significantly improve after active anti-infective treatment (vancomycin 1 g every 12 h), percutaneous catheter drainage from the psoas major and gluteus maximus, and other treatments. CT re-examination on June 2, 2020 showed that the abscess in the psoas major was similar to that reported in the previous scan (Figure 1). Bilateral pleural effusion had further progressed. Re-examination on June 3, 2020 revealed the following: WBC, $23.59 \times 10^9 /L$; NEUT %, 0.902; CRP, 113.2 mg/L; creatinine, 176 μmol/L; Na, 126 mmol/L; PCT, 2.57 ng/mL. The patient was transferred to the intensive care unit (ICU) on June 3, 2020.

Conditions upon transfer to the ICU on 3 June 2020 were as follows: fever, temperature of 37.9 °C; shortness of breath, respiratory rate 33 bpm; stable circulation; and fast heart rate, 116 bpm. As the patient had multiple renal calculi accompanied by ureteral calculi, indwelling urinary catheter, and a complicated urinary tract infection, common pathogenic bacteria of urinary tract infections, including Enterobacteriaceae bacteria such as Escherichia coli, were assumed to be present. Thus, imipenem and cilastatin sodium (1 g every 8 h) was added to the treatment regimen to treat the urinary tract infection upon transfer to the ICU. The dose of vancomycin was maintained, and blood was drawn to measure the trough concentration.

Pathogenic metagenomics testing on June 4, 2020 revealed Streptomyces aureus presence both in the blood and the right gluteus maximus drainage fluid. Culture of the drained pus continued to show presence of MRSA [sensitive to vancomycin (MIC 1.5 μg/mL, an increase from that of earlier), teicoplanin, linezolid, and daptomycin]. The patient had persistent hyperpyrexia on June 5, 2020, with the highest temperature of 38.9 °C (the duration with a temperature above 38 °C was 13 h). The anterior side of the left leg was red and swollen. Flowing liquid was observed under B-ultrasonography, indicating a new abscess. CT scans of the thighs and lungs also revealed new infectious lesions (Figure 2). The decreases in inflammation indicators were not significant (CRP, 139.62 mg/L; WBC, $26.86 \times 10^9 /L$; NEUT %, 0.883).

FINAL DIAGNOSIS
Psoas abscess, sepsis (MRSA bacteremia), kidney calculi with ureteral calculi, skin and soft tissue infection.

TREATMENT
The trough concentration of vancomycin was 35.18 μg/mL. Although the trough concentration of vancomycin reached the target, infection control was poor. Following these results, the patient was switched from vancomycin to daptomycin (0.5 g daily). At the same time, slight high-density patchy shadows were found in the lower lobes of both lungs; thus, the spread of the infection to the lungs through blood circulation could not be ruled out. Therefore, linezolid was added to treat the possible MRSA infection in the lungs (Figure 3).
Table 1 Antimicrobial-susceptibility of the isolated strain on May 30th and June 7th

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>MIC (mg/mL)</th>
<th>MIC categories</th>
<th>Pre-test</th>
<th>Post-test</th>
<th>Pre-test</th>
<th>Post-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>≥ 0.5</td>
<td></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxacillin</td>
<td>≥ 4</td>
<td></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≤ 0.5</td>
<td></td>
<td>S</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.5</td>
<td></td>
<td>S</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>≥ 8</td>
<td></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>≥ 4</td>
<td></td>
<td>R</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>2</td>
<td></td>
<td>S</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>≤ 0.5</td>
<td></td>
<td>S</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>≤ 0.5</td>
<td></td>
<td>S</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td>≤ 0.12</td>
<td></td>
<td>S</td>
<td>S</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Main treatment course and monitoring. MIC: Minimal inhibitory concentration; R: Resistance; S: Susceptible.

Figure 1 Chest, abdominal, and pelvic computed tomography scans. A: May 27, 2020 computed tomography (CT) scan; B: June 2, 2020 CT scan.

OUTCOME AND FOLLOW-UP

The patient also had a ureteral obstruction, and ultrasound-guided catheter drainage from the left renal pelvis performed on June 5, 2020. On June 6, 2020, fever persisted, but the peak temperature was lower than that observed earlier, with the highest temperature of 38.8 °C (the duration with a temperature above 38 °C was 10 h). The duration of fever was shorter and the values of infection indicators were lower (CRP, 79.86 mg/L; WBC, 19.17 × 10^9/L; NEUT %, 0.841; PCT, 0.61 ng/mL) than those earlier. On June 13, 2020, the patient had stable respiration and circulation, shorter fever duration (the duration with a temperature above 38 °C was 8 h), and decreased levels of infection indicators than those earlier, suggesting that the infection was controlled. Therefore, the patient was transferred back to the general ward for further treatment.

After the transfer to the general ward, the combination of daptomycin (0.5 g daily, June 5–June 23) and linezolid (0.6 g every 12 h, June 5–July 3) was continued to be administered as anti-infection treatment, while imipenem and cilastatin sodium were de-escalated to cefoperazone sodium and sulbactam sodium to combat gram-negative bacteria infection (Figure 3). On June 15, 2020, the culture of the patient drainage was tested negative and no fever was reported. On June 29, 2020, the levels of PCT, WBC, CRP, and NEUT % were 0.21 ng/mL, 10.36 × 10^9/L, 35.56 mg/L, and 0.706, respectively, and no fever was recorded. On July 3, 2020, the patient was in stable condition without fever. Considering the left nephrostomy of the patient and the amelioration of urinary obstruction, the department of urology suggested to maintain the left nephrostomy tube unobstructed, which could be treated after the complete recovery of the patient. Therefore, the patient was discharged on July 3, 2020.
**DISCUSSION**

**Initial treatment plan selection for the psoas abscess and analysis of the reasons for treatment failure**

According to the 2014 Infectious Diseases Society of America Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (SSTIs)[7], the infection of the patient belonged to the category of severe purulent SSTIs, which was treated by incision and drainage of a small volume of fluid. During hospitalization, multiple drainage fluid cultures and next-generation sequencing (blood and drainage fluid samples) indicated MRSA (sensitive to vancomycin MIC 0.5 μg/mL) infection, consistent with the fact that *Streptomyces aureus* is a common pathogen of skin and soft tissue infections. The patient was administered vancomycin (1 g every 12 h) after admission. The levels of infection indicators decreased, but high fever persisted. CT re-examination showed that the abscess was similar to that observed before. As the creatinine level was 176 μmol/L and creatinine clearance rate was 56.4 mL/min, the condition was mild renal insufficiency; hence, it was not necessary to reduce the vancomycin dose of 0.5 g every 8 h (loading dose 1 g). Although the trough concentration of vancomycin on June 5, 2020 was 35.18 μg/mL, the infection continued to spread further from the original site in the psoas major to the thighs, legs, and lungs.

There might have been two reasons for the spread of the infection. First, the MIC value of vancomycin increased; the initial MIC value was 0.5 μg/mL, which increased to 1.5 μg/mL on June 5, 2020, suggesting that the sensitivity to vancomycin decreased. For a long time, vancomycin has been used as the gold standard for the treatment of MRSA infections, but there have been clinical reports on strains with MIC values of 1–2 μg/mL where the underlying infections were associated with treatment failure[8]. According to the latest guidelines on vancomycin in 2020[9], both in vitro and in vivo experiments of vancomycin have shown that the ratio of 24 h area under the concentration-time curve to
MIC (AUC/MIC) can effectively predict the efficacy of vancomycin in \textit{Streptococcus aureus} infection. A study\cite{10} simulated the efficacy of vancomycin in \textit{Streptococcus aureus} infection under different MIC values using a single-compartment pharmacokinetic model and Monte Carlo simulation by including intensive care unit patients; this study concluded that, at an MIC of 1 μg/mL, the daily dose of vancomycin should be at least 3–4 g to achieve a 90% probability of target attainment. According to a systematic review and meta-analysis\cite{11}, a high vancomycin MIC of ≥ 1.5 μg/mL is related to mortality, and it is difficult to achieve a target AUC/MIC of ≥ 400, especially in MRSA bacteremia once the MIC rises beyond a certain value. This also explains why the clinical efficacy in this case was unsatisfactory when the trough concentration of vancomycin reached the target; it was possibly owing to the AUC/MIC failing to reach the target value with the increase in the MIC value of vancomycin. Second, the tissue penetration was poor. Vancomycin is a water-soluble drug with a small volume of distribution value of 0.4–1 L/kg, and its binding rate to plasma albumin is 10%–50%. As this patient had skin and soft tissue infection, the vancomycin concentration in the skin and soft tissues may have been insufficient.

\textbf{Selection of treatment schemes for MRSA bloodstream infections after vancomycin treatment failure}

Under normal circumstances, infections caused by drug-resistant gram-positive cocci can be treated with monotherapies, as drug combinations may increase the incidence of adverse drug reactions and treatment costs. Hence, it is necessary to strictly grasp the indications and avoid misuse of the drug. The best treatment strategy for severe MRSA infections has not yet been determined. The 2011 Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-resistant \textit{Staphylococcus aureus} Infections in Adults and Children\cite{3} propose that MRSA bloodstream infections that cannot be effectively controlled with a single antibacterial agent should be treated with drug combinations. A high dose of daptomycin combined with other drugs (e.g., gentamicin, rifampicin, linezolid, compound sulfamethoxazole tablets, or anti-\textit{Staphylococcus} β-lactam antibiotics) can be chosen for combination treatment. Another novel aminomethylcycline antibiotic Omadacycline has a potential role in the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI) caused by Gram-positive (including MRSA), and as the 2 randomized, controlled studies show Omadacycline had high efficacy and acceptable safety, similar to that of linezolid, in the treatment of ABSSSI caused by gram-positive pathogens, including MRSA\cite{12,13}.

Glycopeptide monotherapies have many shortcomings, including poor tissue permeability, slow bactericidal action, and the emergence of drug-resistant strains\cite{14}. Daptomycin, which has a rapid bactericidal effect on MRSA, may be an ideal treatment option\cite{20}. However, daptomycin needs to be administered at a high dose in patients with high MIC\cite{15}, and the prognosis is poor\cite{16}. Linezolid is the first marketed synthesized oxazolidinone that can inhibit protein synthesis by affecting the 50S subunit of the bacterial ribosome\cite{5}. In addition, a number of \textit{in vitro} and \textit{in vivo} studies as well as case reports have shown the efficacy of daptomycin combined with linezolid. Parra-Ruiz \textit{et al}\cite{17} reported that linezolid fails to achieve bactericidal activity against MRSA for planktonic bacteria (PB) or biofilm-embedded bacteria (BB) within 72 h in pharmacokinetic/pharmacodynamic biofilm models \textit{in vitro}. The sustained bactericidal activity of daptomycin on PB was achieved within 48 h, whereas neither daptomycin nor linezolid exerted bactericidal effects on BB. In contrast, when linezolid was used in combination with daptomycin, the bactericidal effect was significantly increased. The combination showed bactericidal activity against PB and BB in 48 h. Therefore, the daptomycin and linezolid combination therapy is more effective than monotherapy using either of them\cite{17}. Similar results were observed using a simulated endocardial neoplasm model\cite{18}. Two recent studies have reported the same result through an \textit{in vitro} combined drug sensitivity test\cite{19,20}; the synergistic effect was 66%-77% for daptomycin combined with linezolid against MRSA, with no antagonistic effect. We conducted a literature search in PubMed in an attempt to identify all published cases reporting on the efficacy of linezolid and daptomycin combination for MRSA infection. Three cases published in the literature previously were eventually summarized in Table 2. A case report on the effectiveness of this treatment scheme reported, for the first time, a case involving a 62-year-old patient with MRSA bacteremia and MRSA meningitis\cite{21}. Initially, he was administered daptomycin and linezolid because of his allergy to vancomycin. However, the persistent MRSA bacteremia led to the addition of rifampicin because of its anti-MRSA activity and its ability to pass through the blood-brain barrier. Finally, his blood cultures were negative after 10 d of admission. In addition, linezolid combined with daptomycin can be used to treat endocarditis caused by MRSA\cite{22}; this was a case of a 26-year-old patient with endocarditis caused by MRSA complicated by pneumonia. The patient was initially treated with vancomycin combined with gentamicin, but vancomycin was switched to daptomycin (8 mg/kg) because of acute renal injury, and linezolid (600 mg every 12 h) was used to treat the MRSA in the lungs. Thirteen days after switching to daptomycin and linezolid, the MRSA bacteremia test results were negative. Another case very similar to the previous one involved a 36-year-old young female with infective endocarditis complicated by a septic pulmonary embolism who had a history of MRSA bacteremia infection that had occurred a year before this infection\cite{23}. The initial treatment plan for this patient was also vancomycin, but the sensitivity to vancomycin decreased on the fourth day of treatment (MIC 2 μg/mL); hence, the treatment was adjusted with linezolid (600 mg every 12 h) and daptomycin (8 mg/kg), and the blood culture result turned negative after 13 d. In this present case, vancomycin was selected as the initial
Table 2 Clinical factors, treatment details, and outcomes among 3 patients treated with Daptomycin and linezolid for methicillin-resistant Staphylococcus aureus bacteremia and complication.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Ref.</th>
<th>Reason for Daptomycin/linezolid use</th>
<th>Host factors</th>
<th>Complication</th>
<th>Prior antimicrobial therapy</th>
<th>Other active antimicrobials available</th>
<th>Daptomycin/linezolid dose; duration</th>
<th>MIC (mg/mL)</th>
<th>Outcome, follow-up duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kelesidis et al[21], 2011</td>
<td>Allergy 62 y/o with placement of the coatrial and lumbo-peritoneal shunts</td>
<td>Meningitis</td>
<td>Daptomycin</td>
<td>Vancomycin</td>
<td>Daptomycin (NS); linezolid (600 mg twice daily); 4 d</td>
<td>Daptomycin (≤ 0.5 μg/mL), vancomycin (1 μg/mL), linezolid (4 μg/mL), rifampin (0.06 μg/mL)</td>
<td>Clinical cure, NS</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Yazaki et al[22], 2018</td>
<td>Allergy, acute kidney injury 26 y/o woman with surgical closure of ventricular septal defect</td>
<td>Septic pulmonary embolism</td>
<td>Levofloxacin, meropenem, azithromycin, vancomycin, rifampicin, gentamicin</td>
<td>None</td>
<td>Daptomycin (8 mg/kg q48h), linezolid (600 mg q12h); 6 wk</td>
<td>Vancomycin (1 μg/mL), Linezolid (2 μg/mL), Daptomycin (1 μg/mL)</td>
<td>Clinical cure, 2 mo</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Galanter et al[23], 2019</td>
<td>Vancomycin resistance, worsening of septic emboli in both lungs, blood cultures remained positive for MRSA 26 y/o woman with native tricuspid valve endocarditis</td>
<td>Suspected septic embolism</td>
<td>Vancomycin, daptomycin, gentamicin</td>
<td>None</td>
<td>Daptomycin (8 mg/kg iv daily), linezolid (600 mg iv twice daily), 15 d</td>
<td>Daptomycin 1 μg/mL; daptomycin MIC 4 μg/mL (on the 15th day)</td>
<td>Clinical cure, 6 wk</td>
<td></td>
</tr>
</tbody>
</table>

y/o: Year old; NS: Not specified; MRSA: Methicillin-resistant Staphylococcus aureus; MIC: Minimum inhibitory concentration.

treatment drug. After 9 d of vancomycin treatment, the drain culture continued to be positive, and CT re-examination revealed progression of the abscess. Therefore, the combined treatment of daptomycin and linezolid was started. The peak temperature significantly decreased after the second day, and the drain culture turned negative after 11 d without fever. One month later, the patient was stable and was discharged. These combination therapies may be considered, along with daptomycin and linezolid, following vancomycin treatment failure depending on patient-specific risk factors and hospital formulary constraints. Since combination antimicrobial regimens are not always supported by conclusive trials, further studies are needed to confirm the efficacy of specific combination strategies. These combination therapies may be considered, along with daptomycin and linezolid, following vancomycin treatment failure depending on patient-specific risk factors. Further studies are needed to fully understand the mechanisms of the possible synergistic effects between daptomycin and linezolid.

CONCLUSION

In conclusion, we report a case of an abscess in the major psoas muscle complicated with pulmonary infection caused by MRSA that was successfully treated with a combination of daptomycin and linezolid. Our experience shows that the combination therapy of daptomycin and linezolid, instead of vancomycin, is an effective alternative therapy for refractory MRSA bacteremia.
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L-Editor: A
P-Editor: Wang JL

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Isolated scaphoid dislocation: A case report and review of literature

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Peer-review model: Single blind

Abstract

BACKGROUND
Isolated dislocations of the scaphoid are extremely rare types of injuries, commonly associated with severe ligament disruptions, and are occasionally misdiagnosed. Treatment options for dislocations of the scaphoid mainly include closed reduction, with or without internal fixation, and open reduction with ligament repair.

CASE SUMMARY
A 59-year-old male worker sustained a twisting trauma of his right wrist, caused by a moving belt while he was operating a machine. When he presented at our emergency department, the patient complained of swelling, tenderness, and restriction of movement of the right wrist. Radiographs confirmed a primary complex partial radial dislocation of the scaphoid and some chip fractures of the capitate and hamate. Closed reduction with K-wire internal fixation was performed with the assistance of arthroscopy, and an excellent prognosis was achieved.

CONCLUSION
Arthroscopy-assisted reduction is a minimally invasive method to reduce the dislocated scaphoid and maintain the blood supply.

Key Words: Isolated scaphoid dislocation; Classification; Delayed diagnose; Treatment options; Wrist arthroscopy; Case report
Core Tip: Isolated scaphoid dislocations are extremely rare, commonly associated with severe ligament disruptions, and occasionally misdiagnosed. Treatment options for scaphoid dislocations mainly include closed reduction and open reduction with ligament repair. We present the case of a 59-year-old male who suffered an isolated scaphoid dislocation. Closed reduction with K-wire internal fixation was performed with the assistance of arthroscopy, and an excellent prognosis was achieved. Arthroscopy-assisted reduction is an efficient and minimally invasive method of reducing the dislocated scaphoid, while keeping the external ligament and capsule intact, preventing adhesion of the tendons and maintaining the blood supply.

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INTRODUCTION

Isolated scaphoid dislocation is an extremely rare injury, with just a few cases reported in the English literature since the first case was reported in 1930 by Higgs[1]. When we encountered such a case in our department, we reviewed the literature to better understand the cause and treatment of scaphoid dislocations. The mechanism of such injuries is believed to involve the wrist sustaining an axial load in a dorsiflexion and ulnar deviation position. The classifications of these types of injuries were described by Leung et al[2] in 1998.

A variety of treatment methods have been reported, including closed or open reduction, with or without K-wire fixation and arthroscopic assistance, as well as different fixation methods, including suture anchors and screws. Most of these procedures have resulted in an excellent prognosis. We chose arthroscopy-assisted reduction with K-wire internal fixation in a scaphoid type of cast for treatment of our patient and achieved an excellent prognosis.

CASE PRESENTATION

Chief complaints
A 59-year-old male worker sustained a twisting trauma to his right wrist caused by a moving belt while he was operating a machine. The patient complained of swelling, tenderness, and restriction of movement of his right wrist when he presented at our emergency department.

History of present illness
The patient had no history of present illness.

History of past illness
The patient had no relevant medical history.

Personal and family history
The patient had no relevant personal or family history.

Physical examination
The patient’s vital signs were normal. Swelling, tenderness, and restriction of movement of his injured wrist were evident. There were no signs of neurovascular injury.

Laboratory examinations
Findings from laboratory examinations were normal.

Imaging examinations
Radiographs and computed tomography scans revealed a primary complex partial radial dislocation of the scaphoid and some chip fractures of the capitate and hamate (Figure 1).
Figure 1 Initial radiographs demonstrated primary complex partial radial dislocation of the scaphoid; The computed tomography scans demonstrated the chip fractures of the capitate and hamate. A: Posteroanterior and lateral; B: Computed tomography scans.

**FINAL DIAGNOSIS**

Isolated scaphoid dislocation.

**TREATMENT**

Closed reduction was attempted under general anesthesia, and arthroscopy was then performed in the midcarpal and radiocarpal joint. The arthroscopy confirmed a complete tear of the radioscaphocapitate ligament and scapholunate interosseous ligament; the lunotriquetral interosseous ligament was intact. The scapholunate diastasis was Geissler grade IV (Figure 2). As most of the stabilizers of the scaphoid were injured, the scaphoid had become extremely unstable, so it was difficult to stabilize the scaphoid to the lunate in a proper position. Thus, two K-wires were set into the scaphoid as a joystick temporarily, to reduce the scaphoid.

After performing debridement of the injured ligaments, the carpal alignment was maintained by internal fixation with four percutaneous K-wires under arthroscopic guidance and assistance (two to stabilize the scaphoid and lunate, and the other two to stabilize the scaphoid and capitate), which ensured precise reduction of the scapholunate joint (Figure 3). The wrist was postoperatively immobilized in a scaphoid-type cast. Six weeks later, the cast and K-wires were removed, and physical therapy was initiated.

**OUTCOME AND FOLLOW-UP**

At the 6-mo follow-up, the patient had returned to work without any limitations or tenderness of the wrist. The clinical outcomes were assessed according to the modified Mayo wrist scoring system, which consisted of pain, range of motion, grip strength, and function[3]. The outcome was evaluated subjectively using the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire[4] and the Patient-Rated Wrist Evaluation (PRWE) score[5]. Standard lateral and posteroanterior X-rays were used to assess carpal bones. The flexion/extension of the injured wrist was 80°/70° compared with 80°/80° on the contralateral side. The pronation/supination was 80°/90° compared with 90°/90° on the contralateral side (Figure 4). Grip strength was 60 kg compared with 70 kg on the contralateral side. The modified Mayo wrist score was excellent. The DASH and PRWE scores were 16 and 10, respectively, and radiographs revealed neither avascular necrosis of the proximal pole of the scaphoid nor scapholunate diastasis (Figure 5).

**DISCUSSION**

A literature search was performed using isolated or solitary dislocation of the scaphoid as key words; this search identified 58 cases reported in English since the first isolated scaphoid dislocation was reported in 1930[1,26-42]. The classification of isolated scaphoid dislocation is based on the description by Leung et al[2], and can be used to distinguish dorsal dislocation from dorsal intercalated segment instability caused by scapholunate ligament injury, even though the treatment options for these two injuries may be the same. The key difference between these two injuries is that the radioscaphocapitate
Liu SD et al. A case of isolated scaphoid dislocation

Figure 2 Arthroscopy confirmed complete disruption of the scapholunate and radioscaphocapitate ligaments, and scapholunate diastasis was Geissler grade IV. S: Scaphoid; SL: Scapholunate ligament.

Figure 3 Postoperative radiographs showed internal fixation with K-wires. A: Posteroanterior; B: Lateral.

The major cause of isolated scaphoid dislocation injuries was traffic accidents (25/48), among which 15 were motorcycle accidents and 10 were car accidents (Table 1). This might be explained by the injury mechanism. It is believed that the scaphoid is squeezed out of its fossa when the wrist is forced by axial loading into a dorsiflexion and ulnar deviation[15,21,39]. Although this might render a fracture of the styloid or the scaphoid more likely, most of the wrists of the traffic accident victims in this study experienced an axial force while they were holding the steering wheel or the handlebar in a dorsiflexion
Table 1 Summary of the characteristics of the patients diagnosed with isolated scaphoid dislocation

<table>
<thead>
<tr>
<th>Number of cases1</th>
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</thead>
<tbody>
<tr>
<td>Age in yr</td>
<td>18-71</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 44/48</td>
</tr>
<tr>
<td></td>
<td>Female 4/48</td>
</tr>
<tr>
<td>Injured side</td>
<td>Left 23/48</td>
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<td></td>
<td>Right 25/48</td>
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<tr>
<td>Causes of injuries</td>
<td>Traffic accidents (motorcycle; car) 15/48; 10/48</td>
</tr>
<tr>
<td></td>
<td>Entrapment or rolling forces 11/48</td>
</tr>
<tr>
<td></td>
<td>Falling from height 6/48</td>
</tr>
<tr>
<td></td>
<td>Others 6/48</td>
</tr>
<tr>
<td>Delayed diagnosis</td>
<td>17/48</td>
</tr>
<tr>
<td>Reasons for the delays</td>
<td>Missed diagnoses 8/14</td>
</tr>
<tr>
<td></td>
<td>Delayed attendance 6/14</td>
</tr>
<tr>
<td>Complications</td>
<td>Scapholunate diastasis 4/48</td>
</tr>
<tr>
<td></td>
<td>Degenerative joint 5/48</td>
</tr>
<tr>
<td></td>
<td>Scaphoid avascular necrosis 1/48</td>
</tr>
</tbody>
</table>

1Data are presented as cases/recorded cases.

Figure 4 At the 6-mo follow-up, the action of all sides of the carpal bone. A: Normal flexion; B: Slight restriction of extension; C: Supination; D: Pronation. These four movements were observed compared to the contralateral side.

and ulnar deviation position.

The most common causes of isolated scaphoid dislocation after traffic accidents included entrapment or rolling forces (9/48) and falling from height (6/48).

**Classifications of isolated scaphoid dislocation**

The classification of isolated scaphoid dislocation was as described by Leung et al[2]. Only four cases (4/48) were categorized as secondary dislocation, and were all reported by Thompson et al[38]. Among the 44 primary dislocations, 29 were simple (24 partial, 5 total) and 15 were complex (13 partial, 2 total). Almost all of the dislocations were palmar and radial in orientation (Figure 6). Only one dorsal dislocation was reported[13]. That patient’s wrist was forced into dorsiflexion when he tried to prevent a 300 kg barrel from rolling over. The scaphoid, of which the proximal pole was out of its fossa, was found in a tent of the extensor retinaculum and devoid from all its ligamentous attachments; the reduction was made through a dorsal approach. This injury cannot be appropriately explained by the injury mechanism mentioned above; it seemed likely that a direct force on the palmar facet of the scaphoid, not a squeezing force, pushed the scaphoid out of its fossa dorsally. Two cases of palmar and ulnar dislocations were also included in the literature, both of which had median nerve compression by the proximal pole of the scaphoid[2,26].
Figure 5 At the 6-mo follow-up, radiographs revealed neither avascular necrosis of the proximal pole of the scaphoid nor scapholunate diastasis. A: Posteroanterior; B: Lateral.

Delayed diagnosis
In approximately 35% of the cases (17/48), diagnosis of isolated scaphoid dislocation was delayed, with the time delay ranging from 2 d to 9 mo. In three cases, the reasons for the delays were not mentioned in the literature; the others are summarized in Table 1. It is astonishing that in over half of the delayed cases (8/14), the delays were due to missed diagnoses. Four of these cases were diagnosed as a sprain without any X-ray at the first visit, while the others were misdiagnosed as a normal or scaphoid fracture, or overlooked due to concomitant injuries after an X-ray examination. As a delay of approximately 1 wk in diagnosis might result in the failure of closed reduction and a poor prognosis, such as stiffness and arthritis, it is very important for surgeons to diagnose precisely at the first visit[2,15].

Treatment options: Closed reduction or open reduction
Thirty-one percent of the cases (15/48) underwent closed reduction successfully (Table 2). All of these cases were diagnosed without delay, and the scaphoid was only partially dislocated[17,21,22]. Twelve of the 15 cases were immobilized by casts without any internal fixation, and most had fully recovered wrist functions after follow-up (durations of 3 mo to 10 years). The exception to this involved two cases
classified as secondary dislocation, where the patients suffered from severe stiffness and mild pain of the wrist, as reported by Thompson et al.[38]. The other three were immobilized using K-wires to reduce the scapholunate diastasis under arthroscopic assistance and achieved good outcomes as well.[17,21,22]. It was reported that 69% of the perilunate dislocations that achieved initial anatomical reduction after closed reduction might lose reduction later.[43], so Szabo et al.[21] recommended that all reduced scaphoids should be stabilized with K-wires in a cast, even though the scapholunate joint showed no diastasis.

Eventually, 69% of the cases (33/48) underwent open reduction, including all 17 delayed diagnosis cases and 7 total dislocation-type cases. It was suggested that a delayed diagnosis of almost 1 wk made open reduction inevitable due to changes in the soft tissues[2,15], and this idea was supported by the literature. As all the ligaments to stabilize the scaphoid were compromised in the total dislocation-type, it seemed impossible to reduce the scaphoid through traction and dorsiflexion of the wrist.

Five of the open reduction cases were due to residual scapholunate diastasis after closed reduction. One cause for the residual scapholunate diastasis was that the scapholunate interosseous ligament was invaginated into the scapholunate interval, preventing reduction of the scapholunate diastasis. Another cause might be the scaphoid paradox, which is that to close the scapholunate gap, radial angulation is required, and to obtain correct scapholunate angulation, ulnar deviation is required.[44]. A retrospective review of the perilunate dislocations showed that ligament repair with internal fixation maintained the anatomy of scapholunate reduction better than closed reduction and pinning.[45]. A case report by Horton et al.[17] suggested that ligament reconstruction through open surgery provided excellent anatomic and functional results. However, the use of wrist arthroscopy has expanded in both diagnosis and treatment of wrist abnormalities in recent years, and carpal instabilities, especially scapholunate dislocation caused by scapholunate interosseous ligament injuries, are commonly treated with arthroscopic assistance.[44-46]. We believe that arthroscopy might demonstrate great advantages in the treatment of isolated scapholunate dislocations, as it allows extrication of the invaginated ligament and reduction of the diastasis through a joystick under direct vision, and can even enable minimally-invasive repair of the injured ligament.

For open reduction, a dorsal approach was chosen in 12 cases, a volar approach in 9 cases, and a radial approach in 3 cases (Table 2). Some authors recommended the volar approach for better vision and proper preservation of the dorsal blood supply and the superficial branch of the radial nerve[9]. Attention should be paid to palmar-ulnar scaphoid dislocations; open reduction in a volar approach is recommended because in all cases with such types of dislocation, the median nerve was compressed by the proximal pole of the scaphoid, and nerve decompression was necessary.[2,26].

Possible complications of isolated scapholunate dislocation might be degenerative joint and carpal instability, which are likely to be seen in neglected cases[6,7]. However, in this literature review, 4 of the 48 cases showed scapholunate diastasis during the follow-up after open reduction, although in none of them was diagnosis delayed[16,21,33,38]. A degenerative joint developed in 5 cases (5/48), and of those, diagnosis was delayed in 3, with delay time ranging from 2.5 mo to 9 mo before the patients underwent salvage procedures[13,26,38].

Another rare complication was scaphoid avascular necrosis. To date, only 1 case showed necrosis of the scaphoid classified as primary complex total palmar radial dislocation[21]. The others, even the total dislocations in which the scaphoid had detached from all of its surrounding soft tissues, showed no necrosis. It seemed that the undisturbed intraosseous vascular channels inside the intact scaphoid.

### Table 2 Summary of treatment options

<table>
<thead>
<tr>
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<th>Number of cases</th>
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<tbody>
<tr>
<td>Closed reduction</td>
<td></td>
</tr>
<tr>
<td>Cast immobilization</td>
<td>15/48</td>
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<tr>
<td>K-wire fixation</td>
<td>12/15</td>
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<tr>
<td>Open reduction</td>
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<tr>
<td>Dorsal approach</td>
<td>33/48</td>
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<tr>
<td>Volar approach</td>
<td>12/33</td>
</tr>
<tr>
<td>Radial approach</td>
<td>9/33</td>
</tr>
<tr>
<td>Dorsal + volar</td>
<td>3/33</td>
</tr>
<tr>
<td>Salvage operation</td>
<td>1/33</td>
</tr>
<tr>
<td>Not mentioned</td>
<td>5/33</td>
</tr>
</tbody>
</table>

1Data are presented as cases/recorded cases. PRC: Proximal row carpectomy; STT: Scaphotrapeziotrapezoid.
allowed rapid revascularization from the surrounding soft tissues[2]. A delay in diagnosis was believed to be a key adverse factor for poor prognosis because of secondary finger stiffness, stiffness of the wrist, and degenerative changes[26].

A variety of casts were introduced by surgeons, but there is still a lack of clinical research to demonstrate which type of cast is the most appropriate. The dominant factor at present might be the surgeon’s preference.

Limitations
There are some limitations to this study. First, as a case report, only 1 patient was diagnosed and treated, so there were no group comparisons of other treatment options. Second, the follow-up period was short. As we did not repair the scapholunate interosseous ligament directly during the operation, whether the ligament was healed or just scar-connected was unknown. Further observation is necessary.

CONCLUSION
Isolated scaphoid dislocation is a rare type of injury that can be diagnosed easily with radiography. However, delayed diagnosis of such cases may cause poor prognosis. Treatments for these injuries include closed reduction, with or without internal fixation, and open reduction with ligament repair, which seems to have become more commonly adopted in recent years. As arthroscopy is used in the diagnosis and treatment of wrist abnormalities more widely, we consider arthroscopy-assisted reduction an efficient and minimally invasive method of reducing the dislocated scaphoid while keeping the external ligament and capsule intact, preventing adhesion of the tendons and maintaining the blood supply.

FOOTNOTES

Author contributions: Liu SD was the patient’s surgeon, reviewed the literature, and helped draft the manuscript; Yin BS, Han F, and Jiang HJ reviewed the literature and helped draft the manuscript; all authors approved the version submitted.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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

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).

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Dual biologic therapy with ocrelizumab for multiple sclerosis and vedolizumab for Crohn’s disease: A case report and review of literature

Michael Au, Nikola Mitrev, Rupert W Leong, Viraj Kariyawasam

Abstract

BACKGROUND
Little is known about the safety and efficacy of using two or more biologics for the treatment of immune-mediated diseases, including Crohn’s disease (CD).

CASE SUMMARY
This case report and narrative review demonstrate the potential safety of dual biologic therapy (DBT) in a 45-year-old female with two separate immune-mediated diseases. She had a history of multiple sclerosis for which she was receiving treatment with ocrelizumab, and she had been recently diagnosed with CD after presenting with diarrhoea. The CD diagnosis was confirmed radiologically, endoscopically, histologically, and biochemically. The patient received treatment with vedolizumab, a gut-specific inhibitor of the α4β7 integrin on leukocytes. No adverse reactions were observed for the duration of treatment. The...
safety of ocrelizumab and vedolizumab for the treatment of different immune-mediated diseases was demonstrated.

CONCLUSION
DBT may be a safe and effective option for the treatment of refractory disease or multiple immune-mediated diseases. Newer biologics, which have improved safety profiles and gut specificity, may provide promising avenues for treatment. However, caution must be exercised in the appropriate selection of biologics given their inherent immunosuppressive properties, side effects, and efficacy profiles. Current evidence suggests that biologic therapy is not associated with a worse prognosis in patients with coronavirus disease 2019, but treatment decisions should be made in a multidisciplinary setting. Further research from controlled trials is needed to better understand the safety profile of DBT in CD. The immunopathological mechanisms underlying DBT also remain to be clarified.

Key Words: Dual biologic therapy; Combination; Immunosuppression; Safety; Autoimmune; Case report

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Core Tip: This paper describes the use of two biologics for the treatment of Crohn's disease and multiple sclerosis. Only a few papers have reported the safety and efficacy of these treatments due to inherent concerns regarding immunosuppression, infection, and malignancy. We present the case of a patient who was safely treated with vedolizumab and ocrelizumab. The combination of biologics may be a safe and effective treatment for immune-mediated diseases.

INTRODUCTION
Biologics play an important role in treating the full spectrum of Crohn's disease (CD). Biologics are a group of drugs derived from living biological sources that undergo complex processes, such as recombinant DNA processes, genetic isolation, or protein purification[1]. Biologics can be divided into monoclonal antibodies (mAbs), receptor modulators, and enzyme modulators[2]. In CD, biologics are incorporated into the treatment regimen when a response to thiopurines and glucocorticoids cannot be achieved[3]. Biologics used for the treatment of CD include inhibitors of tumour necrosis factor-α (TNF-α) (infliximab, adalimumab, and certolizumab), inhibitors of α4β7 integrins on leukocytes (vedolizumab and natalizumab), and inhibitors of the p40 subunit of interleukins (IL)-12 and IL-23 (ustekinumab)[4]. Patients who respond to biologic therapy show improved clinical outcomes, can avoid surgery, and have a reduced hospitalisation rate, fewer complications, and improved quality of life[5,6].

In the setting of CD, dual biologic therapy (DBT) refers to the use of two different biologic agents to achieve remission. Typically, biologics have been used alone or in combination with other immunomodulators to enhance the therapeutic response and prevent the formation of human anti-chimeric antibodies (HACAs). The use of DBT has been cautioned due to side effects, including immunosuppression, infections, and malignancy[7,8]. Newer biologics such as vedolizumab and ustekinumab offer improved safety profiles that do not cause systemic immunosuppression and lower the risk of HACA formation; no cases of progressive multifocal leukoencephalopathy (PML) from John Cunningham virus (JCV) have been reported; and theoretically, there is a lower risk of malignancy due to the gut-specific activity of these biologics[9,10].

Few studies have explored the safety and efficacy of using DBT for CD, and further details regarding the safety of concurrent use of multiple biologics as indicated for different immune-mediated disorders remains to be explored[11,12]. Whether a cumulative immunosuppressive effect exists with DBT remains to be clarified, resulting in hesitancy in the widespread use of DBT. In a systematic review with a pooled analysis of patients with inflammatory bowel diseases (IBDs) receiving DBT with TNF-α inhibitors, vedolizumab, or ustekinumab, clinical improvement was observed in all patients, with seven out of 18 patients experiencing mild side effects but no serious adverse events[13]. The current evidence is promising, and DBT appears safe, but further controlled trials are required. Furthermore, the coronavirus disease 2019 (COVID-19) pandemic presents new challenges to the clinical setting and
raises concerns over the safety of biologic therapy[14]. The following case report demonstrates the safety of DBT in a patient receiving two biologics for separate immune-mediated diseases and provides an update on recent developments from research into the use of DBT for CD.

**CASE PRESENTATION**

**Chief complaints**
A 45-year-old female presented with diarrhoea associated with ileal CD, which was diagnosed four months prior to presentation, without strictures or fistulising complications.

**History of present illness**
Colonoscopy demonstrated active ileitis with a Simple Endoscopic Score for Crohn’s disease of 5 (2, 1, 2, 0).

**History of past illness**
After a brief good clinical response to budesonide therapy and the resolution of diarrhoea, recurrence of the symptoms occurred despite almost 10 wk of treatment.

**Personal and family history**
The patient had a history of multiple sclerosis (MS) and had been receiving treatment for the past five years with ocrelizumab, a humanised anti-CD20 B cell depletory drug with similar properties to rituximab, with which it shares a similar epitope. Anti-CD20 therapy has been associated with immune-mediated colitis; however, it is not a recognised cause of ileitis. At the time of review, the patient was not taking any other medication or nonsteroidal anti-inflammatory drugs. The patient had been previously treated with fingolimod and natalizumab for her MS. However, natalizumab was subsequently withdrawn, as she was positive for JCV.

**Physical examination**
The clinical examination findings were unremarkable.

**Laboratory examinations**
Her faecal calprotectin was elevated at presentation (> 1000 μg/g). Other pathogenic causes of diarrhoea, such as bacteria, parasites, and viruses, were excluded on the basis of blood test and stool culture results. Histopathological analysis of a terminal ileum biopsy sample demonstrated patchy mild active inflammation.

**Imaging examinations**
Active ileitis, with the involvement of 30 cm from the ileal-caecal junction and an increased bowel wall thickness of 5 mm without upstream small bowel dilatation, was confirmed on magnetic resonance enterography.

**MULTIDISCIPLINARY EXPERT CONSULTATION**
The patient was referred for multidisciplinary care given her complex medical history. She was counselled on the potential need for surgical management. In conjunction with the patient, the decision was made to commence vedolizumab with induction and maintenance therapy.

**FINAL DIAGNOSIS**
The patient was diagnosed with CD with active terminal ileitis, and she safely commenced DBT given her concurrent MS.

**TREATMENT**
The patient received treatment with vedolizumab in conjunction with her usual treatment with ocrelizumab for her MS. Because the biochemical response after the first three months was inadequate, the dose of vedolizumab was escalated to 300 mg every 4 wk, which resulted in a good clinical and biochemical response. The patient’s diarrhoea and abdominal pain resolved, her C-reactive protein
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CRP decreased from 47 mg/L prior to dose escalation to 28 mg/L following dose escalation, and her erythrocyte sedimentation rate decreased from 17 mm/h pre-treatment to 5 mm/h post-treatment. During maintenance therapy, the patient completed monthly follow-ups, and she did not develop any adverse reactions.

OUTCOME AND FOLLOW-UP

Unfortunately, after 5 mo of therapy, her diarrhoea returned, despite achieving therapeutic levels of vedolizumab at 33 μg/mL. Repeat magnetic resonance enterography demonstrated terminal ileitis with some worsening interval changes, including a bowel wall thickness increase to 7 mm in the terminal ileum but no upstream dilation or complications (Figure 1). The Simplified Modified Magnetic Resonance Index of Activity (MaRIA) score of the terminal ileum was 3, suggesting severe disease. Repeat CRP analysis showed an increase to 52 mg/L. Following multidisciplinary discussion, azathioprine was added to her DBT, as the patient wished to avoid surgery. To date, the patient has safely completed five months of DBT without any adverse side effects noted (Figure 2).

DISCUSSION

Review of the current literature

Significant gaps still exist in the understanding of the use of multiple biologic therapies in patients with CD. This case report demonstrated the short-term safety of the use of two biologics, ocrelizumab and vedolizumab, in a patient with different immune-mediated conditions. Only a few studies have attempted to elucidate the safety and efficacy of DBT for refractory CD, but some of the results were promising. In a retrospective study by Yang et al[15], 22 patients who had CD refractory to a single biologic underwent 24 trials of DBT (consisting of either infliximab, adalimumab, vedolizumab, ustekinumab, certolizumab, or golimumab), with 50% achieving a clinical response and 41% achieving clinical remission. Adverse events occurred in three trials due to infection, malignancy, or drug-induced lupus[15]. Additionally, Kwapisz et al[16] described 14 patients with CD and one patient with ulcerative colitis (UC) treated with combination biologics for refractory disease. Eleven patients had symptomatic improvement, with 10 patients achieving a reduction in their corticosteroid dose requirements and only three patients requiring surgery. Adverse events in this case series included three hospitalisations and four infections treated with antibiotics[16]. In the only randomised controlled trial investigating DBT in CD, Sands et al[17] investigated 79 patients with active CD despite infliximab treatment in a multicentre double-blind, placebo-controlled trial. A similar overall incidence of adverse events between patients who were administered natalizumab and infliximab and those who were administered placebo with infliximab was observed, and positive trends towards greater efficacy were seen in the patients who received natalizumab and infliximab[17]. Further evidence is needed to investigate the safety and efficacy of DBT in controlled settings. A current trial is underway to examine the use of DBT (vedolizumab and adalimumab) with methotrexate for patients with newly diagnosed CD who are at higher risk for complications[18]. Additional studies are needed to gain further insight into the immunopathological mechanisms underlying DBT and to clarify whether an additive or synergistic effect occurs.

Case discussion

In this case report, DBT was used for the treatment of two different immune-mediated disease entities. Limited evidence is available on the use of multiple biologics for different immune-mediated disease entities, with most studies examining the role of DBT in refractory disease. To the best of our knowledge, only one other case series, by Fumery et al[19], reported the use of DBT with ocrelizumab and vedolizumab, which was administered to one patient. No adverse events were observed for a period of 6 mo in this patient, who had been diagnosed with UC and MS[19].

One differential diagnosis that needs to be made for the patient presented here is ocrelizumab-induced colitis, which has been reported in case reports[20]. The presentation of ocrelizumab-induced colitis may be similar to that of new-onset CD[21]. Rituximab, another CD20-depleting drug, has also been reported to be possibly associated with colitis[22]. This condition cannot be excluded for the patient in this case report. However, disease activity restriction to the terminal ileum, as well as the prolonged duration of ocrelizumab use in this patient prior to the onset of diarrhoea, favoured the diagnosis of CD rather than medication-induced colitis. Consideration should be given to medication-induced colitis in patients receiving biologics who have symptoms of colitis, although the differentiation of medication-induced colitis from IBD can be difficult[23].

In the era of the COVID-19 pandemic, the safety of DBT needs to be considered, and COVID-19 concerns were a part of this patient’s pre-immunosuppression workup. In one case report, a patient receiving DBT with adalimumab and ustekinumab for CD had a positive severe acute respiratory
Figure 1 Repeat magnetic resonance enterography (original images). A: Axial T2 image demonstrating bowel wall thickening (arrowheads) and T2 hyperintensity within the bowel wall (arrow), consistent with mural oedema; B: Coronal contrast-enhanced T1 fat-suppressed image demonstrating mural hyperenhancement (arrowhead) and extensive mesenteric vascular congestion, known as the ‘comb sign’ (arrows).

Figure 2 Timeline of events. MS: Multiple sclerosis; MDT: Multidisciplinary Team; MRE: Magnetic resonance enterography.

system coronavirus 2 (SARS-CoV-2) result, but the patient was asymptomatic and the infection did not affect the course of treatment, with the patient safely continuing DBT[14]. To date, there is no evidence to suggest a worse prognosis in patients with SARS-CoV-2 infection receiving biologics[24]. The SECURE-IBD registry demonstrated that TNF-$\alpha$ antagonist treatment was not associated with severe COVID-19[25]. However, further evidence is required to determine whether DBT confers increased immunosuppression and increased severity of SARS-CoV-2 infection.

The choice of biologic agent in this case report was made in a multidisciplinary setting. Consideration was given to natalizumab, but the risk of PML from JCV reactivation has been reported[26]. Furthermore, TNF-$\alpha$ inhibitors are contraindicated for MS due to case reports of demyelination[27]. The gut-specific integrin inhibitor vedolizumab has been given preference, and in this case scenario, vedolizumab initially led to a favourable response. In the treatment of IBD, combination therapy incorporating vedolizumab is theoretically a safe approach given its specificity[9]. The specificity and safety of vedolizumab provide new opportunities for its use in DBT, particularly with other systemic immunosuppressants such as ocrelizumab, which can cause profound B cell depletion.

However, in patients with extraintestinal manifestations, gut-specific vedolizumab may not be as effective as TNF-$\alpha$ inhibitors. In fact, in a case report by Hirten et al[28], a patient who had a brief overlap in infliximab and vedolizumab treatment experienced a flare of an extraintestinal manifestation of CD when infliximab was withdrawn and a flare of mucosal symptoms when vedolizumab was
withdrawn, with improvements in symptoms when biologics were restarted in both instances[28]. Another case report of a patient with UC and spondylarthritis described the successful control of both diseases with vedolizumab and etanercept[29]. Privitera et al[30] also retrospectively examined sixteen patients receiving dual biologics or one biologic and one small molecule, either for refractory IBD or for IBD with extraintestinal manifestations. A clinical response was reported by all patients, with only three patients experiencing an adverse event, which included a perianal abscess, a cutaneous reaction, and drug-induced liver injury[30]. Indeed, if the indications for each combination therapeutic are carefully considered, dual ‘targeted’ therapies may be an avenue of treatment in certain patients. Considering the current evidence, DBT can be considered safe in some limited circumstances. Careful selection of DBT, discussion with a multidisciplinary team, and an understanding of the patient’s history and the emerging literature are all needed prior to the commencement of treatment.

**Limitations**

Several limitations of this case report should be noted. Although the short-term safety of DBT has been demonstrated, the efficacy of DBT remains to be clarified. Vedolizumab is a promising and excellent therapeutic choice for many patients, as demonstrated in the GEMINI studies[31]. Further research, particularly in the form of randomised controlled trials examining the efficacy of DBT with vedolizumab, is needed.

**CONCLUSION**

DBT offers a new treatment strategy to patients with CD and those with different immune-mediated conditions. In addition, the combination of biologics may be an avenue of treatment for patients who have been refractory to existing treatment regimens or those with multiple immune-mediated diseases. Vedolizumab and ocrelizumab in combination may be safe for the treatment of patients with different immune-mediated diseases, such as CD and MS. However, careful selection of biologics with respect to patient characteristics in multidisciplinary settings is required. Further evidence is needed to guide clinical decision-making and the selection of biologics, particularly in the form of randomised controlled trials.

**ACKNOWLEDGEMENTS**

Images courtesy of Dr. Jessica Yang, Radiologist, Macquarie University Hospital and Concord Repatriation General Hospital.

**FOOTNOTES**

**Author contributions:** Au M compiled data, reviewed records, performed literature review, and wrote first draft; Mitrev N and Kariyawasam V reviewed records, reviewed literature, and reviewed draft; Leong RW reviewed records.

**Informed consent statement:** All involved persons (subjects or legally authorised representative) gave their informed consent prior to study inclusion.

**Conflict-of-interest statement:** Dr Rupert W Leong is currently serving on the advisory boards of AbbVie, Aspen, BMS, Celgene, Chiesi, Ferring, Glutagen, Hospira, Janssen, MSD, Novartis, Pfizer, and Takeda. The authors declare no other conflicts of interest.

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Au M et al. Dual biologics in a patient with CD


Cardiac rehabilitation in a heart failure patient after left ventricular assist device insertion and subsequent heart transplantation: A case report

Tae Woong Yang, Seunghwan Song, Hye Won Lee, Byeong-Ju Lee

**Abstract**

**BACKGROUND**

Insertion of a left ventricular assist device (LVAD) and heart transplantation (HT) improve the survival of patients with heart failure. In addition, cardiac rehabilitation (CR) further increases the functional capacity. This case report describes a successful case of CR after LVAD insertion and subsequent HT.

**CASE SUMMARY**

In the present case, during the LVAD insertion period, peak oxygen consumption (VO$_2$) increased by 12.16% after CR. HT was performed 7 mo after the LVAD insertion, and the patient participated in phases I and II CR. The peak VO$_2$ increased from 17.24 to 22.29 mL/kg/min. This improvement was more significant than that reported in previous studies on CR after LVAD insertion or HT. The patient's quality of life also improved. The total average score of the short form-36 questionnaire increased from 29.5 points at admission to 53.3 points 9 mo after HT.

**CONCLUSION**

A tailored CR program after LVAD insertion or HT may improve the patients' quality of life and increase survival.
INTRODUCTION

Heart transplantation (HT) is the last resort for patients with end-stage heart failure (HF). HT improves the survival of patients with HF[1]; furthermore, a better prognosis can be expected with cardiac rehabilitation (CR) after HT[2]. The limited supply of donor organs remains a major barrier for HT. Mechanical circulatory support, such as a left ventricular assist device (LVAD), is widely used to overcome this limitation. LVAD is used either as a bridge-to-transplant (BTT) or as a destination treatment (DT), especially in patients ineligible for HT due to their poor condition[3]. CR after LVAD insertion improves functional capacity[4]. Herein, we report a successful case of CR after LVAD insertion and subsequent HT.

CASE PRESENTATION

Chief complaints
A 53-year-old man was admitted to the cardiology department because of dyspnea.

History of present illness
Transthoracic echocardiography showed severe mitral regurgitation, mitral chordae rupture, and an ejection fraction of 24%. Despite valve replacement, the patient had a poor prognosis; consequently, HT was planned. The patient urgently required HT, although a donor heart was unavailable; therefore, continuous-flow type LVAD (Heartmate II, Abbott, IL, United States) insertion was performed 1 mo after admission.

History of past illness
The patient was diagnosed with dilated cardiomyopathy with atrial fibrillation.

Personal and family history
The patient had chronic kidney disease and had been taking anti-thrombotic medications due to old cerebral infarction. There was no specific family history of related heart disease.

Physical examination
During the physical examination, the patient had a blood pressure of 90/60 mmHg, heart rate of 106 bpm, body temperature of 36.2 °C, respiratory rate of 16 breaths/min, and oxygen saturation of 99% when oxygen was supplied at 2 L/min via a nasal cannula.

Laboratory examinations
The serum pro-brain natriuretic peptide level was elevated to 5250 pg/mL, and the serum creatinine level was also elevated to 1.73 mg/dL.

Imaging examinations
Chest X-ray showed cardiomegaly with pulmonary edema.
Yang TW et al. CR for HF patient with LV assist device and heart transplantation

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Figure 1 Cardiac rehabilitation program by phase. A: Incentive spirometry training in intensive care unit after left ventricular assist device (LVAD) insertion; B: The patient marched and ambulated with the help of medical staff after LVAD insertion; C: First cardiopulmonary exercise test after LVAD insertion; D: Phase II cardiac rehabilitation after heart transplantation.

FINAL DIAGNOSIS

The patient was finally diagnosed with acute aggravation of HF.

TREATMENT

After LVAD insertion, phase I CR, which included chest physiotherapy and aerobic exercise using a portable lower limb ergometer, was conducted in the intensive care unit with a focus on preventing respiratory complications, joint contracture, and muscle atrophy (Figure 1A).

The patient was made to march and to ambulate in the general ward (Figure 1B). The first cardiopulmonary exercise test (CPET) was conducted 3 mo after the LVAD insertion (Figure 1C). The patient's cardiac parameters were as follows: Peak oxygen consumption (VO₂), 18.01 mL/min/kg; respiratory exchange ratio, 1.02; minute ventilation (Vₑ)/volume of exhaled CO₂ (VₑCO₂) slope, 29.7; resting heart rate (HR), 100 beats per minute (bpm); maximum HR, 140 bpm; and heart rate recovery (HRR), 4 bpm after 1 min. The intensity of exercise was determined by the Karvonen formula using HR.

OUTCOME AND FOLLOW-UP

After discharge, the patient participated in the phase II CR program and peak VO₂ increased by 12% of the initial value to 20.20 mL/min/kg. HT was performed 7 mo after the LVAD insertion. During phase I CR, the exercise intensity was determined using a rating of perceived exertion (RPE) scale instead of the HR. Four months after HT, peak VO₂ decreased to 17.24 mL/min/kg, and HRR began after 2 min. The phase II CR comprised aerobic and resistance exercises twice a week for 12 wk. After completing the CR program, peak VO₂ increased by 30% to 22.29 mL/min/kg (Table 1).

The patient’s quality of life also improved. The total average score of the short-form-36 questionnaire increased from 29.5 before the LVAD insertion to 53.3 points 9 mo after HT.
DISCUSSION

There are several cases of CR after LVAD insertion where LVAD was used as a DT, but not as a BTT[5, 6]. Furthermore, few cases have been reported worldwide in which CR was performed after LVAD insertion and subsequent HT. The patient demonstrated a greater improvement in cardiopulmonary parameters than those reported in previous studies[2,4], although 8 mo had passed between admission and HT. The patient underwent an LVAD insertion and HT sequentially, and each phase required different considerations. Major considerations during phase I CR were exercise intensity and sternal precautions; therefore, low-intensity exercise, such as that which elevates HR by 20 bpm or an RPE of 12, was used (Table 2). In addition, resistance band exercises that focused on hip flexors and knee extensors were performed. The intensity of the resistance exercise was set to about 30% of one repetition maximum. Strength can be estimated using increase in band length from that of the initial length and material of the band. Moreover, based on the Holten diagram, resistance exercise was performed at an intensity that could be performed for 4-5 sets with a short interval of 15 repetitions per set. After median sternotomy, trunk and arm activities were restricted postoperatively to ensure adequate healing and the band elongation ratio was set to 75% to limit the range of motion.

During phase II CR after the LVAD insertion, the exercise intensity was set based on the Karvonen formula after CPET. Usually, aerobic exercise intensity for patients with cardiovascular disease was set to 40-80% of the exercise capacity using the Karvonen formula. The patient was classified as belonging to the high risk group according to the American Association of Cardiovascular and Pulmonary Rehabilitation Risk Stratification Criteria because the rest ejection fraction was < 40% and congestive heart failure occurred. Therefore, the target intensity was set to 40%–55%. The phase II CR was conducted for 3 mo, twice a week. As a continuous-flow type LVAD was inserted in the patient, blood pressure could be measured with a vascular Doppler device. Blood pressure was measured before, during, and after exercise, and the mean arterial pressure was monitored to maintain it between 70 and 90 mmHg. Hypertension would affect the LVAD capacity to pump blood forward; hypotension and LVAD blood flow alterations might be related to under-filling of the left ventricle secondary to high pump speed, RV failure, and arrhythmias[7]. LVAD may increase the risk of cerebrovascular disorders caused by thrombus; therefore, it is vital to monitor the pump speed and flow rate. Care of the driveline is also essential; an inappropriate position could cause pressure injury, and excessive sweating could cause wound infection. Additionally, since excessive sweating and dehydration can reduce venous return and negatively affect LVAD function, regular water intake was recommended before and after exercise. Furthermore, rapid changes of posture from supine to upright positions were avoided. To reduce the risk of adverse events, warming up and cooling down were performed gradually for 10 min each. Breath-holding Valsalva maneuver was avoided, and the patient's vital signs and condition were

<table>
<thead>
<tr>
<th>Table 1 Results of serial cardiopulmonary exercise tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol</td>
</tr>
<tr>
<td>Duration</td>
</tr>
<tr>
<td>VO2peak, mL/min/kg (% of the predicted)</td>
</tr>
<tr>
<td>VO2 at AT, mL/min/kg</td>
</tr>
<tr>
<td>METs</td>
</tr>
<tr>
<td>Resting HR, bpm</td>
</tr>
<tr>
<td>Maximum HR, bpm (% of the predicted)</td>
</tr>
<tr>
<td>HR after 1 min</td>
</tr>
<tr>
<td>Resting BP, mmHg</td>
</tr>
<tr>
<td>Maximum BP, mmHg</td>
</tr>
<tr>
<td>VE/VCO2 slope</td>
</tr>
<tr>
<td>RER</td>
</tr>
</tbody>
</table>

LVAD: Left ventricular assist device; HT: Heart transplantation; VO2peak: Peak oxygen consumption; VO2 at AT: Oxygen uptake at the anaerobic threshold; MET: Metabolic equivalent task; HR: Heart rate; HRR-1 min: Heart rate recovery in one minute; BP: Blood pressure; LVAD: Left ventricular assist device; HT: Heart transplantation; 1LVAD was conducted on May 20, 2019, and HT was conducted on December 20, 2019.

VO2: Volume of exhaled carbon dioxide; RER: Respiratory exchange ratio; NM: Not measurable.
Table 2 Rehabilitation program

<table>
<thead>
<tr>
<th>Aerobic exercise</th>
<th>Exercise type</th>
<th>Intensity</th>
<th>Duration of one session</th>
<th>Sessions/d</th>
<th>Days/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post LVAD</td>
<td>Supervised indoor walking</td>
<td>HR &lt; resting HR + 20 or RPE of 12</td>
<td>5-10 min, increase up to 20-30 min</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Lower limb ergometer</td>
<td>10-20 Watt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>Lower limb ergometer, treadmill, box step up</td>
<td>40%-55% based on the Karvonen formula</td>
<td>Warm-up 10 min, main exercise 20 min, cool-down 10 min</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Post HT</td>
<td>Supervised indoor walking</td>
<td>RPE of 12</td>
<td>5-10 min, increase up to 20-30 min</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Lower limb ergometer</td>
<td>10-20 Watt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>Lower limb ergometer, treadmill, box step up</td>
<td>RPE of 13</td>
<td>Warm-up 10 min, main exercise 20 min, cool-down 10 min</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resistance training</th>
<th>Exercise type</th>
<th>Strength % of 1RM</th>
<th>Repetitions per set</th>
<th>Sets per exercise/d</th>
<th>Days/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Resistance band exercises</td>
<td>20%-30%</td>
<td>8-15</td>
<td>3-5</td>
<td>2-3</td>
</tr>
<tr>
<td>Phase II</td>
<td>Overhead press, biceps curl, leg press machine, squat</td>
<td>40%-60%</td>
<td>8-15</td>
<td>3-5</td>
<td>2-3</td>
</tr>
</tbody>
</table>

LVAD: Left ventricular assist device; HT: Heart transplantation; HR: Heart rate; RPE: Rating of perceived exertion; RM: Repetition maximum.

monitored for 15 min after exercise.

In a previous study on CR after LVAD, peak VO$_2$ increased by approximately 10%[4]. In the present case, peak VO$_2$ improved by 12.16%, despite the prolonged hospitalization. The patient did not experience any LVAD-associated adverse events. The patient had a gout attack and underwent cholecystectomy for acute cholecystitis; therefore, hospital stay was extended to 5 mo. The patient was able to secure sufficient rehabilitation sessions during the hospitalization period and maintain a relatively long phase I CR. Even after the phase II CR was implemented, the medical staff and the patient continued to communicate to encourage the continuation of rehabilitation treatment. In addition, when the patient moved to a place nearby the hospital, access to the rehabilitation center improved further. The participation rates in CR among patients with HF remain low, ranging from 14% to 43% worldwide[8]. Longer and continuous exercise training interventions could improve physical fitness and quality of life. Also, a tailored exercise program for each phase led to improvement in the patient's quality of life. In phase I CR, low-intensity exercise for the purpose of reconditioning was performed in consideration of the patient's overall condition. In phase II CR, exercise capacity was improved by performing moderate- or high-intensity exercise. Mechanisms contributing to the greater fatigability in patients with HF are likely caused by alterations in the skeletal muscle metabolism, resulting in greater glycolytic capacity and reduced oxidative capacity of the muscle and reduced blood perfusion to the muscle[9]. In this case, the time interval from acute aggravation of HF to LVAD insertion was about 1 mo. For this reason, although a decrease in skeletal muscle dysfunction occurred, this change was relatively reversible and could be overcome by continuing rehabilitation.

A denervated autonomic nervous system is a key physiological change after HT. Loss of vagal inhibition to the sinoatrial node causes resting tachycardia with an HR of 100 bpm. The chronotropic response is caused by changes in blood catecholamine concentration owing to the loss of sympathetic innervation. As a result, the HR response to exercise is blunted, with a lower peak HR (20% approximately)[10]. The exercise intensity should be determined based on RPE. Even in the same phase of CR, the target intensity settings were different after LVAD insertion or HT, so that CR was organically intervened at each stage. In this case, the maximum HR decreased from 159 to 107 bpm after HT, and HRR began 2 min after the peak exercise. According to the Fick equation, the peak VO$_2$ also decreased from 20.20 to 17.24 mL/min/kg.

The patient participated in phases I and II CR, and peak VO$_2$ increased from 17.24 to 22.29 mL/min/kg at 5 mo after HT. Compared to a previous study in which VO$_2$ increased by 2.34 mL/min/kg, the patient described herein showed a greater improvement in functional capacity[2]. The maximum HR rose from 64% of the predicted value to 77%, indicating sympathetic reinnervation; however, HRR was still delayed. Since parasympathetic reinnervation is expected to continue for 2 years after HT, further follow-up is necessary[11,12].
CONCLUSION

The number of end-stage HF patients requiring LVAD or HT is gradually increasing. During CR in these patients, proper exercise prescription and a tailored exercise program for each phase are essential. One-year survival after HT is at least 85%, and median survival exceeds 12 years. Therefore, further research is needed to elucidate the impact of improved functional capacity after CR on the survival rate.

FOOTNOTES

Author contributions: Lee BJ, Song SH, and Lee HW contributed to subject assessment; Yang TW, Lee BJ, Song SH, and Lee HW contributed to drafting of the manuscript and data interpretation; Yang TW, Lee BJ, Song SH, and Lee HW contributed to study conception, design, and supervision; all authors issued final approval for the version to be submitted.

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Large retroperitoneal atypical spindle cell lipomatous tumor, an extremely rare neoplasm: A case report

Jung-Min Bae, Chang-Yeon Jung, Woo-Sung Yun, Joon Hyuk Choi

Abstract

BACKGROUND

Atypical spindle cell lipomatous tumor (ASLT) is a rare soft tissue neoplasm with a low potential for malignancy. ASLT frequently occurs in the limb and limb girdles. However, large retroperitoneal ASLTs are extremely rare. There was no concrete case report of retroperitoneal ASLTs.

CASE SUMMARY

An 18-year-old woman presented with abdominal pain and a palpable mass. Abdominal computed tomography revealed a large fatty mass that was approximately 30 cm in size and filled the entire abdominal cavity. Surgical excision was indicated. The tumor did not invade the adjacent organs. The pelvic cavity was then too narrow to dissect smoothly. The mass was successfully excised without tumor rupture or adjacent organ injury. Microscopically, the neoplasm was a well-differentiated adipocytic neoplasm. Immunohistochemical staining showed that the spindle cells were positive for CD34 and desmin, in addition to multifocal positivity for S100 protein. These histological features were consistent with an ASLT. The patient’s postoperative course was uneventful. At the 12-mo follow-up, no evidence of recurrence or metastasis was observed.

CONCLUSION

To the best of our knowledge, our study is the first concrete report of a large retroperitoneal ASLT in the English literature. In the large retroperitoneal ASLT located in the pelvic cavity, which made it too narrow and tight to dissect, complete excision is difficult but very important because of recurrence risk. Although large retroperitoneal ASLTs are considered extremely rare, their...
detection is important for accurate evaluation and management. Owing to their significant rarity, retrospective multicenter case studies are required to determine the clinicopathologic characteristics.

**Key Words:** Neoplasms; Retroperitoneal space; Spindle cell; Case report

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**Core Tip:** To the best of our knowledge, our study is the first concrete report of a large retroperitoneal atypical spindle cell lipomatous tumor (ASLT) in the English literature. ASLT is a rare soft tissue neoplasm. Additionally, retroperitoneal ASLT is extremely rare. In the large retroperitoneal ASLT located in the pelvic cavity, which made it too narrow and tight to dissect, complete excision is difficult but very important because of recurrence risk.

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**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i8.2584

### INTRODUCTION

Atypical spindle cell lipomatous tumor (ASLT) is a rare soft tissue neoplasm with a low potential for malignancy or benign characteristics. To date, its etiology remains unknown. ASLT was first described in 1994[1], and for several decades, its diagnosis has been controversial and remains challenging. Recently, a diagnostic consensus has been reached[2].

According to a previous large case study, ASLT frequently occurs in the limb and limb girdles in two-thirds of cases, with a predilection for the hands and feet. However, large retroperitoneal ASLTs are extremely rare. Because of the tight pelvic cavity in the present case, surgical excision was very difficult.

In our study, we present the case of an 18-year-old woman diagnosed with a large retroperitoneal ASLT. Despite the surgical difficulty, the postoperative course was uneventful, and no evidence of recurrence or metastasis was observed at the 12-mo follow-up.

We also conducted a review of the literature. To the best of our knowledge, this is the first concrete report of a large retroperitoneal ASLT in the English literature.

This study was approved by the Institutional Review Board (IRB) of Yeungnam University Medical Center (IRB No. 2021-06-020). The patient provided written informed consent for the publication of the case details at admission.

### CASE PRESENTATION

**Chief complaints**

An 18-year-old asian woman presented to our surgery department with abdominal pain, discomfort, and a palpable mass.

**History of present illness**

About several months previously, this patient felt abdominal discomfort. However, this patient did not further evaluation.

**History of past illness**

The patient had no other previous medical history.

**Personal and family history**

The patient had no personal or family history of similar illnesses.

**Physical examination**

The initial blood pressure was 120/80 mmHg; heart rate, 86 beats/minute; respiratory rate, 14 breaths/minute; and body temperature, 36.9 °C at admission.
Her bowel sounds were normoactive and regular. Physical examination revealed non-specific tenderness throughout the abdomen. However, a very large mass was palpated from the epigastric area to the pelvic area.

**Laboratory examinations**
The initial laboratory examination revealed normal levels of leukocytes and hemoglobin.

**Imaging examinations**
Abdominal computed tomography revealed a large fatty mass with a complex soft tissue component. The tumor was approximately 30 cm × 20 cm × 10 cm in size and filled the entire abdominal cavity (Figure 1A). The tumor pushed up the abdominal viscera from the pelvic cavity.
The results led us to consider retroperitoneal neoplasm, including retroperitoneal liposarcoma.

**FINAL DIAGNOSIS**
Microscopically, the neoplasm was a well-differentiated adipocytic neoplasm with a variable myxoid or collagenous stroma, and the pathologic margin was negative. Delicate and ropey collagen bundles were observed. There was an admixed spindle cell component that showed mild nuclear atypia and hyperchromatia, greater than that usually seen in a benign lipoma, but lesser than that usually seen in a well-differentiated liposarcoma. Immunohistochemical staining showed that the spindle cells were positive for CD34 and desmin, in addition to multifocal positivity for S100 protein, but were negative for MDM2. FISH analysis (fluorescence in situ hybridization) shows no MDM2 amplification (Figure 2). Rb staining revealed positive findings, that is, normal/retained status.
A final diagnosis is ASLT in retroperitoneum based on the immnohistocheminal staining and FISH analysis of the tumor tissue.

**TREATMENT**
Surgical excision was indicated, and elective exploration was performed thereafter. Laparotomy revealed a huge retroperitoneal tumor. The abdominal organs were normal. The tumor did not invade the adjacent organs. However, it extended to the pelvic cavity and severely attached to the anterior surface of the coccyx and sacrum; the pelvic cavity was then too narrow to dissect smoothly. The peritumoral dissection in pelvic cavity was very difficult and the dissection was performed little by little dissection manner in both lateral pelvic wall surface, anterior coccyx surface and posterior pubic ramus surface. Intra-operative bleeding amount was about 700cc. However, no transfusion was performed in post-operative periods.
Therefore, the surgery was performed for 8 h. The mass was successfully excised without tumor rupture or adjacent organ injury. Gross and microscopic examinations in frozen section biopsy revealed negative surgical margins. The tumor weighed approximately 5000 g, had an egg-shaped appearance, and was 38 cm × 24 cm × 11.5 cm in size (Figure 1B).
The cut surface showed a large fatty mass with diffuse heterogeneous fibrotic change. No hemorrhage or necrosis was observed (Figure 1C).

**OUTCOME AND FOLLOW-UP**
The patient's postoperative course was uneventful, and recovery after surgery was satisfactory; at the 12-mo follow-up, no evidence of recurrence or metastasis was observed (Figure 3). At the time of preparation of this article, the patient is alive and well.

**DISCUSSION**
ASLT was first described in 1994[1]. It was previously called spindle cell liposarcoma, differentiated spindle cell liposarcoma, and atypical spindle cell lipoma. Although its diagnosis has been controversial and remains challenging for some time, consensus that ASLT is a subtype of spindle cell lipoma with features different from those of atypical lipoma-like tumor/well-differentiated liposarcoma has been reached[2]. In 2017, researchers suggested that ASLT and atypical pleomorphic lipomatous tumor (APLT) belong to the same morphologic spectrum, named atypical spindle cell/pleomorphic lipomatous tumor (ASPLT)[3]. Additionally, ASPLT is described in the 5th edition of the World Health Organization (WHO) classification of soft tissue and bone tumors in 2020[4]. Although ASPLT has
Figure 1 Abdominal computed tomographic findings and gross findings. A: Large fatty mass with a complex soft tissue component. The tumor was filled the entire abdominal cavity and pushed up the abdominal viscera from the pelvic cavity; B: The tumor weigh approximately 5000 g, had an egg-shaped appearance, and measures 38 cm × 24 cm × 11.5 cm in size; C: The cut surface show a large fatty mass with diffuse heterogeneous fibrotic change. No hemorrhage or necrosis is observed.

Figure 2 Microscopic findings. A: The neoplasm shows spindle cells with mild nuclear atypia and hyperchromatia. There are admixed adipocytes (Hematoxylin and eosin stain, × 100); B: The variation of adipocytic size and myxoid stroma are present (Hematoxylin and eosin stain, × 100); C: The spindle cells are negative for MDM2 (Immunohistochemical stain, × 200); D: Fluorescence in situ hybridization shows no MDM2 amplification.

similar clinicopathologic and biological features, ASLT and APLT have different morphological spectra [3].

According to the largest series on ASLTs, the male-to-female sex ratio was 3:2, and the median patient age was 54 years[2]. ASLT develops in the limb and limb girdles in two-thirds of cases, with a predilection for the hands and feet and an approximately equal distribution between superficial and deep sites. They less commonly occur in the head and neck, genitals, and trunk, with very rare retroperitoneal involvement[2].
The mean size of reported tumors ranges from 5 to 8.5 cm\(^5\). However, our case developed a tumor in the retroperitoneum with a size of 38 cm.

Interestingly, the clinical findings of our case, including the patient’s age and sex and tumor location and size, are different from the previously published characteristics of ASLT\(^2\).

The frequent clinical manifestations of ASLT are persistent or enlarged soft tissue masses, nodules, or swelling, sometimes with tenderness. The rare clinical complaints include skin ulceration, local pain, cutaneous vascular markings, cough and hemoptysis, proptosis, night sweats, and abdominal discomfort\(^2\).

Microscopically, the ASLT in our case consisted of a poorly marginated proliferation of mildly atypical spindle cells set in a fibrous or myxoid stroma, with a variably prominent admixed adipocytic component showing variation in adipocyte size and scattered nuclear atypia, frequently with univacuolated or multivacuolated lipoblasts. Tumor cellularity and the relative proportions of the different components highly varied\(^2\).

Although the tumor margins in ASLT are often ill defined with invasion to the surrounding tissues\(^2\), no such invasion was observed in our case.

The definite diagnosis of atypical adipocytic neoplasm with spindle cell features remains challenging for several decades. Recently, a diagnostic consensus has been reached owing to a better biological understanding with substantial contributions from cytogenetics, molecular genetics, and immunohistochemical correlates\(^2\).

CD34 expression is often observed in ASLTs, which is helpful for diagnosis\(^2,3,5\). Rb protein expression loss is present in 57% of ASLT\(^2\). In a previous study, the diagnostic sensitivity of CD34 was 64%, and MDM2 expression was not observed in ASLT. Weak and/or focal expression of MDM2 or CDK4 is occasionally present but is always present in the absence of genomic amplification\(^2\).

Molecular studies have shown deletions or losses of 13q14, including RB1 and its flanking genes RCBTB2, DLEU1, and ITM2B in a significant subset of atypical spindle cell/pleomorphic lipomatous tumors and a consistent absence of MDM2 amplification\(^2,3,6\).

In addition, monosomy 7 has been reported in some cases\(^7\).

In our case, MDM2 expression was negative, and amplification was absent. The negativity of MDM2, CDK4, and FISH for MDM2 amplification highlights critical biological differences between ASLT and dedifferentiated liposarcoma\(^2,5\).

ASLTs can show a wide variety of microscopic features, and differential diagnosis is important and difficult. In our review, differential diagnosis of spindle cell-poor to spindle cell-rich variant of ASPLT was introduced\(^5\). The spindle cell-associated variants were spindle cell/pleomorphic lipoma, atypical lipomatous tumor/well-differentiated liposarcoma, dedifferentiated liposarcoma, pleomorphic liposarcoma, mammary-type myofibroblastoma, cellular angiofibroma, and solitary fibrous tumors.

The treatment of ASLT involves complete excision, similar to other soft tissue malignant neoplasms. In a large retrospective series, the local recurrence rate was approximately 12%. However, distant metastases were not observed. When complete excision was performed, further oncologic treatment was not required. In previous studies, preoperative or postoperative chemotherapy and radiotherapy were performed in several patients. However, the effectiveness or necessity of chemo-therapy or radiotherapy remains unknown\(^2\).
ASLT is classified as a benign neoplasm according to the 2020 WHO classification of tumors of soft tissue and bone[4]. However, several researchers believe that ASLT has a low potential for malignancy or has an intermediate biological potential[2]. Therefore, in our case of a large retroperitoneal ASLT located in the pelvic cavity, which made it too narrow and tight to dissect, complete excision is difficult but very important. Therefore, the surgeon should excise and dissect the tumor carefully without tumor spillage.

According to a large retrospective series, tumor recurrence may develop from 6 mo after the initial surgery; nevertheless, recurrence-related death may not be observed[2].

As mentioned above, large retroperitoneal ASLTs are extremely rare. In the largest series of ASLT cases, retroperitoneal ASLT was found in only two patients. However, the clinical data of these two retroperitoneal ASLT cases, including the patients’ age and sex, tumor size, and prognosis, were not available. Therefore, to the best of our knowledge, our study is the first concrete report of a large retroperitoneal ASLT in the English literature.

CONCLUSION

In conclusion, our study presents a case of a large retroperitoneal ASLT treated with complete excision. In the large retroperitoneal ASLT located in the pelvic cavity, which made it too narrow and tight to dissect, complete excision is difficult but very important. Although large retroperitoneal ASLTs are considered extremely rare, their detection is important for accurate evaluation and management. Owing to their significant rarity, retrospective multicenter case studies are required to determine the clinicopathologic characteristics.

FOOTNOTES

Author contributions: Jung CY, Yun WS, and Bae JM performed the surgery; Jung CY, Yun WS, Choi JH, and Bae JM wrote the manuscript; Choi JH performed the histopathologic diagnosis; Bae JM was the patient’s doctor, who revised the manuscript; all authors have read and approved the final manuscript.

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REFERENCES


Hepatocellular carcinoma effective stereotactic body radiotherapy using Gold Anchor and the Synchrony system: Two case reports and review of literature

Sakue Masuda, Toshitaka Tsukiyama, Yumiko Minagawa, Kazuya Koizumi, Makoto Kako, Takeshi Kinbara, Uojima Haruki

Abstract

BACKGROUND
Radiotheraphy for hepatocellular carcinoma (HCC) is considered to have limited efficacy because of treatment intensity considering that the irradiated area includes the liver, which is highly radiosensitive. In this report, we present two cases in which tumor control by surgical resection, radiofrequency ablation, transcatheter arterial chemoembolization (TACE), and lenvatinib administration was difficult, but stereotactic body radiotherapy (SBRT) using the Synchrony system by Radixact™ and Gold Anchor® (GA) was effective.

CASE SUMMARY
A 60-year-old man had a single 10-cm HCC in the right lobe. Viable lesions remained after TACE, and levels of alpha-fetoprotein and protein induced by vitamin K antagonists II (PIVKA-II) decreased and quickly re-elevated. We performed SBRT with GA. Three weeks after implantation, localized radiotherapy (SBRT; 40 Gy/5 fractions) was performed using the Synchrony system by Radixact™. Four weeks later, the viable lesion had disappeared, and the PIVKA-II levels decreased. A 77-year-old man had a single 12-cm HCC in the right lobe. The patient experienced recurrence after hepatectomy. Further recurrence occurred after TACE, and we performed SBRT with GA. Because of the proximity of the HCC to the gastrointestinal tract, localized radiotherapy (SBRT; 39 Gy/13 fractions) to the HCC was performed 3 wk after implantation using the Synchrony system by Radixact™ and Gold Anchor® (GA) was effective.
system by Radixact™. Four weeks later, the viable lesion had disappeared on computed tomography, and the PIVKA-II levels decreased.

**CONCLUSION**

SBRT using the Synchrony system and GA can deliver a large dose accurately and safely, and could have a high therapeutic effect.

**Key Words:** Fiducial marker; Hepatocellular carcinoma; Gold Anchor®; Radixact™; Stereotactic body radiotherapy; Case report

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**Core Tip:** Radiotherapy using fiducial markers has been performed for hepatocellular carcinoma (HCC) for several years. However, the Gold Anchor® (GA) used in this report is a new fiducial marker with a small diameter, which is expected to reduce the incidence of complications. The Synchrony system by Radixact™ is also a new radiation device, which is useful in respiratory motion management and allows complete tracking of the HCC in which the GA is implanted. Radiotherapy using these devices was highly effective for HCC that could not be controlled by surgery, transcatheter arterial chemoembolization, or molecular targeted drugs.

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**INTRODUCTION**

Hepatocellular carcinoma (HCC) ranks as the sixth cause of cancer incidence and the fourth cause of cancer-related deaths worldwide[1]. There are various treatment methods for HCC, including surgical resection, radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), systemic chemotherapy, and radiotherapy[2]. Since the major risk factors for HCC include chronic hepatitis and liver cirrhosis, many patients have an underlying liver disease at the time of treatment. In addition to tumor and technical factors, the patient's liver function has a significant impact on determining the optimal treatment for HCC. Delis et al[3] and Bruix et al[4] reported that only 10%-30% of HCC cases are indicative of curative surgery because most HCC is diagnosed at intermediate or advanced stages. Radiotherapy is not included in the Barcelona Clinic Liver Cancer staging treatment allocation scheme; however, evidence showing that radiotherapy may be a potential tool for primary treatment or for bridging/downsizing purposes is growing[5]. A variety of technological progress has led to more accurate and dose-escalated radiotherapy, particularly stereotactic body radiation therapy (SBRT)[6]. SBRT sufficiently reduces the dose to adjacent organs due to its sharp dose fall-down outside of the target, while enhancing the biological effectiveness of a large single dose[7]. However, with SBRT it can be difficult to track tumors in the liver due to respiratory motion management (RMM)[8]. SBRT with RMM is becoming more common; however, RMM is often performed with breath-holding or fixation of the trunk. For a more focused and accurate delivery of SBRT, fiducial markers are used to locate tumors in the liver[9]. Using Gold Anchor® (GA) (Naslund Medical AB, Huddinge, Sweden), a new marker of fine diameter, we performed SBRT in two cases and thereby confirmed its efficacy. The GA used in these cases is characterized by a low risk of complications and high visibility on computed tomography (CT) and magnetic resonance imaging (MRI)[9].

**CASE PRESENTATION**

**Chief complaints**

Case 1: For treatment of HCC.

Case 2: For further management of HCC.
History of present illness

Case 1: The patient was a 60-year-old man with alcoholic cirrhosis. For three years, he underwent regular CT examinations annually, and CT revealed a single 10-cm HCC in the right lobe (Figure 1A).

Case 2: The patient was a 77-year-old man with hepatitis B infection. He underwent regular CT examinations annually at a nearby hospital. Four years ago, CT revealed a single HCC measuring 12-cm in the right lobe (Figure 2A). The patient underwent hepatectomy at the same institution, but recurrence occurred (Figure 2B). TACE was then performed to treat the recurrence; however, there was further recurrence (Figure 2C). The patient was subsequently admitted to our hospital for further management of the HCC.

History of past illness

Case 1: The patient was diagnosed with hypertension, diabetes, and gout 10 years ago, and with alcoholic cirrhosis and angina 3 years ago. He had been taking the following medications: Telmisartan, amlodipine basilate, febuxostat, empagliflozin linagliptin, aspirin, pitavastatin calcium hydrate, and diltiazem hydrochloride.

Case 2: The patient was diagnosed with hepatitis B seven years ago at a nearby hospital. He was previously diagnosed with benign prostatic hyperplasia. He was not on any medication.

Personal and family history

Case 1: He had been drinking 50-100 g of alcohol daily for 40 years.

Case 2: He rarely drank. He was exposed to the atomic bomb in World War II.

Physical examination

Cases 1 and 2: There were no findings of anemia or jaundice. The abdominal findings were also unremarkable.

Laboratory examinations

Case 1: Blood tests showed negative hepatitis virus markers (Table 1), and Child-Pugh status was A.

Case 2: Blood tests were positive for hepatitis B core antibody (Table 1), and Child-Pugh status was A.

Imaging examinations

Case 1: Contrast-enhanced CT revealed a typical 10-cm HCC in the right lobe. The contrast enhanced the HCC in the early phase and washed out in the late phase (Figure 1A).

Case 2: Contrast-enhanced CT revealed a typical 12-cm HCC in the right lobe. The contrast stained the HCC in the early phase and washed out in late phase (Figure 2A).

FINAL DIAGNOSIS

Case 1

The final diagnosis was HCC due to alcoholic liver cirrhosis.

Case 2

The final diagnosis was HCC due to hepatitis B infection.

TREATMENT

Case 1

TACE was performed twice for HCC, but in both instances, viable lesions remained, and levels of alphafetoprotein and protein induced by vitamin K antagonists-II (PIVKA-II) decreased then quickly re-elevated. A third TACE was performed; however, the results were similar to the previous TACEs: 2.5 cm of viable lesions remained, and the once-decreased PIVKA-II level immediately increased again (Figure 1B-D). Therefore, we decided to perform SBRT with GA; an interventional radiology specialist with 30 years of experience selected a 22G needle and implanted two GAs within 2 cm of the HCC (Figure 3). One week after implantation, CT registration was performed, and radiotherapy was planned. Three weeks after implantation, localized radiotherapy (SBRT; 40 Gy/5 fractions) was performed for HCC using the Synchrony system by Radixact™ (Accuray Japan K.K., Tokyo, Japan).
Table 1 Laboratory examination in cases 1 and 2

<table>
<thead>
<tr>
<th>Laboratory examination</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells</td>
<td>8100/μL</td>
<td>4200/μL</td>
</tr>
<tr>
<td>Hb</td>
<td>15.6 g/dL</td>
<td>15.1 g/dL</td>
</tr>
<tr>
<td>Ht</td>
<td>45.90%</td>
<td>43.50%</td>
</tr>
<tr>
<td>MCV</td>
<td>94.2 fl</td>
<td>94.2 fl</td>
</tr>
<tr>
<td>PLT</td>
<td>162000/μL</td>
<td>141000/μL</td>
</tr>
<tr>
<td>PT-INR</td>
<td>0.96</td>
<td>1</td>
</tr>
<tr>
<td>PT%</td>
<td>107%</td>
<td>100.50%</td>
</tr>
<tr>
<td>T-BIL</td>
<td>0.6 mg/dL</td>
<td>1.3 mg/dL</td>
</tr>
<tr>
<td>AST</td>
<td>62 U/L</td>
<td>18 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>60 U/L</td>
<td>14 U/L</td>
</tr>
<tr>
<td>γGTP</td>
<td>689 U/L</td>
<td>68 U/L</td>
</tr>
<tr>
<td>ALP</td>
<td>423 U/L</td>
<td>249 U/L</td>
</tr>
<tr>
<td>TP</td>
<td>8 g/dL</td>
<td>7.1 g/dL</td>
</tr>
<tr>
<td>ALB</td>
<td>3.8 g/dL</td>
<td>4 g/dL</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.10%</td>
<td>5.50%</td>
</tr>
<tr>
<td>BUN</td>
<td>16.4 mg/dL</td>
<td>21.7 mg/dL</td>
</tr>
<tr>
<td>CRE</td>
<td>0.68 mg/dL</td>
<td>1.05 mg/dL</td>
</tr>
<tr>
<td>CRP</td>
<td>0.524 mg/dL</td>
<td>0.149 mg/dL</td>
</tr>
<tr>
<td>AFP</td>
<td>276.8 ng/mL</td>
<td>3.6 ng/mL</td>
</tr>
<tr>
<td>PIVKA-II</td>
<td>33224 mAU/mL</td>
<td>44 mAU/mL</td>
</tr>
<tr>
<td>CEA</td>
<td>5.9 ng/mL</td>
<td>4.5 ng/mL</td>
</tr>
<tr>
<td>HBs antigens</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>HBc antibody</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>HCV antibody</td>
<td>(-)</td>
<td>(-)</td>
</tr>
</tbody>
</table>

AFP: Alpha-fetoprotein; PIVKA: Protein induced by vitamin K antagonists; TP: Total protein; Alb: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Cr: Creatinine; CRP: C-reactive protein; Hb: Hemoglobin; PLT: Platelet count; PT: Prothrombin time; PT-INR: International normalized ratio of prothrombin time; T-BIL: Total bilirubin; WBC: White blood cells; HBc: Antibody hepatitis B core antibody; HBs: Antigen hepatitis B surface antigen; HCV: Antibody hepatitis C virus antibody.

Case 2

We performed TACE twice for HCC in our hospital, but both times viable lesions remained. The PIVKA-II level decreased but quickly re-elevated. A third TACE was performed; however, the results were similar to the previous TACEs: 2 cm of viable lesions remained, and the decreased PIVKA-II level increased again (Figure 2D and E). Therefore, we decided to perform SBRT with GA, and two GAs were implanted within 2 cm of the HCC with a 22G needle. In this case, the biloma was complicated after hepatectomy at the previous hospital, and the puncture route for GA implantation passed near the site (Figure 4). One week after implantation, CT registration was performed, and radiotherapy was planned. Because of the proximity of the HCC to the gastrointestinal tract, localized radiotherapy (SBRT; 39 Gy/13 fractions) to the HCC was performed 3 wk after implantation using the Synchrony system by Radixact™.

OUTCOME AND FOLLOW-UP

Case 1

Four weeks later, CT showed that the viable lesion had disappeared and the PIVKA-II levels decreased (Figure 5). There were no complications of grade 3 or higher during the clinical course (Figure 6). No
Figure 1 Computed tomography of case 1. A: On admission; B: After the first transcatheter arterial chemoembolization (TACE); C: After the second TACE; D: After the third TACE. Orange arrowhead: Hepatocellular carcinoma before TACE; yellow arrowhead: Viable lesion after TACE.

Figure 2 Computed tomography in case 2. A: Before surgical resection at a nearby hospital; B: At the time of recurrence; C: Before Transcatheter arterial chemoembolization (TACE) at our hospital; D: After the first TACE at our hospital; E: After the third TACE at our hospital. Orange arrowhead: Hepatocellular carcinoma (HCC) before surgical resection at a nearby hospital; blue arrowhead: recurrence of HCC; yellow arrowhead: Viable lesion after TACE.

recurrence has been observed at 9 mo after SBRT with GA.

**Case 2**

Four weeks later, the viable lesion had disappeared on CT and the PIVKA-II levels decreased (Figure 7). In this case, the puncture route for GA implantation passed near the biloma. As a result, the biloma developed complications from infection (Figure 8), which improved through conservative treatment. There were no other complications of grade 3 or higher during the clinical course (Figure 9). Recurrence occurred 7 mo after SBRT with GA; however, without the short-term recurrence seen after TACE, progression-free survival was longer with this treatment.

**DISCUSSION**

Regarding early-stage HCC, it is standard to undergo curative treatments, such as surgical resection (partial liver resection or liver transplantation) and percutaneous ablation, most commonly RFA. Regarding intermediate-stage HCC, many patients undergo TACE as their first local regional treatment [5,8]. However, such treatments have limitations in locally advanced cases. For example, TACE is contraindicated in cases with portal vein thrombosis, malignant portal vein thrombosis, and untreatable arteriovenous fistula. RFA is contraindicated in cases with bleeding disorders and can be difficult in tumors near the diaphragm, digestive tract, pancreas, hepatic hilum, and major bile ducts or vessels.
Furthermore, Lin et al.[11] reported that RFA was less effective for HCCs larger than 4 cm. Patients who do not satisfy the Milan criteria or San Francisco criteria are not commonly indicated for surgical resection[5]. It has also been reported that patients with intermediate- to advanced-stage HCC have a high recurrence rates. Five-year tumor recurrence rates after surgical resection and RFA may be more than 50% and up to 80%, respectively. These high recurrence rates include patients who undergo TACE [8,12]. In our case, one patient had a recurrence after surgery and again after TACE. In the other case, recurrence occurred after TACE. Bearing in mind the aforementioned reasons, as well as the fact that radiotherapy is constantly evolving due to technological innovation, radiotherapy is expected to be the fourth local therapy available for HCC[5,8,10].

Currently, there are useful treatment guidelines for managing HCC from America[13,14], Europe [15], Japan[16], Korea[17], China[18], and Taiwan[19]. There is a variety of evidence on the efficacy of radiotherapy for HCC, but phase III randomized trials are lacking. Therefore, based on the current guidelines, radiation therapy is not mentioned or is listed as having a limited role. However, modern radiotherapy has become increasingly important in the management of patients with HCC due to two
First, advances in radiotherapy techniques, for example SBRT and proton therapy, have allowed for more accurate delivery of radiation to enhance tumor control and reduce complications in organ close to the HCC. Second, the development of molecular targeted drugs and checkpoint-blockade immunotherapy has prolonged the overall survival of patients with HCC, reaffirming the importance of local tumor control. In this regard, several clinical trials of SBRT for HCC are underway[8,10]. The reason for choosing radiotherapy in the present cases was that they showed local recurrence and were refractory to surgery, TACE, or chemotherapy; in addition, RFA was difficult because, in the first case, the recurrence was close to the inferior vena cava, whereas in the second case, it was close to the left branch of the portal vein.

SBRT builds on the principle of delivering high doses per fraction using steep dose gradients and smaller margins of uncertainty. A large dose of radiation is typically defined as one over 2 Gy. SBRT delivers extremely precise high doses in a limited number of treatment fractions (usually 3-6 fractions at > 5 Gy per fraction) over a treatment course of 1-2 wk[8]. High doses of radiation in a few fractions

**Figure 5** Computed tomography before and after stereotactic body radiation in case 1. Yellow arrowhead: Viable lesion after the third transcatheter arterial chemoembolization; blue arrowhead: Disappearance of the contrast effect of the tumor after stereotactic body radiation.

**Figure 6** Clinical course in case 1. Orange arrows: Viable lesion; blue arrows: Disappearance of the contrast effect of the tumor after stereotactic body radiation. AFP: Alpha-fetoprotein; PIVKA-II: Protein induced by vitamin K antagonists-II; SBRT: Stereotactic body radiation; TACE: Transcatheter arterial chemoembolization.
Figure 7 Computed tomography before and after stereotactic body radiation. A: Computed tomography (CT) before stereotactic body radiation (SBRT); B: CT after SBRT. Yellow arrowhead: Viable lesion after the third transcatheter arterial chemoembolization; blue arrowhead: Disappearance of the contrast effect of the tumor after SBRT.

Figure 8 Computed tomography of infected biloma. Blue arrows: Infected biloma.

allows for a higher proportion of cancer cell death while reducing the chance of tumor DNA repair or repopulation[5]. Kim et al[20] reported that patients in the high-dose group achieved higher relative objective responses. To deliver high doses safely, image guidance and RMM are required. However, it is difficult to track a tumor in the liver during radiotherapy. Therefore, fiducial markers are used to track tumors in the liver. RMM using the Synchrony system with Radixact™ in combination with fiducial markers has higher accuracy and shorter irradiation time than other RMMs. The irradiation area to normal liver tissue is narrow, the treatment time is short, and posture maintenance is easy since it tracks HCC under free breathing. This makes it easier to deal with patients with impaired liver function and older patients who have difficulty maintaining a posture for a long time. SBRT with GA and Radixact™ is advantageous for HCC, which is more dose-dependent than several other organ cancers, and for
normal liver cells, which are more radiosensitive than the lung[21,22].

There are no complications specific to Radixact™, but specific complications associated with SBRT and GA should be considered. Commonly used fiducial markers are 0.35-1.1 mm in diameter. Larger markers are relatively easy to identify on CT or MRI. However, larger needle diameters increase the frequency of implantation metastases, bleeding, and the occurrence of serious complications[23,24]. In addition, the risk of bleeding is particularly high in patients with cirrhosis. Major complications after fiducial marker placement include pain, migration of fiducial markers, implantation of metastases, bleeding, and infection. Although the rate of complications is 12%-14%, complications other than pain are rare[25,26]. However, the fiducial marker is a relatively new method for HCC, and the accumulation of data is still limited. Referring to the data of percutaneous image-guided liver biopsy with comparable puncture needle thickness, the rate of implantation metastases was 3%, of bleeding was 2%, and of infection was 0.35%[23,24,27]. In fiducial markers, the tumor itself is not punctured; therefore, the risk of implantation metastases is expected to be lower than that of percutaneous image-guided liver biopsy. In one of our cases, the puncture route was in the vicinity of a biloma complicated by surgical resection which led to infection of the biloma. Although complications of infection due to fiducial marker placement are very rare, care should be taken when there is a biloma on the puncture route. In this case, we believe that infection could have been avoided by changing the puncture route.

The GA used in this study is characterized by its small diameter which can reduce the risk of complications. Another feature is that the GA can be implanted in a zigzag or spherical shape owing to its concavo-convex shape, and pure gold contains 0.5% pure iron, which results in low migration and highly visibility on CT and MRI[9].

Ultrasound-guided placement, CT-guided placement, and endoscopic ultrasound-guided placement have been performed, and each method has the same success and complication rates[25,28,29]. Because of the risk of fiducial marker migration, multiple implantations are recommended. Placing the fiducial markers in close proximity to each other or on the same plane of the CT may cause the irradiator to misidentify them during radiation therapy. Therefore, we performed CT-guided placement to improve the accuracy of GA placement.

One of the advantages of SBRT over conventional radiotherapy is that the total dose to adjacent organs is low owing to the rapid dose fall-off inherent in SBRT. Nonetheless, even with SBRT, potential liver-related toxicities include sequelae associated with radiation-induced liver disease (RILD), including fatigue, abdominal pain, ectopic hepatomegaly, ascites, and elevated liver enzymes, which can usually develop within 4 months of radiotherapy[10]. In addition to these findings, patients may also experience jaundice, thrombocytopenia, and changes in coagulation factors. A review of the prospective literature shows that adverse events of grade 3 or higher are rare, with most studies reporting less than 12%[5]. It should be noted that patients with a Child-Pugh classification of B7 or lower have a lower risk of RILD compared to patients with a Child-Pugh classification of B8 or higher.
In our cases, no RILD was observed even 4 mo after SBRT. Another report stated that the concurrent use of SBRT with sorafenib should be avoided because it is likely to cause grade 3 gastrointestinal disorders and tumor rupture. Therefore, lenvatinib, a molecular targeted drug similar to sorafenib, was discontinued during the SBRT treatment period in our cases.

As described above, SBRT with GA and the Synchrony system can be considered a useful fourth local therapy for HCC. However, the irradiation range is limited by the patients’ liver function; in the literature, most patients treated with SBRT have Child-Pugh classification of A and have a few tumors (often < 3 tumors).

CONCLUSION
SBRT combined with GA and the Synchrony system by Radixact™ is minimally invasive, highly accurate, and can deliver a large dose of radiation to HCC.

In our cases, tumor control was difficult with surgery, TACE, or molecular targeted drugs; however, SBRT combined with GA and the Synchrony system by Radixact™ was highly effective for HCC. The GA used in this report is a new fiducial marker with a small diameter which is expected to reduce the incidence of complications. The Synchrony system by Radixact™ is also a new radiation device that is useful in RMM and allows complete tracking of the HCC in which the GA is implanted.

The method and systems used in this study are considered safe and effective, and we would like to use them in future work for the treatment of HCC in which tumor control by surgical resection, RFA, TACE, and molecular targeted drug administration is difficult. However, this is a case report and further research, such as phase III trials, is needed.

FOOTNOTES
Author contributions: Masuda S, Koizumi K, Kako M, Kinbara T, and Uojima H were the patient’s hepatologists, reviewed the literature, and contributed to manuscript drafting; Masuda S and Minagawa Y reviewed the literature and contributed to manuscript drafting; Tsukiyama T and Minagawa Y were the radiologists and performed the radiotherapy and contributed to manuscript drafting; Tsukiyama T analyzed and interpreted the imaging findings; Masuda S, Uojima H, Tsukiyama T, and Minagawa Y were responsible for the revision of the manuscript and for important intellectual content; all authors issued final approval for the version to be submitted.

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10.5152/dir.2018.17525]


Mantle cell lymphoma with endobronchial involvement: A case report

Yi-Zong Ding, Dao-Qiang Tang, Xiao-Jing Zhao

Abstract

BACKGROUND
Mantle cell lymphoma (MCL) is a subtype of Non-Hodgkin's lymphoma (NHL). MCL frequently affects extranodal sites while endobronchial involvement is uncommon. Only 5 cases of MCL with endobronchial involvement have been previously reported.

CASE SUMMARY
A 56-year-old male patient arrived at the hospital complaining of a dry cough. A mass in the right upper lobe of the lung was revealed in Chest computed tomography (CT). Right lung hilar and mediastinal lymphadenopathies were also found by CT scan. The patient was diagnosed with central-type lung cancer with multiple lymph node metastases after positron emission tomography (PET) CT scan examination. The fiber optic bronchoscope examination revealed diffuse neoplasm infiltration in the inlet of the right upper lobar bronchos. The patient was finally diagnosed with MCL based on the bronchoscopy and mediastinoscopy biopsy results.

CONCLUSION
MCL could masquerade as central type lung cancer. An endobronchial biopsy examination is necessary for the early diagnosis of MCL.

Key Words: Mantle cell lymphoma; Endobronchial involvement; Central type lung cancer; Endobronchial biopsy; Bronchoscopy; Mediastinoscopy; Case report

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We reported a case of mantle cell lymphoma (MCL) with endobronchial involvement. MCL with endobronchial involvement is very rare. Only five such cases have been previously reported. Positron emission tomography-computed tomography is recommended for differential diagnosis and detection of extranodal sites of MCL. A pathological diagnosis can be made based on an endobronchial biopsy by bronchoscopy but doctors should prompt efforts to establish enough tissues.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i8.2604

INTRODUCTION
Mantle cell lymphoma (MCL) is a subtype of Non-Hodgkin's lymphoma (NHL). Over expression of cyclin D1 and reciprocal chromosomal translocation t(11;14)(q13;q32) are the distinguishing features of MCL[1,2]. MCL represents approximately 4%-6% of all NHL[3,4]. This disease is more often diagnosed in male patients in their 60s and almost all patients present with advanced stages III-IV of the disease. Extranodal involvements, include the bone marrow, gastrointestinal tract, liver, spleen, skin, Waldeyer's ring, lacrimal glands and central nervous system, are very common[5,6]. Even though, airway involvement is very rare[7-9]. We represent here a case of MCL with endobronchial as well as multiple lymph node involvement. Bronchoscopy and mediastinoscopy biopsies of the endobronchial and mediastinal lymph nodes were done to confirm the diagnosis.

CASE PRESENTATION
Chief complaints
A 56-year-old male patient arrived at the hospital complaining of dry cough for two months.

History of present illness
The patient suffered from dry cough for the past two months prior to his visit to our hospital. The chest computed tomography (CT) scan performed at the local hospital revealed a mass in the right upper lobe of the lung, with right lung hilar and mediastinal lymphadenopathies.

History of past illness
The patient had no prior medical history and was a smoker with 30 pack-years.

Personal and family history
The patient was healthy and have no personal or family history of tumors.

Physical examination
The patient presented mild coarse breath sounds in the right upper lung during auscultation.

Laboratory examinations
Laboratory tests revealed an increased percentage of neutrophilic leukocytes (78.4%) with normal hematocrit and platelet count values. His CYFRA 21-1 level was 4.03 ng/mL, which was far above the maximum normal limit (3.3 ng/mL). Other tumor markers were all in the normal range.

Imaging examinations
Chest enhanced CT scans revealed a central-type mass in the right lung with enlarged lymph nodes in the right lung hilar, mediastinal and bilateral axillary areas (Figure 1A). The CT also displayed thickening of the right bronchial wall (Figure 1B). PET-CT showed an increased uptake of 18-fludeoxyglucose in the mass of the right lung hilum and the fear of malignancy was a major concern. This examination also revealed lymph node metastases in the right lung hilar, mediastinal, celiac, right cervical, right supraclavicular and bilateral axillary areas (Figure 2).

Bronchoscopic examinations
Flexible bronchoscopy revealed mucosal infiltrative changes at the level of the right upper lobe inlet and the right upper lobe bronchus was obstructed (Figure 3). The other bronchial mucosa was normal. The
Ding YZ et al. MCL with endobronchial involvement

Figure 1 Chest enhanced computed tomography scan. A: Right central type lung mass with enlarged lymph nodes in the right lung hilar, mediastinal and bilateral axillary areas; B: The computed tomography scan also displayed thickening of the right bronchial wall.

Figure 2 Positron emission tomography - computed tomography showed an increased uptake of 18-fluodeoxyglucose in the mass of the right lung hilum and revealed lymph node metastases in the right lung hilar, mediastinal, celiac, right cervical, right supraclavicular and bilateral axillary areas.

mucosal endobronchial biopsy at the level of the right upper lobe inlet showed lymphoid hyperplasia. These cells were CD20 positive B-cells and Bcl-2, CD5, CD19, and cyclin D1 were also expressed. This result indicates the possibility of MCL. As the tissue sample of the endobronchial biopsy was insufficient, a mediastinoscopy biopsy of the mediastinal lymph nodes was scheduled.

**Mediastinoscopy examinations**

Subcarinal lymph node biopsy was performed under mediastinoscopy. The specimen also showed lymphoid hyperplasia. The immunohistochemical staining showed that these cells were positive for Bcl-2, CD5, CD19, CD20, Cyclin D1 and SOX11 while negative for Bcl-6, CD3, CD10, CD21 and CD23. The percentage of Ki67 positive cells was 25% (Figure 4). Therefore, the diagnosis of MCL was confirmed.

**FINAL DIAGNOSIS**

The final diagnosis for this patient was MCL.
Ding YZ et al. MCL with endobronchial involvement

Figure 3  Flexible bronchoscopy displayed mucosal infiltrative changes at the level of the right upper lobe inlet and the right upper lobe bronchus was obstructed.

Figure 4  Mucosal endobronchial biopsy at the level of the right upper lobe inlet showing lymphoid hyperplasia. A: H&E staining; B and C: With immunohistochemical staining, these cells were found to be positive for CD5 and SOX11; D: The percentage of Ki67-positive cells was 25% (Original magnification × 200).

TREATMENT

After the diagnosis of MCL, the patient was transferred to the hematology department of another hospital. The therapy was proceeded to rituximab and bendamustine maintenance.

OUTCOME AND FOLLOW-UP

The review of recent communication exchanges with his wife indicated that he was tolerating chemotherapy well, with early signs of clinical response a year after the diagnosis.
**Table 1** Mantle cell lymphoma with endobronchial involvement

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Age</th>
<th>Gender</th>
<th>Time between MCL first diagnosis and endobronchial involvement</th>
<th>Smoking history</th>
<th>Presenting symptoms</th>
<th>CyclinD1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figgis <em>et al.</em></td>
<td>53</td>
<td>Female</td>
<td>More than three years (second relapse)</td>
<td>N/A</td>
<td>Cough, dyspnoea, wheeze</td>
<td>N/A</td>
</tr>
<tr>
<td>Miyoshi <em>et al.</em></td>
<td>70</td>
<td>Female</td>
<td>Five years (fifth relapse)</td>
<td>N/A</td>
<td>Stridor, respiratory failure</td>
<td>Positive</td>
</tr>
<tr>
<td>Inai <em>et al.</em>[2]</td>
<td>86</td>
<td>Male</td>
<td>Two years (first relapse)</td>
<td>N/A</td>
<td>Dyspnoea</td>
<td>N/A</td>
</tr>
<tr>
<td>Katono <em>et al.</em>[2]</td>
<td>87</td>
<td>Male</td>
<td>0 (diagnosed by endobronchial biopsy)</td>
<td>Never-smoker</td>
<td>Dyspnoea on exertion</td>
<td>Positive</td>
</tr>
<tr>
<td>Tong <em>et al.</em>[1]</td>
<td>65</td>
<td>Male</td>
<td>0 (diagnosed by endobronchial biopsy)</td>
<td>Current smoker with 40 pack-years</td>
<td>Productive cough, dyspnoea</td>
<td>Positive</td>
</tr>
<tr>
<td>Current case</td>
<td>56</td>
<td>Male</td>
<td>0 (diagnosed by endobronchial biopsy)</td>
<td>Current smoker with 30 pack-years</td>
<td>Cough</td>
<td>Positive</td>
</tr>
</tbody>
</table>

N/A: Not applicable; MCL: Mantle cell lymphoma.

**DISCUSSION**

MCL is a kind of B cell aggressive NHL with the feature of hyperplasia of B-cells. These B-cells is a subset arising from antigen-experienced B cells resembling those found in the follicular mantle zones[1]. Immunohistochemical staining was positive for Bcl-2, CD5, CD19, CD20 and cyclin D1 and negative for Bcl-6, CD10 and CD23[9]. According to the latest research, SOX11 has been described as a very important diagnostic marker when cyclin D1 is negative as it is equally expressed in D1-positive and D1-negative MCL[9].

Although MCL was more likely to have extranodal involvement, endobronchial involvement is uncommon[5,6]. As far as we know, only 5 cases of MCL with tracheobronchial involvement have been represented in the literature (Table 1)[1,2,10-12]. Lymphoma with endobronchial involvement is divided into two types: Diffuse submucosal infiltration (type I) and localized solitary mass (type II)[13]. Interestingly, all 5 cases exhibited a type I pattern[13]. In contrast, the case presented in this report exhibited a type II pattern, and the mechanisms of endobronchial metastasis may be caused by direct bronchial invasion from a parenchymal mass or mediastinal mass.

Type II endobronchial MCL has a large chance of being diagnosed as central-type lung cancer. PET-CT was useful in the differential diagnosis and detection of extranodal involvement. In addition, for detecting both nodal and extranodal involvement in patients with MCL, PET has a high sensitivity[14].

The diagnosis of MCL should be made on the basis of lymph node biopsy results, tissue, bone marrow, or blood phenol type[5]. Typical positive results of immunohistochemistry and morphology of infiltrating small-to-medium-sized cells were displayed in most cases[15]. In cases where endobronchial involvement is suspected, bronchoscopy with endobronchial biopsy results is an important and useful diagnostic tool. However, it is worth mentioning that the sample of tissue may be too small to determine a pathological diagnosis. In this case report, the patient underwent mediastinoscopy to obtain sufficient tissue from mediastinal lymph nodes, and then the diagnosis of MCL was confirmed.

MCL is one of the most difficult-to-treat B-cell lymphomas[1]. In previously untreated patients, conventional chemotherapy is the most common treatment and the remission rates is high. However, relapse within a few years is common and median survival of five to seven years is low[9]. Proteasome inhibitors, mTOR inhibitors, and lenalidomide are available in addition to conventional chemotherapy for the treatment of relapsed MCL patients[1]. But their mechanisms of action and determinants of efficacy were still unclear[9].

**CONCLUSION**

In conclusion, we have reported a case of MCL with endobronchial involvement. MCL with endobronchial involvement is very rare and can be misdiagnosed as central-type lung cancer. PET-CT is recommended in MCL for differential diagnosis and the detection of extranodal sites. A pathological diagnosis can be based on bronchoscopy and endobronchial biopsy, but doctors are required to focus their efforts on collecting appropriate samples of tissue.
FOOTNOTES

**Author contributions:** Ding YZ collected the clinical data and wrote the manuscript; Tang DQ analyzed the clinical data; and Zhao XJ designed the work; all authors read and approved the final manuscript.

**Informed consent statement:** A written informed consent was obtained from the patient included in this case report.

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REFERENCES


Fatal systemic emphysematous infection caused by *Klebsiella pneumoniae*: A case report

Jun-Qiang Zhang, Chan-Chan He, Bo Yuan, Rui Liu, Yu-Jing Qi, Zi-Xia Wang, Xiao-Na He, Yu-Min Li

**Abstract**

**BACKGROUND**
Systemic emphysematous infection caused by *Klebsiella pneumoniae* (*K. pneumoniae*) is a rare but severe infection which can be lethal if the diagnosis is delayed.

**CASE SUMMARY**
We report a rare case of systemic emphysematous infection via hematogenous dissemination from a liver abscess caused by *K. pneumoniae*, complicated by multiple organ dysfunction syndrome, septic shock, bacteremia, emphysematous cystitis, prostate and left seminal vesicle abscesses in a diabetic patient. The patient simultaneously presented with spontaneous pneumoperitoneum secondary to rupture of the emphysematous liver abscess. His condition after admission deteriorated rapidly and he died within a short period. This disease is a great challenge for the clinician as *K. pneumoniae* can cause multifocal emphysematous infections and fulminant septic shock. Pneumoperitoneum following spontaneous rupture of the liver abscess can result in intra-abdominal sepsis that further increases mortality rate. Moreover, appropriate site-specific intervention and adequate drainage of numerous emphysematous liver lesions are difficult.

**CONCLUSION**
Early diagnosis followed by efficient antibiotic therapy and surgical management are essential for systemic emphysematous infection.

**Key Words:** *Klebsiella pneumoniae*; Emphysematous liver abscess; Pneumoperitoneum; Emphysematous cystitis; Emphysematous prostate abscess; Septic shock

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Core Tip: Systemic emphysematous infection caused by *Klebsiella pneumoniae* is a rare but lethal infection. The combination of emphysematous liver abscess, emphysematous cystitis, prostate and left seminal vesicle abscesses, bacteremia, septic shock and multiple organ dysfunction syndrome are even rarer. The patient simultaneously presented with spontaneous pneumoperitoneum secondary to rupture of the emphysematous liver abscess, which is an extremely rare clinical condition inducing intra-abdominal sepsis that further increases the mortality rate.

INTRODUCTION

*Klebsiella pneumoniae* (*K. pneumoniae*) is a Gram-negative pathogenic bacterium belonging to the *Enterobacteriaceae* family, usually causes various infections including pneumonia, urinary tract infections, hepatobiliary infections and intra-abdominal infections[1]. *K. pneumoniae* strains are divided into the classical group and hypervirulent group. Classical *K. pneumoniae* is an opportunistic pathogen and primarily infects critically ill and immunocompromised patients, and causes health-care associated infections; the hypervirulent pathotype usually infects healthy individuals and causes community-acquired infections[2-3]. In recent years, several studies have reported a distinctive clinical syndrome, invasive *K. pneumoniae* liver abscess syndrome (IKLAS), which typically occurs in patients with diabetes mellitus (DM) and is characterized by a liver abscess, bacteremia, and hematogenous extrahepatic infection at sites such as the eye, brain, or lung. We report a rare case of IKLAS presenting with multiple organ dysfunction syndrome (MODS), septic shock, bacteremia, numerous emphysematous liver abscesses, pneumoperitoneum, emphysematous cystitis, prostate and left seminal vesicle abscesses in a diabetic patient whose infection progressed rapidly and died within a short period.

CASE PRESENTATION

**Chief complaints**
A 66-year-old man was admitted to our hospital with a 14-d history of worsening fatigue, anorexia, nausea and vomiting, and a 3-d history of confusion and jaundice.

**History of present illness**
Fourteen days prior to hospital admission, he suffered from fatigue, anorexia, nausea and vomiting. The patient did not visit his doctor, the symptoms of nausea and vomiting gradually improved but fatigue and anorexia persisted. His family members found that he had been showing signs of confusion and jaundice 3 d earlier. He vomited 50 mL of coffee-colored gastric contents one day earlier. He had no fever, abdominal pain and lower urinary tract symptoms.

**History of past illness**
His past medical history included acute gastric ulcer perforation which was repaired 40 years earlier, hypertension treated with amlodipine and hydrochlorothiazide, type 2 DM without regular control treated with metformin, acarbose and insulin for 10 years, chronic prostatitis and chronic diarrhea for the past 10 years, and a cerebral infarction 8 years and 3 mo previously. He had acute calculous cholecystitis with hypotension 2 mo ago and received empirical antibiotics with ceftazidime 2.0 g and ornidazole 0.5 g intravenous route every 12 h for 10 days, blood and bile cultures and cholecystectomy were not performed.

**Personal and family history**
No relevant family history, travelling history or animal contact was reported.

**Physical examination**
His initial vital signs were as follows: blood pressure 70/50 mmHg, pulse 110 bpm, respiratory rate 30 breaths/min, and body temperature of 36.5 °C. The Acute Physiology and Chronic Health Evaluation II score was 23, and the Sequential Organ Failure Assessment score was 13. He demonstrated confusion, icteric sclera, normal cardiopulmonary auscultation, a soft, non-tender abdomen, and acrocyanosis with scattered marble patches on wet and cold lower limbs.
Laboratory examinations
Markedly raised inflammatory parameters were found including the following: white blood cell count 18.8 × 10^9/L (93% neutrophils and 1% lymphocytes), C-reactive protein 315 mg/L, interleukin 6 > 5000 pg/mL, and procalcitonin (PCT) 70 ng/mL. Serum biochemical tests showed total bilirubin 210.9 μmol/L, direct bilirubin 165.7 μmol/L, alanine aminotransferase (ALT) 940 U/L, aspartate aminotransferase (AST) 3870 U/L, alkaline phosphatase 1429 U/L, lactate dehydrogenase (LDH) 7852 U/L, blood urea nitrogen 48.1 mmol/L and creatinine 339.3 μmol/L. The level of blood glucose and glycosylated hemoglobin A1c (HbA1c) was 10.25 mmol/L and 8.4% respectively. A coagulation panel demonstrated a prothrombin time (PT) of 21.3 s, prothrombin time activity (PTA) 39%, international normalized ratio (INR) 1.9, activated partial thromboplastin time (APTT) 38.7 s and D-dimer 7.25 μg/mL. Arterial blood gas analysis revealed a pH of 7.273, undetectable PCO₂ (A fall in PCO₂ was beyond the range of the Point-of-Care Testing device), PO₂ 90.2 mmHg and lactate 20 mmol/L. In addition, routine urine analysis revealed numerous red blood cells (50-60/high power field), white blood cells (35-40/high power field), bilirubin and albuminuria. The patient was not anemic (blood Hb 133 g/L) and hematocrit was 39.7%. Serology showed that human immunodeficiency virus, syphilis, hepatitis B and C were all negative.

Imaging examinations
An abdominal computed tomography (CT) scan displayed numerous emphysematous hepatic abscesses, rupture of some liver abscesses and gas formation in the right subphrenic area (Figure 1). Pelvic CT showed intramural gas formation in the bladder and an enlarged prostate and left seminal vesicle with abnormal air accumulation (Figure 2). Chest CT revealed pulmonary infiltrates in the right lower lobes and small right pleural effusions.

FINAL DIAGNOSIS
The clinical diagnosis was IKLAS with septic shock and MODS accompanied by emphysematous prostate and left seminal vesicle abscesses and cystitis.

TREATMENT
Empirc antimicrobial treatment with meropenem was administered along with fluid resuscitation and vasoactive support with noradrenaline. Continuous veno-venous hemofiltration was then initiated for acute kidney injury and persistent inflammatory state after adequate fluid resuscitation. A consultant hepatobiliary surgeon suggested an emergency surgical exploration but this was refused by his family. We attempted percutaneous liver abscess drainage guided by bedside ultrasound, but did not succeed due to liver abscess cavities totally occupied by air and pneumoperitoneum. His condition rapidly deteriorated, he developed emerging thrombocytopenia, decreased Hb, a progressive increase in serum enzyme levels in addition to severe metabolic acidosis, persistent renal failure and liver dysfunction, and subsequently developed respiratory failure, disseminated intravascular coagulation and coma. At that time, his laboratory examinations showed lactate 30 mmol/L, pH 7.193, HCO₃⁻ 11.6 mmol/L, base excess −18.4 mmol/L, SO₂ 89.6%, PO₂/FiO₂ 159, platelets 28×10⁹/L, Hb 86 g/L, INR 3.37, PT 39 s, PTA 21%, APTT 57.7 s, D-dimer 7.25 μg/mL, ALT 1501 U/L, AST 6012 U/L, CK 1700 U/L and LDH 12356 U/L. The patient was immediately intubated and mechanical ventilation was initiated. Despite these aggressive treatments, the patient’s condition was critical and exacerbated, with persistent MODS and hemodynamic instability despite large doses of noradrenaline (2.5 μg/kg/min).

OUTCOME AND FOLLOW-UP
Twenty-two hours after admission, the patient died. Two days later, cultures from peripheral blood and urine specimens revealed *K. pneumoniae* with a positive string test, but antimicrobial susceptibility testing was not carried out.

DISCUSSION
The first case series of IKLAS was described in Taiwan in 1986[4] and it subsequently emerged as a global infectious disease although the majority of cases were found in southeast Asia. Our patient had a rare clinical condition with a poor prognosis and had distinctive clinical features such as ruptured emphysematous liver abscesses with concomitant pneumoperitoneum, emphysematous prostate and...
left seminal vesicle abscesses and emphysematous cystitis. The patient was in a critical condition complicated by MODS (kidney, liver, circulation, respiratory, coagulation) and rapidly deteriorated following admission. The fatal infection was caused by a strain of hypervirulent \textit{K. pneumoniae} identified by a positive string test, which was more virulent than classical \textit{K. pneumoniae} and capable of causing multiple sites of infection due to hematogenous spread\cite{3}.

The etiology of IKLAS is unknown. Our patient suffered from chronic diarrhea without abdominal pain and fever which may be noninfectious and functional diarrhea and is not considered the etiologic factor for IKLAS, even though gastrointestinal colonization is a major reservoir for \textit{K. pneumoniae}-induced infections\cite{5}. He had acute calculous cholecystitis with hypotension 2 mo ago and received empirical antibiotics for 10 d without blood and bile cultures and cholecystectomy. Therefore, we speculated that the liver abscesses were attributable to the cholecystitis with inadequately management that led bacteria to invade the liver parenchyma via the gallbladder bed. In addition, several studies have shown that DM is a significant risk factor for IKLAS\cite{6} and poor glycemic control tends to increase the rate of disseminated infection\cite{7}. Our patient had DM for 30 years and his HbA1c was 8.4\% on admission, the immunosuppression related to DM may predispose patients to the development of IKLAS.
Emphysematous liver abscess is a rare but life-threatening infection which is characterized by hepatic parenchymal emphysematous change. In rare circumstances, emphysematous liver abscesses are prone to spontaneous rupture resulting in secondary peritonitis and intra-abdominal sepsis which can further increase mortality rate[8]. Our patient presented with pneumoperitoneum secondary to spontaneous rupture of emphysematous liver abscesses, with no evidence of hollow viscus perforation. Multiple emphysematous liver abscesses that spread throughout the liver resulted in severely destructive hepatic tissue, and extensive gas formation in the abscess was vulnerable to spontaneous rupture as gas increases the tension within the abscess cavity. Gas in the abscess is believed to be due to the fermentation of glucose into carbon dioxide by K. pneumoniae under anaerobic conditions[9-10]. In patients with numerous abscesses, it is difficult to locate and drain all the lesions via percutaneous, laparoscopic or surgical intervention, thus the mortality rate is reported to be extremely high at 27%-30%[9]. Control of the infectious source is very important, failure to timely surgery or percutaneous drainage is our limitation and the lessons should be learned.

The multifocal emphysematous infections in our patient consisting of liver abscesses, cystitis, prostate and seminal vesicle abscesses are extremely rare. Emphysematous cystitis is characterized by the presence of gas in and around the bladder wall and can be treated successfully with bladder drainage and antibiotics[11]. Emphysematous prostate abscess is not often diagnosed at an early stage due to non-specific symptoms and may be confirmed by CT which shows gas and abscess accumulation in the prostate[12]. Surgical drainage of a prostate abscess can be performed by the transrectal, transperineal or transurethral approach[13]. It is recommended in critically ill patients, such as our case, that CT-guided transperineal drainage of an emphysematous prostate abscess should be performed[14].

K. pneumoniae is the common pathogen associated with emphysematous infections. Among the members of the K. pneumoniae complex which consists of seven K. pneumoniae-related species, K. variicola is frequently misidentified as K. pneumoniae by routine clinical microbiology diagnostics in most modern laboratories[15]. More recently, K. variicola is recognized as a cause of emphysematous infections[16] with a higher mortality rate when compared to K. pneumoniae[17]. Thus, clinicians should be aware of the potential of K. variicola involvement as emphysematous infections and identify K. variicola among K. pneumoniae infections based on mass spectrometry and genome sequencing[18-19].

CONCLUSION

IKLAS is a rare but severe infection which can be lethal if the diagnosis is delayed and can progress to septic shock and MODS. Spontaneous pneumoperitoneum secondary to ruptured emphysematous liver abscesses can induce intra-abdominal sepsis that further increases the mortality rate. Early diagnosis followed by efficient antibiotic therapy and surgical management are essential for these life-threatening infections.

FOOTNOTES

Author contributions: Zhang JQ and He CC designed the report; Zhang JQ wrote the manuscript; Liu R and Wang ZX collected the patient’s clinical data; Yuan B, Qi YJ, and He XN were the attending doctors and performed clinical treatment; Li YM revised the paper.

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REFERENCES


Takotsubo cardiomyopathy misdiagnosed as acute myocardial infarction under the Chest Pain Center model: A case report

Li-Ping Meng, Peng Zhang

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Abstract

BACKGROUND
With the spread and establishment of the Chest Pain Center in China, adhering to the idea that “time is myocardial cell and time is life”, many hospitals have set up a standardized process that ensures that patients with acute myocardial infarction (AMI) who meet emergency percutaneous coronary intervention (PCI) guidelines are sent directly to the DSA room by the prehospital emergency doctor, saving the time spent on queuing, registration, payment, re-examination by the emergency doctor, and obtaining consent for surgery after arriving at the hospital. Takotsubo cardiomyopathy is an acute disease that is triggered by intense emotional or physical stress and must be promptly differentiated from AMI for its appropriate management.

CASE SUMMARY
A 52-year-old female patient was taken directly to the catheterization room to perform PCI due to 4 h of continuous thoracalgia and elevation of the ST segment in the V3–V5 lead, without being transferred to the emergency department according to the Chest Pain Center model. Loading doses of aspirin, clopidogrel and statins were administered and informed consent for PCI was signed in the ambulance. On first look, the patient looked nervous in the DSA room. Coronary angiography showed no obvious stenosis. Left ventricular angiography showed that the contraction of the left ventricular apex was weakened, and the systolic period was ballooning out, showing a typical “octopus trap” change. The patient was diagnosed with Takotsubo cardiomyopathy. Five days later, the patient had no symptoms of thoracalgia, and the serological indicators returned to normal. She was discharged with a prescription of medication.

CONCLUSION
Under the Chest Pain Center model for the treatment of patients with chest pain showing ST segment elevation, despite the urgency of time, Takotsubo cardiomyo-
opothy must be promptly differentiated from AMI for its appropriate management.

**Key Words:** Chest pain center; Takotsubo cardiomyopathy; Acute myocardial infarction; Percutaneous coronary intervention; Case report

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**Core tip:** Under the Chest Pain Center model for the treatment of patients with chest pain with ST segment elevation, despite the urgency of time, Takotsubo cardiomyopathy must be promptly differentiated from myocardial infarction for its appropriate management.

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**INTRODUCTION**

With the spread and establishment of the Chest Pain Center in China, adhering to the idea that “time is myocardial cells and time is life”, many hospital have set up a standardized process that ensures that acute myocardial infarction (AMI) patients who meet emergency percutaneous coronary intervention (PCI) guidelines are sent directly to the DSA room by the prehospital emergency doctor, saving the time spent on queuing, registration, payment, re-examination by the emergency doctor, and obtaining consent for surgery after arriving at the hospital. In the emergency ambulance, if the diagnosis of AMI is clear, the prehospital emergency doctor informs the Chest Pain Center to prepare the DSA room, and loading doses of aspirin, clopidogrel and statins are administered to the patient. Meanwhile, informed consent for PCI surgery is acquired before arriving at the hospital.

As before, when the patient arrives at the emergency department and is diagnosed with AMI, the cardiologist is invited for consultation. Whether to start the emergency PCI process is decided by the cardiologist according the medical history, patient symptoms, electrocardiogram (ECG), and other laboratory tests; most patients who are taken to the DSA room are patients with AMI. According to the “bypass emergency department” model, which was set up by the Chest Pain Center to save time for patients with AMI, the decision of whether to start the emergency PCI process is made by the prehospital emergency doctor who is not a cardiologist. Sometimes, some diseases similar to AMI are not identified accurately. We have seen some patients during emergency coronary angiography with typical thoracalgia symptoms and ST segment elevation in an ECG, but with no obvious abnormalities. Coronary spasm, thrombotic autolysis, myocarditis, pheochromocytoma, aortic dissection, and other diseases need to be routinely identified[1]. In this case, we report a patient with Takotsubo cardiomyopathy who was misdiagnosed with AMI.

**CASE PRESENTATION**

**Chief complaints**

A 52-year-old female patient was taken directly to the catheterization room to undergo PCI due to 4 h of continuous thoracalgia”.

**History of present illness**

Four hours before admission, the patient experienced sudden right thoracalgia, which could be felt on the back of the sternum and under the xiphoid process. It presented as a dull swelling pain, without shortness of breath or palpitations.

**History of past illness**

The patient had no documented medical history.

**Personal and family history**

The patient had no documented personal or family history.
Physical examination
The patient looked nervous and no obvious abnormality was found in the patient’s physical examination.

Laboratory examinations
A prehospital ECG showed an upslope elevation of 0.05–0.15 mV in the ST segment of the V3–V5 lead with a towering and upright T wave (Figure 1).

Imaging examinations
Coronary angiography was performed directly after admission, and no obvious stenosis was observed. Left ventricular angiography showed that the contraction of the left ventricular apex was weakened, and the systolic period was ballooning out, showing a typical “octopus trap” change (Figure 2).

FINAL DIAGNOSIS
A final diagnosis of Takotsubo cardiomyopathy was made.

TREATMENT
According to the ECG combined with the patient’s medical history, the patient was diagnosed with AMI. The Chest Pain Center of our hospital started the detour emergency procedure. In the ambulance, the patient and his family members were informed of the initial diagnosis of AMI, which required PCI, and informed consent for the surgery was signed. Loading doses of aspirin, clopidogrel and statins were administered simultaneously. The patient was taken directly to the DSA room without a visit to the emergency department for further medical examination.

Coronary angiography was performed directly after admission, and no obvious stenosis was observed. Intraoperative troponin was reported at 0.38 mg/mL. During coronary angiography, abnormal heartbeat was noted and the patient was asked for her medical history during the operation. The patient reported that her husband had died unexpectedly 2 d earlier; thus, a broken heart syndrome (Takotsubo cardiomyopathy) was suspected. Left ventricular angiography showed that the contraction of the left ventricular apex was weakened, and the systolic period was ballooning out, showing a typical “octopus trap” change (Figure 2). The results of portable intraoperative ultrasound showed that the myocardial activity in the left ventricular wall was not satisfactory, and there was a small amount of regurgitation in the mitral, tricuspid and aortic valves. No other treatment was administered in the catheter room, and the patient was admitted with the diagnosis of Takotsubo cardiomyopathy.

After admission, the symptoms of thoracalgia were alleviated, and the patient was put under ECG monitoring and treated with aspirin, clopidogrel (antiplatelet medication), metoprolol to reduce sympathetic tension, isosorbide mononitrate to dilate blood vessels, and candesartan to improve ventricular remodeling. On the day of admission, the patient was administered 25.78 ng/mL troponin, 103.9 U/L creatine kinase isoenzyme, 339.9 U/L lactate dehydrogenase, and 109.2 pg/mL B-type natriuretic peptide. Cardiac ultrasound showed uncoordinated left ventricular wall movement, decreased diastolic function, and decreased ST segment in the V3–V5 lead of the ECG. During the treatment period, the myocardial enzyme spectrum and troponin continued to decline in the patient.

OUTCOME AND FOLLOW-UP
Five days later, the patient had no symptoms of thoracalgia, and the serological indicators returned to normal. She was discharged with a prescription of medication.

DISCUSSION
Takotsubo cardiomyopathy, also known as broken heart syndrome or acute stress cardiomyopathy, was first described and proposed by Japanese scholar Hikaru Sato and his colleagues in 1990. Eighty percent of cases occur in middle-aged and postmenopausal women and are often induced by sudden mental stimulation or physical stress. Patients have thoracalgia similar to that seen in MI, and ECGs show ST segment elevation, T-wave inversion, and release of a spectrum of myocardial enzymes. Since the central chamber on a ventriculogram is similar in shape to a Japanese octopus trap (Figure 2), this is also referred to as octopus trap cardiomyopathy. The Mayo Clinic in 2007 defined the disease as having the following symptoms: (1) Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid
Meng LP et al. Takotsubo cardiomyopathy misdiagnosed as AMI

Figure 1 Prehospital electrocardiogram showing an upslope elevation of 0.05–0.15 mV in the ST segment of the V3–V5 lead with a towering and upright T wave.

Figure 2 Left ventricular angiography showing weakened contractions of the left ventricular apex. The systolic apex is bulbous, showing typical "octopus-trap"-like changes.

segments with or without apical involvement with regional wall motion abnormalities extending beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present; (2) Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) New electrocardiographic abnormalities (either ST segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and (4) Absence of pheochromocytoma myocarditis[5]. Different from AMI, in which the blocked blood vessels need to be reopened as soon as possible, the primary treatment for Takotsubo cardiomyopathy is to remove the factor causing psychological stress and regulate the mental state of the patient and relax their mood. The intense preoperative conversation regarding PCI and the urgent operation process for AMI according to the Chest Pain Center model can aggravate a patient’s psychological condition, increasing the release of cardiac neuronal and systemic catecholamines, finally leading to aggravation of the progression of Takotsubo cardiomyopathy[6].

Therefore, the differential diagnosis of AMI and Takotsubo cardiomyopathy is particularly important for the prehospital emergency doctor.

Sent directly to the DSA room from the ambulance, the patient did not undergo an ECG; therefore, incongruity of left ventricular wall movement was difficult to detect. As she was also not asked about her medical history in detail, the cardiologist was unaware that she had experienced recent psychological stress. The emergency coronary angiography showed no obvious abnormality, and the surgeon first considered a diagnosis of thrombus autolysis, but noticed an abnormal heartbeat during the operation. Combined with the fact that the patient was a middle-aged woman, Takotsubo cardiomyopathy was suspected. After asking the patient about her medical history during the operation, the surgeon learned that the patient had suffered a major psychological blow due to the unexpected death of her husband 2 d earlier. The patient underwent left ventricular angiography, in which the surgeon found that the contraction of the left ventricular apex was weakened and the systolic period was
bulbous, showing typical octopus trap changes (Figure 2). The results of the portable intraoperative ultrasound showed that the myocardial activity of the left ventricular wall was uncoordinated. The patient’s history and the above examination results met the diagnostic criteria for Takotsubo cardiomyopathy proposed by the Mayo Clinic.

With the establishment of the Chest Pain Center and improvement of the detour emergency procedures for patients with acute coronary syndrome, we have seen many patients during emergency coronary angiography with typical thoracalgia symptoms and ST segment elevation in ECGs, but with no obvious abnormalities. Coronary spasm, thrombotic autolysis, myocarditis, pheochromocytoma, aortic dissection, and other diseases have been routinely identified[1]. In this case, cardiac imaging abnormalities were observed intraoperatively, and left ventricular angiography was performed to confirm the diagnosis. Patients who detour the emergency department according to the Chest Pain Center procedures do not undergo complete preoperative preparation and do not receive routine evaluation tests such as chest X-rays and echocardiograms. Consent for PCI was obtained from the patient and her family members in the ambulance in transit. The surgeon was unaware of the patient’s history of acute psychological stress and did not consider a diagnosis of Takotsubo cardiomyopathy. Dana et al looked at cases over the last decade and found that Takotsubo cardiomyopathy accounted for about 7% of patients initially diagnosed with MI. The number of patients with Takotsubo cardiomyopathy was far less in our previous clinical work and has been reported to increase in recent years as more cardiologists recognize the condition[7-9]. For patients with normal emergency coronary angiography, this disease should be considered in the routine differential diagnosis. The accuracy of diagnosis can be improved by asking about the medical history prior to operation and performing portable cardiac ultrasound on the surgical platform.

CONCLUSION

Under the Chest Pain Center model for treatment of patients with chest pain showing ST segment elevation, despite the urgency of time, Takotsubo cardiomyopathy must be promptly differentiated from AMI for its appropriate management.

FOOTNOTES

Author contributions: Meng LP and Zhang P contributed equally to this work; Meng LP and Zhang P performed the surgery; Meng LP and Zhang P wrote the paper.

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Cystic teratoma of the parotid gland: A case report

Hong-Sheng Liu, Qiao-Ying Zhang, Jia-Feng Duan, Gang Li, Jia Zhang, Peng-Feng Sun

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Abstract

BACKGROUND
Teratoma is a common tumor, but rarely occurs in the parotid region. Only nine cases have been reported in the current literature. Although it is generally detected in infancy or childhood, it is commonly asymptomatic. Computed tomography (CT) and magnetic resonance imaging (MRI) have important roles in the diagnosis of teratoma.

CASE SUMMARY
A 36-year-old man developed a lump located below the left auricular lobule 3 years ago. Physical examination revealed a nearly-circular tumor in the left parotid gland region with a defined border, firm texture, and significant movement. Calcification, fat, keratinized substances, and typical fat-liquid levels was observed on CT and MRI. A diagnosis of cystic teratoma of the parotid gland was established preoperatively and confirmed by postoperative pathology. Following surgery, the patient developed temporary facial paralysis. There was no recurrence of teratoma during the 15-mo follow-up period.

CONCLUSION
When an asymptomatic mass in the parotid region is identified, parotid gland teratoma should be included in the differential diagnosis. Imaging examinations are helpful in the diagnosis.

Key Words: Teratoma; Parotid gland cyst; Literature review; Computed tomography; Magnetic resonance imaging; Case report
Core Tip: We report an unusual case of teratoma in the parotid gland and review the related literature. The clinical characteristics and imaging features are described. Sufficient knowledge on teratoma, especially the computed tomography and magnetic resonance imaging characteristics, is essential for correct diagnosis and treatment.

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INTRODUCTION
Teratoma is a kind of tumor that develops from germ cells and is most usually found in the coccyx, ovaries, and testicles. Teratoma of the parotid gland, on the other hand, is uncommon. Shadid et al[1] reported the first incidence of teratoma in the parotid gland in 1975. Most parotid gland teratomas develop slowly and have clinical characteristics comparable to other benign parotid gland tumors. We report an unusual case of a giant cystic teratoma, which was located in the deep lobe of the left parotid gland extending into the parapharyngeal space. The diagnosis was made preoperatively by computed tomography (CT) and magnetic resonance imaging (MRI) and was further confirmed by postoperative pathology. The clinical and imaging findings are described. In order to further understand teratoma of the parotid gland, we also review the current literature, hoping to provide a basis for preoperative imaging diagnosis and differential diagnosis, and provide a reliable reference for clinical treatment planning.

CASE PRESENTATION

Chief complaints
A 36-year-old man developed a lump that was accidentally found below the left auricular lobule 3 years ago.

History of present illness
There was no sign of redness, swelling, suppuration, pain, or rupture. The patient had no fever or weight loss during this period. Ultrasonography suggested a cystic lesion of the parotid gland, while CT examination indicated a lipoma at a local hospital. The patient refused tumor excision recommended by the local hospital as the growth was not obvious. However, the lump had grown progressively over the last 6 mo and he occasionally experienced facial discomfort.

History of past illness
The patient denied other medical history.

Personal and family history
The patient denied any history of personal or familial diseases.

Physical examination
A nearly-circular tumor with a clear boundary, hard texture, and high mobility was observed in the left parotid gland area. The temperature and color of the surface skin were normal. Facial nerve function was not weakened. No enlarged cervical lymph nodes were found.

Laboratory examinations
No other abnormalities were found on laboratory examinations.

Imaging examinations
A tumor measuring approximately 3.0 cm x 2.8 cm x 2.9 cm was observed in the deep lobe of the left parotid gland on CT. The tumor was well-bounded and cystic. It comprised variable densities of substances, including a substantial amount of fat and a tiny amount of soft tissue-like parts that were
perhaps keratinized. The medial part of the cyst wall was eggshell-like and extended into the parapharyngeal space (Figure 1). The mass on plain and enhanced MRI appeared as two ‘gourd’-like independent lesions, showing short T1 and long T2 signals, combined with medium T1 and T2 signals and line-like short T2 separation. In the fat saturation sequence, the mass had a complete capsule and a low signal. This was accompanied by lipid levels, which were not significantly enhanced (Figure 2A-C).

**FINAL DIAGNOSIS**

The preoperative imaging features suggested a benign lesion, which was further diagnosed as a teratoma of the parotid gland. And it was confirmed by the postoperative pathology.

**TREATMENT**

The patient underwent tumor resection and facial nerve decompression. The tumor was located in the deep lobe of the parotid gland. The cystic wall of the tumor was thick and tough and it was filled with yellow fat-like keratinized substances. As the cyst was very large, some of the contents were extracted. The upper part of the tumor was tightly linked to the cartilage of the external auditory canal. The medial portion of tumor expanded into the deep of styloid process and the lateral skull base. To protect the facial nerve from pressure caused by the tumor, the trunk of the facial nerve was discovered at the root of the mastoid process.

The tumor was completely removed after separation from the external auditory canal, facial nerve, and adjunct tissues. Neither the external auditory canal nor the facial nerve trunk was damaged. The tumor was sent for pathological examination. In general, the tumor was comprised of sac liquid, and the thickness of the cystic wall was approximately 0.1 mm. The cyst was bordered with stratified squamous epithelium, superficial keratosis, and sebaceous gland cells under the microscope. The fibrous cyst wall contained sebaceous gland cells, cartilage, and adipose tissue. A small amount of keratinous material was found in the cyst cavity. There was no cellular atypia seen, and the surrounding parotid tissues were normal.

**OUTCOME AND FOLLOW-UP**

The ultimate diagnosis was a mature parotid cystic teratoma (Figure 3A and B). The patient complained of moderate facial paralysis postoperatively which recovered well within 4 mo. There was no recurrence of the teratoma during the 15-mo follow-up period.

**DISCUSSION**

Teratoma is a common germ cell tumor that most commonly affects the gonads. It also presents in extragonadal sites, including the sacrococcygeal, retroperitoneal, mediastinal, and pineal regions. In addition, 3% to 5% of teratomas are located in the head and neck[2,3]. However, it rarely occurs in the parotid gland. By reviewing the relevant literature, only nine individuals with parotid gland teratoma were reported globally between 1975 and 2019 (Table 1)[1,4-11]. Although we made substantial efforts, we failed to access the detailed information of patients 2 and 6. Finally, only eight cases (including the present case) of teratoma in the parotid gland with complete information were analyzed.

Teratomas occur more frequently in females[12]. Approximately 90% of teratomas of the head and neck develop during children or infancy[13], while few develop in adulthood. Of the eight patients, six were female (75.0%), and two were male (25.0%), with a ratio of 3:1. The mean age was 22.3 years (range, 9-36 years). The patient in this case was a 36-year-old male, the oldest of these individuals with parotid gland teratoma to date. All of the individuals had unilateral lesions, with four (50.0%) on the left and four (50.0%) on the right sides. In this case, the lesion was found in the deep lobe of the parotid gland and extended into the parapharyngeal region. However, the superficial lobe of the parotid gland was involved in most cases and extended into the deep lobe in only one case. The maximum diameter of the lesions ranged from 1.0 cm to 3.2 cm. Onset of the lesion ranged from 2 wk to 4 years, with an average of 11 mo. All patients visited the hospital with a painless mass and did not have symptoms such as restricted mouth opening, hearing impairment, or facial nerve paralysis.

Teratomas have the potential to differentiate into somatic cells. According to Batsakis *et al*[14], most teratomas involve ectoderm, mesoderm, and endoderm components and may differentiate into skin, nerve, bone, and fat tissues. In addition, Teratomas are also either cystic (containing fluids, sebum debris, hair, and fat) or solid (including more complicated tissues). They consist of mature and
Table 1 Information of patients with teratoma in the parotid gland

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Gender</th>
<th>Age (year)</th>
<th>Side/site</th>
<th>Tumor Preoperative imaging finding</th>
<th>Operation</th>
<th>Postoperative complication</th>
<th>Follow-up/recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shadid EA et al[1], 1975</td>
<td>Female</td>
<td>24</td>
<td>Right, superficial lobe and involving the deep lobe</td>
<td>1.5 Cystic</td>
<td>Tumor resection, superficial lobectomy</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ayudhya NS et al[4], 1991</td>
<td>Female</td>
<td>35</td>
<td>Left</td>
<td>NA NA</td>
<td>NA NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pirodda A et al[3], 2001</td>
<td>Female</td>
<td>18</td>
<td>Left, posteroinferior of the superficial lobe</td>
<td>1 Cystic</td>
<td>Parotidectomy</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Wang G D et al[6], 2003</td>
<td>Female</td>
<td>21</td>
<td>Right, superficial lobe</td>
<td>3.0 × 2.0 NA</td>
<td>Tumor resection</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Yang D R et al[7], 2004</td>
<td>Female</td>
<td>26</td>
<td>Right,</td>
<td>2.0 × 1.5 Cystic and fat</td>
<td>Tumor resection, parotidectomy</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Superficial lobe, recurrent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oudidi A et al[8], 2007</td>
<td>NA NA</td>
<td>NA NA</td>
<td>NA NA</td>
<td>NA NA</td>
<td>NA NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ohta M et al[9], 2009</td>
<td>Female</td>
<td>17</td>
<td>Left, superficial lobe</td>
<td>3 Cystic and fat</td>
<td>Parotidectomy</td>
<td>NA</td>
<td>6 mo, none</td>
</tr>
<tr>
<td>Lenan SHAO et al[10], 2009</td>
<td>Male</td>
<td>28</td>
<td>Right, anterior of the superficial lobe</td>
<td>2 Cystic</td>
<td>Tumor resection, parotidectomy</td>
<td>None</td>
<td>2 years, none</td>
</tr>
<tr>
<td>Yin RJ et al[11], 2017</td>
<td>Female</td>
<td>9</td>
<td>Left, inferior of the superficial lobe</td>
<td>3.0 × 2.4 × 3.2 Cystic</td>
<td>Parotidectomy</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>This report</td>
<td>Male</td>
<td>36</td>
<td>Left, deep lobe, extending into the parapharyngeal space</td>
<td>3.0 × 2.8 × 2.9 Cystic, fat and calcification</td>
<td>Tumor resection, partial parotidectomy</td>
<td>Moderate facial paralysis, recovered within 4 mo</td>
<td>15 mo</td>
</tr>
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<td></td>
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<td>None</td>
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</tr>
</tbody>
</table>

Figure 1 Axial-view contrast-enhanced computed tomography image. The mass was located in the deep lobe of the left parotid gland. The medial part extended to the parapharyngeal space. Eggshell-like calcification was observed in the cyst wall. The cyst components were in different density, including a large amount of fat and a small number of keratinized substances.

Immature components or both. This helps differentiate teratomas from epidermoid cysts and dermoid cysts. The majority of benign teratomas are cystic and are often referred to as mature cystic teratomas. Ohta et al[9] reported that a mature cystic teratoma might be identified by the presence of skin appendages and cartilage tissues in the cyst wall. In this case, the cyst wall featured a stratified squamous epithelial lining, sebaceous gland cells, hyaline cartilage, and well-differentiated fatty tissues, indicating that it was a mature cystic teratoma. The clinical manifestations of teratoma are usually not typical and the diagnosis mainly depends on imaging examinations, including ultrasonography, CT,
Figure 2 Magnetic resonance imaging images. A: T1WI axial view; B: Coronal view of fat-saturated sequence in T2WI; C: T1WI enhancement. The lesion had a complete capsule and presented as short T1 and long T2 signals, combined with medium T1 and T2 signals and line-like short T2 separation. It had a complete capsule showing low signal in the fat saturation sequence. It was accompanied by fat-liquid level, which was not significantly enhanced on enhanced magnetic resonance imaging.

Figure 3 Histopathological analysis of the teratoma. A and B: The cyst wall was lined with a stratified squamous epithelium. Hyaline cartilage, sebaceous glands, and fat tissue were seen in the fibrous capsule wall (HE × 50).

and MRI. Ultrasonography commonly shows heterogeneous hyperechoic signals containing multiple components and with an uneven echo. However, it has limitations regarding teratomas located deep in the tissues. CT and MRI are essential for preoperative diagnosis. On CT, calcification and fat elements are visualized in mature teratomas and the appearance of hypoattenuating fat within the cyst and calcifications in the cyst wall are strongly predictive of teratoma [15]. In addition, the presence of teeth, tufts of hair, and a fat-fluid level is also helpful in the diagnosis of teratoma. MRI allows better observation of soft tissues and is specific for fat signals. As fat contains more hydrogen protons, it shows a high signal on T1WI and T2WI and a low signal in the MRI sequence of fat suppression [16]. This helps to enhance tissue contrast and decrease artifacts, which is important for teratoma detection. The use of CT and MRI can offer a qualitative diagnosis as well as a good view of the lesion’s location and scope, as well as its connection to nearby tissues. Calcification, fat, keratinized substances, and the typical fat-liquid levels were observed on CT and MRI in the present study. The lesion looked like a gourd on CT and MRI because it protruded into the parapharyngeal space. Lipoma, dermoid cyst, epidermoid cyst, branchial cleft cyst, vascular tumor, and pleomorphic adenoma must all be separated from teratoma in the parotid gland with atypical imaging features.

Similar to other benign tumors in the parotid gland, surgery is preferred for parotid teratomas. Surgery usually involves partial parotidectomy or total parotidectomy with facial nerve preservation. The extent of parotid resection depends on the location and size of the lesion [10,17]. Studies on postoperative complications are rare, and there was no mention of postoperative complications among the patients observed in previous studies. In the present study, the superficial lobe of the parotid gland was not involved and it was retained during surgery. The patient suffered from temporary moderate facial paralysis (he was not able to completely close his left eyelid) after decompression of the facial nerve. This recovered well postoperatively within 4 mo. Teratoma recurrence in the parotid gland is
exceedingly rare. The teratoma recurred in situ in one case, according to the existing literature[7]. Incomplete resection of the tumor might lead to recurrence, which should be avoided. Our patient showed no sign of recurrence during the 15-mo follow-up period and is still being followed.

CONCLUSION

In summary, teratoma located in the parotid gland is extremely rare. The differential diagnosis of fat in the parotid gland tumor should prompt consideration of the possibility of teratoma. The presence of calcification, fat, and a fat-liquid level on preoperative CT and MRI scans may aid in the diagnosis and localization of a teratoma in the parotid gland. However, histopathological examination is required to confirm the final diagnosis. Surgical removal of a teratoma of the parotid gland is the recommended and successful treatment, and facial nerve function should be preserved. Patients with a parotid teratoma have a fair prognosis, but they should be monitored closely.

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FOOTNOTES

Author contributions: Liu HS and Zhang QY carried out the study, participated in collecting the data, and drafted the manuscript; Zhang J and Sun PF performed the data collection and participated in study design; Li G and Duan JF participated in data interpretation and manuscript revision; all authors have read and approved the final manuscript.

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CASE REPORT

Silver dressing in the management of an infant's urachal anomaly infected with methicillin-resistant *Staphylococcus aureus*: A case report

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Abstract

BACKGROUND
Symptomatic urachal anomalies are rare disorders. The management of urachal remnants has historically been surgical excision because of the connection between urachal remnants and risk of malignancy development later in life. However, recent literature suggests that urachal anomalies that do not extend to the bladder can be treated with conservative management. In this case, we report a newborn with an infected urachal remnant who was treated with a combination of antibiotics and a silver-based dressing and finally recovered well.

CASE SUMMARY
Female baby A, weighing 2.88 kg at 38\textsuperscript{w} wk of gestational age, was referred to the hospital because of a red, swollen umbilicus approximately 2 cm × 2 cm in size with yellow purulent exudate. Through physical and ultrasound examination, the baby was finally diagnosed with a urachal anomaly. We first used oxacillin to prevent infection for 3 d. On the 4\textsuperscript{th} day, microbiology testing of the umbilical exudate revealed the presence of methicillin-resistant *Staphylococcus aureus* (MRSA). We changed the treatment with oxacillin to vancomycin for systemic infection and treated the umbilical inflammation with a silver sulfate dressing. After 5 d, the symptoms of the umbilicus disappeared, and we discontinued silver dressing application. On the 12\textsuperscript{th} day, umbilical exudate testing was negative for MRSA. On the 14\textsuperscript{th} day, the baby's blood testing showed a white blood cell count...
of 14.7 × 10^9/L, neutrophil percentage of 27.8%, and C-reactive protein level of 1.0 mg/L, suggesting that the infection had been controlled. We stopped treatment, and the baby was discharged with no complications. In this case, the infected urachal anomaly was cured with silver dressing and antibiotic application instead of surgical methods, which was a different course from that of some other urachal remnant cases.

CONCLUSION
Anomalies that do not connect with the bladder can be treated with nonoperative management, including application of conservative antibiotics and local intervention with silver-based dressings. Silver sulfate dressings are absolutely safe for neonates with judicious use, and they play an established role in preventing infection without resistance, which is a common problem with other antibiotics and antiseptics.

Key Words: Urachal anomaly; Infection; Neonate, Infant; Silver dressing; Case report

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Core Tip: Immediate surgical excision of urachal remnants has been generally recommended before. However, patients suffer multiple postoperative complications, resulting in re-operation. Recently, accumulating evidence has indicated that a nonoperative approach may be a safe, reasonable alternative to surgical intervention, especially in patients under 6 mo old. Here, we report a case of urachal anomaly with infection that managed with non-surgical therapy, including: Infection control, wound management and nutrition support. After 2 wk, umbilical symptoms fully recovered. Reoccurring symptoms were not found during follow-up.

INTRODUCTION
The urachus is a connection between the fetal bladder and the allantois. With the descent of the bladder toward the pelvis, the urachus is stretched, finally leading to obliteration of its lumen[1]. On rare occasions, the process of obliteration is incomplete, resulting in urachal remnants (URs). There are four types of urachal anomalies: patent urachus, urachal sinus, urachal cyst, and vesicourachal diverticula [2]. According to previous reports, URs occur in 1.6% of children under 15 years old[3], and the incidence of infant urachal anomalies is less than 1/150000[4], which is very rare. Urachal cysts are the most commonly reported anomaly, while sinuses are 2nd in frequency[5]. Ultrasound is often used as the primary imaging diagnostic tool for urachal anomalies[5]. However, there is no consensus or guideline on the management of URs. Many studies have reported that remnants may lead to inflammation, infection, umbilical discharge, and even abdominal pain, pelvic disease or malignancy at later ages if the URs are not removed[2,6,7]. Thus, immediate surgical excision of URs has previously been generally recommended[6,8].

However, surgical excision has been suggested to be perhaps too aggressive because several studies have shown that some children with surgical lesions do not benefit from prophylactic excision. In addition, the risk of urachal cancer is vanishingly remote among those with URs. In contrast, patients suffer multiple postoperative complications, resulting in reoperation[3,9]. Recently, accumulating evidence has indicated that a nonoperative approach may be a safe, reasonable alternative to surgical intervention, especially in patients under 6 mo old[3]. Use of silver dressings for acute and chronic open wounds has been advocated. Most silver dressings are bactericidal and fungicidal and are especially effective against methicillin-resistant Staphylococcus aureus (MRSA). MRSA is one of the most important gram-positive bacteria causing hospital infections, and it is resistant to commonly used antibiotics. Here, we report a case of a urachal anomaly with MRSA infection managed with antibiotics and silver dressings.
CASE PRESENTATION

Chief complaints
The patient was admitted to the hospital with umbilical swelling and exudate beyond 4 d.

History of present illness
Female baby A, weighing 2.88 kg at 38⁺5 wk of gestational age, was referred to the hospital because of a red, swollen umbilicus with yellow purulent exudate, paroxysmal crying and decreased milk intake.

History of past illness
Cefaclor was taken orally 2 d before admission, but the umbilical symptoms did not improve and were accompanied by progressively increased secretions.

Personal and family history
Female baby A was delivered by cesarean section at 38⁺5 wk gestational age to a gravida 1 para 1 mother. Complications during pregnancy and infant Apgar scores were unclear.

Physical examination
Physical examination revealed a manifestation of maturity, sensitive reaction, variegation all over the body, no fever, and umbilical swelling approximately 3 cm × 3.5 cm in size with yellow purulent umbilical urinary discharge (Figure 1). A tract into the umbilicus was observed, approximately 2 cm in length. No urine overflowed, and no stool was discharged from the baby's umbilicus.

Laboratory examinations
On the day of admission, her blood count showed a white blood cells (WBC) count of 18.9 × 10⁹/L, neutrophil percentage of 32.2%, hemoglobin (HGB) level of 116 g/L, platelet count of 445 × 10⁹/L, and C-reactive protein (CRP) level of 22.0 mg/L. Biochemistry showed blood glucose level of 9.0 mmol/L and procalcitonin (PCT) level of 0.17 ng/mL. On the 2nd day after admission, cerebrospinal fluid testing was positive, with a protein count of 776 mg/L, red blood cell count of 110 × 10⁶/L, chloride level of 122 mmol/L, and glucose level of 3.30 mmol/L. On the 3rd day, the WBC count was 16.1 × 10⁹/L, the neutrophil percentage was 29.4%, the HGB level was 114 g/L and the CRP level decreased to 11.2 mg/L. On the 4th day, microbiology of the umbilical exudate revealed the presence of MRSA. On the 6th day, the drug concentration of vancomycin was 10.3 µg/mL. On the 13th d after admission, the blood count showed a WBC count of 14.7 × 10⁹/L, neutrophil percentage of 27.8%, and CRP level of 1.0 mg/L, and baby was finally discharged.

Imaging examinations
On the 2nd day after hospitalization, ultrasonography (US) images showed a fluid-filled uneven hypoechoic structure just below the navel at a distance of 1.5 cm, and a weak point-like echo flow could be seen with no connection to the bladder.

FINAL DIAGNOSIS
The patient was eventually diagnosed with an infected urachal anomaly: Urachal sinus.

TREATMENT
Before US examination, it was unclear whether there was a sinus tract connected to the abdomen. During this period, we kept the umbilicus clean and dry using iodine as a skin disinfectant. After US examination suggested that there was a blind end within the umbilicus and bladder, we provided the following treatment: (1) Infection control: Empirical antibiotics (oxacillin) were administered for 3 d. When the umbilical secretion culture suggested positivity for MRSA, we then implemented contact isolation for this baby and changed the oxacillin to vancomycin as a systemic antibiotic for 2 wk; (2) Wound management: When microbiology of umbilical exudate revealed the presence of MRSA, we managed the umbilical infection with topical silver sulfate dressings. Aseptic operation was strictly obeyed before using silver sulfate dressings. The dressing change process was as follows (Figure 2): First, we rinsed the umbilicus and sinus with a warm 0.9% sodium chloride solution after visible blinding on US was confirmed. A silver dressing was lightly packed into the sinus, and no-sting barrier film was sprinkled to protect the periumbilical skin. Finally, the samples were covered with foam dressings and sterile gauze locally on the red, swollen umbilical area, to absorb exudate. We continued silver dressing application for 5 d and changed the dressing every 2-3 d according to exudate volume.
When signs of umbilical inflammation decreased and symptoms of a red, swollen umbilicus disappeared, we stopped using the silver sulfate dressings; and (3) Nutrition support: An intravenous infusion of 10% glucose was provided along with premium powdered formula. With the above-described treatment, the symptoms of the umbilicus were alleviated after 14 d, and the patient was discharged.
OUTCOME AND FOLLOW-UP

On the 8th day of hospitalization, the infant’s umbilical cord had completely healed without redness, swelling or exudation (Figure 3). On the 9th day, the US image showed no liquid occupancy. On the 14th day after hospitalization, the infection indicators decreased, umbilical symptoms fully dissipated, and the baby was discharged (Figure 4). Reoccuring urachus anomaly symptoms were not found during the 3 m follow-up by US.

DISCUSSION

Asymptomatic URs present in as much as 2% of the general population. Symptomatic URs always manifest as urachal sinus, urachal fistula, urachal cyst or urachal diverticulum, and all of these manifestations can be complicated with infection[10]. Infected URs present with local signs and symptoms such as purulent drainage, warmth, abdominal pain, erythema and other abnormal appearances of the umbilicus[8,11]. The first and most common presentation of infected URs is periumbilical inflammation, which is consistent with our case. Yellow umbilical urinary discharge was also observed in this case, which is also consistent with previous reports. However, we did not find urinary retention or irritative voiding through physical examination, differing from other series. URs have also been reported to present with some rare manifestations, such as bowel and ureteral obstruction[12] and peritonitis[13]. However, we did not find these severe symptoms in this case. Infected URs present with or without laboratory evidence of infectious processes[14]. In our case, a positive wound culture was predictive of the underlying infectious process. Staphylococcus is reported as the predominant skin-related organism, which suggests that the genitourinary tract is neither the source of infection nor likely infected by the kidney or bladder[8].

Urachal diagnostic guidelines are currently lacking. Lurachal disorders are always reliably diagnosed by history taking and US examination, voiding cystourethrogram (VCUG), computed tomography and fistulography[15]. US is recommended as the primary imaging method because of its shorter turnaround time and lack of exposure to radiation and because it is easily accessible[9]. In the detection of urachal anomalies by US, a positive predictive value of 83% and a sensitivity of 79% have been found[5]. Choi et al.[8] reported that US was diagnostic in 100% of urachal cysts. VCUG is an invasive procedure, adding additional cost, which is inconvenient for infants[14]. Fistulography is suggested to distinguish vitelline duct remnants from urachal remnants[8]. In our case, urachal anomaly was confirmed by clinical symptoms and US findings. Umbilical serous drainage and periumbilical erythema were noticed by physical examination. US scanning revealed the presence of a urachal sinus.

In the case of URs, there is debate regarding optimal management. Few reports have provided guidelines for therapeutic approaches in children, but these approaches remain controversial[16]. Surgical intervention has historically been the standard of care for patients with URs. However, side effects such as wound infection and bladder leakage have been found after surgical excision. Dethlefs et al.[3] retrospectively reviewed 103 pediatric patients diagnosed with a UR and found that postoperative complications occurred in 14.7% of patients who underwent UR excision and that 1 patient underwent reoperation because of bladder leakage. Choi et al.[8] reported 1 postoperative wound infection and 1 bladder leakage case among 26 UR cases. In contrast, other nonoperative URs resolved without recurrent symptoms.

UR excision has been advised to preventing the risk of malignant transformation later in life. However, it has been suggested that there is no association between URs in early childhood and later urachal carcinoma[17]. Surgical resection should be restricted to children older than 1 year with multiple clinical episodes[10]. Recently, conservative management has been advocated for children who are diagnosed with URs that are disconnected from the bladder within the 1st year of life[2]. Studies have reported that urachuses often involve spontaneous presentation within the first year of birth along with complete resolution of symptoms after nonoperative management, which differs from the case for adults, who require necessary surgical intervention[10,16,18]. Lipskar et al.[16] reported 7 urachal anomalies treated with nonoperative management. Three infected urachal cysts were initially managed with antibiotics and then percutaneous drainage of abscesses guided by radiology. In a 2014 retrospective study including 27 patients, the authors preferred a conservative strategy, restricting the surgical option for a persistent patent urachus case and two reinfections of unsolved urachal cyst cases[19]. Other studies have also recommended a conservative approach for children under 1 year old, and nonoperative treatment did not adversely affect the overall outcome[6]. In conclusion, the management of URs has shifted toward nonoperative approaches, including antibiotic treatment and radiographic monitoring. However, evidence of nonoperative management is still limited.

Systemically administered antibiotics are used for invasive infection, and topical antibacterials are used for an open surface wound. There are different available dressings impregnated with broad-spectrum antibiotics, such as neomycin, polymyxin and mupirocin. However, these dressings risk allergy and resistance development[20]. Current evidence supports the use of silver dressings to decrease the bacterial load in wounds of adult and pediatric populations. Most silver dressings can be
used in acute and chronic open wounds because they are bactericidal and fungicidal and are especially effective against resistant organisms such as MRSA. In addition, silver exerts an antimicrobial effect in the presence of wound exudate. Previous studies have shown that topical silver may kill MRSA. Case studies\cite{21,22} have demonstrated that silver dressings can be used to manage local MRSA infections in surgical revision wounds. Silver dressings can reduce the need for systemic antibiotics or even clear bacteria successfully without the use of systemic antibiotics in some patients. However, the use of silver-containing products in infants has not been evaluated rigorously. Thus, silver toxicity should be considered\cite{23}.

Few studies have included the use of silver dressings to control local infections of urachal anomalies. Galati \textit{et al}\cite{17} reported only 1 patient that underwent surgical excision among 9 urachal sinus patients after initial management consisting of local intervention with sulfate nitrate and management of local infection. However, silver nitrate was reported to be proinflammatory and to possibly cause staining \cite{24}. In this case, we proposed that infected UR could be managed with antibiotics for general infection and local intervention with silver sulfate dressings for umbilical inflammation, without any complications related to the silver dressings. Through follow-up US scanning after discharge, we found that the child did not experience any other symptoms of urachal anomalies. The urachal tract regressed according to clinical and US monitoring. Thus, we hypothesized that antibiotics along with topical agents may be an alternative therapeutic option for infected URs. Other varieties of silver dressings have also been reported in treating skin breakdown in preterm infants and have achieved a good effect.
According to the manufacturer’s instructions, it is recommended to change dressings as often as required, at least once 1 wk, depending on the clinical status of the wound and exudate volume[27]. Some scholars have suggested that silver dressing use should be limited to no longer than 2 consecutive weeks because of silver toxicity. Principles of wound management in pediatric patients in the UK recommend application of silver dressings for 2-4 wk in infants[23]. In this case, we applied silver dressings for up to 5 d and changed them every 2-3 d, according to umbilical drainage and clinical status. Once umbilical drainage stopped, we discontinued silver dressing application in case of silver toxicity or other potential effects. As a result, the neonate recovered well, without any adverse effects. At 3 m of follow-up, no recurrent symptoms were observed.

CONCLUSION

Urachal anomaly is a rare disorder that has historically required surgical management. In anomalies that do not extend to the bladder, a conservative option may be an alternative. Antibiotic treatment is usually advocated in fighting systemic infection. In some special cases, topical medicines are needed to prevent local inflammation. Among a variety of antimicrobial dressings, silver-based dressings play a major role against microorganisms. Silver sulfate has not been reported to have any related complications. Thus, we concluded that appropriate use of silver sulfate dressings may be safe and successful in managing MRSA-infected URs in neonates. However, there are still some limitations. For example, there is insufficient and inadequate evidence proving the safe duration of silver dressings for the treatment of URs.

FOOTNOTES

Author contributions: Shi ZY contributed to the design, analysis, and write the manuscript; Hou SL analyzed the data and revised the manuscript; Li XW contributed to revise the manuscript; all authors read and approved the final manuscript.

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Informed consent statement: Parents of the patient were informed about the treatment-related risks and solutions. In addition, informed written consent was obtained from the patient's parents for publication of this report and any accompanying images.

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Drain-site hernia after laparoscopic rectal resection: A case report and review of literature

Jin Su, Cheng Deng, Hui-Ming Yin

Abstract

BACKGROUND
Drain-site hernia (DSH) has an extremely low morbidity and has rarely been reported. Small bowel obstruction is a frequent concurrent condition in most cases of DSH, which commonly occurs at the ≥ 10 mm drain-site. Here we report a rare case of DSH at the lateral 5 mm port site one month postoperatively without visceral incarceration. Simultaneously, a brief review of the literature was conducted focusing on the risk factors, diagnosis, and prevention strategies for DSH.

CASE SUMMARY
A 76-year-old male patient was admitted to our institution with intermittent abdominal pain and a local abdominal mass which occurred one month after laparoscopic radical resection of rectal cancer one year ago. A computed tomography scan showed an abdominal wall hernia at the 5 mm former drain-site in the left lower quadrant, and that the content consisted of the large omentum. An elective herniorrhaphy was performed by closing the fascial defect and reinforcing the abdominal wall with a synthetic mesh simultaneously. The postoperative period was uneventful. The patient was discharged seven days after the operation without surgery-related complications at the 1-mo follow-up visit.

CONCLUSION
Emphasis should be placed on DSH despite the decreased use of intra-abdominal...
drainage. It is recommended that placement of a surgical drainage tube at the ≥ 10 mm trocar site should be avoided. Moreover, it is advisable to have a comprehensive understanding of the risk factors for DSH and complete closure of the fascial defect at the drainage site for high-risk patients.

**Key Words:** Drain-site hernia; Abdominal hernia; Laparoscopic surgery; Surgical drainage; Risk factor; Case report

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**Core Tip:** Drain-site hernia (DSH) is rarely reported at the 5 mm trocar site. In most cases, we prefer to place a large drainage tube at the ≥ 10 mm trocar site and directly remove it postoperatively without any measures to manage the fascial defects, and fail to continuously monitor co-existing disorders which may accelerate DSH formation. These situations may result in the development of DSH in some cases. Here, we report a rare case associated with a literature review to briefly summarize the risk factors, diagnosis, and prevention strategies for DSH.

**INTRODUCTION**

Drain-site hernia (DSH) is a special type of abdominal incisional hernia. It is rarely reported and may potentially lead to severe consequences both in laparotomy and laparoscopy, such as visceral incarceration and even strangulation. The prevalence of DSH ranges from 0.1% to 3.4% according to the literature[1]. The most critical risk factor related to DSH is still the trocar size, especially those ≥ 10 mm. However, the development of DSH may also be attributed to the following causes, such as improper placement of the intra-abdominal drainage tube, the unstitched fascial defect following removal of the drainage tube and co-existing disorders that may affect fascia healing or increase intra-abdominal pressure. At the same time, there are still insufficient relevant recommendations for managing surgical drains and DSH prevention strategies. Here, we present a rare case of DSH at the lateral 5 mm trocar site. In addition, a literature review was carried out to briefly identify the risk factors, diagnosis, and prevention strategies for DSH.

**CASE PRESENTATION**

**Chief complaints**

A 76-year-old male patient [body mass index (BMI), 21.5 kg/m$^2$] was admitted to the General Surgery Department of our institution due to local abdominal distension in the left lower flank and intermittent abdominal pain for one year.

**History of present illness**

Before admission, the patient had undergone laparoscopic rectal resection one year ago in our institution. During the operation, five trocars were used in this patient, including a 10 mm trocar inserted at the umbilical site, two 5 mm trocars in the left flank, a 12 mm trocar and a 5 mm trocar in the right flank, respectively. Fascia layers were closed by an absorbable suture at the ≥ 10 mm trocar site. A 20 FR soft rubber tube was inserted in the left lower quadrant stoma port to drain excessive blood and exudates. The drainage tube was removed five days postoperatively following gastrointestinal function recovery, and the drainage liquid was ≤ 20 mL/d. The fascia layer at the drain site was not closed due to a tiny defect. The postoperative period was uneventful and the patient was discharged on the ninth day after the operation. The patient reported no discomfort postoperatively. However, one month later, there was abdominal bulging in the left lower flank in the standing position, which disappeared in the supine position. Little attention was paid to this initially; however, the patient felt a gradual progression of the abdominal bulge, accompanied by occasional dull abdominal pain over time.
**History of past illness**
The patient had a history of chronic bronchitis combined with intermittent cough without regular medical treatment. He also has a history of hypertension, coronary heart disease, and a laparoscopic cholecystectomy. The patient showed well controlled blood pressure without cardiovascular system symptoms. There were no restrictions on his daily activities.

**Personal and family history**
The patient had no remarkable personal and family history.

**Physical examination**
According to the physical examination after admission, the patient was found to have a local palpable mass (3 cm in length) in the left lower flank above the former drain-site and an abdominal wall defect (2 cm in length). Tenderness and rebound tenderness were not observed in the abdomen.

**Laboratory examinations**
Routine serological examinations were performed without obvious abnormalities.

**Imaging examinations**
A preoperative computed tomography scan confirmed the diagnosis and showed an abdominal wall hernia at the drainage site in the left lower quadrant, and the content consisted of the omentum majus (Figure 1). The detected abdominal wall fascial defect was 2 cm in diameter.

**FINAL DIAGNOSIS**
The clinical manifestations and auxiliary examinations carried out in this patient confirmed the diagnosis of left lower abdominal DSH.

**TREATMENT**
An elective herniorrhaphy was performed with intraoperative discovery of partial omentum entrapped in the abdominal wall defect, close to the subcutaneous tissue layer. Ischemic necrosis of the omentum was not found. We released the adhesive omentum and put it back into the abdominal cavity, and adopted the Sublay repair of the hernia. The fascial defect was continuously closed with a slowly-absorbable suture, and a polypropylene mesh prosthetic was applied to strengthen the abdominal wall.

**OUTCOME AND FOLLOW-UP**
The patient recovered well during the postoperative period and was discharged seven days after the operation. Follow-up of the patient one month postoperatively revealed no surgery- or mesh-related complications.

**DISCUSSION**
DSH is a special type of trocar site hernia (TSH). TSH is widely recognized to be divided into three types based on clinical characteristics and onset time[2]. Specifically, the early-onset type appears at a very early stage after surgery, usually presenting as small bowel obstruction. The late-onset type develops several weeks after surgery or even later, with the manifestation of local abdominal bulging without visceral incarceration. While the special type that arises immediately after surgery involves postoperative dehiscence of the whole abdominal wall.

As suggested in a previous retrospective study by Nacef et al[3], the trocar size is the dominant risk factor for TSHs. TSHs usually occur in the umbilical incision position, especially when the trocar size is ≥ 10 mm. It has been reported that over 82% of TSHs occurred at the umbilicus site, with an extremely high rate of 96% when the trocar size was larger than 10 mm[4]. In addition, the prevalence of TSH can be further increased when the fascial defect at the trocar site is not sutured. It is commonly acknowledged that a non-bladed trocar can decrease tissue trauma, resulting in the reduced incidence of TSH [5]. A TSH can also occur at the non-bladed trocar site. As a result, it is highly recommended that the port ≥ 10 mm in size should be sutured regardless of the designed scheme of the trocar[6,7]. Accumulated data has been reported concerning the occurrence of TSH at the 8 mm trocar site with the
application of robotic techniques in abdominal surgery[8]. However, the occurrence of TSH at 5 mm and 3 mm trocar sites is rarely reported, and preoperative weakness or defects in the fascia plane at the trocar site and excessive manipulation at the trocar site can both raise the risk of TSH. In order to prevent TSH, it is practicable to apply early detection and effective intraoperative measures to reinforce the fascia layer[9]. Some additional risk factors related to TSH include advanced age, gender (female), obesity (BMI > 30 kg/m²), diabetes mellitus, enlargement of incision, infection, prolongation of operative time, co-existence of hernia, unstitched fascia planes, insufficient muscle relaxation before trocar removal, etc. However, the most critical factors are still the trocar size, and obesity[10].

Similar to the mechanisms of TSH mentioned above, most DSHs occur at the ≥ 10 mm port site. Manigrasso et al[11] reported a case of DSH at a 10 mm port site in the right lower quadrant before the drainage tube was removed. This was partially attributed to the inappropriate insertion of an intra-abdominal drain to a large port site. Similarly, Gao et al[12] described a DSH case which occurred at the 10 mm port site in the left lower quadrant within a short time after the removal of a drainage tube. The pivotal reasons were obesity of the patient and an unstitched fascial defect. Both cases described above underwent emergency surgery due to small bowel incarceration. However, there are rare reports of DSH at the 5 mm port site. Moreaux et al[13] and James et al[14] reported cases which occurred at the 5 mm port site from several hours to several days after the drainage tube was removed. These cases were largely caused by the suction effect resulting from drain removal and a postoperative complication (e.g., respiratory tract infection), respectively. Furthermore, the majority of DSH cases that occurred several weeks to several months after surgery commonly had concurrent visceral incarceration, such as Richter hernias or appendix trapping to the former drain-site[15,16].

With regard to the case reported herein, the DSH occurred at the 5 mm drain-site in the left lower quadrant, not at the ≥ 10 mm port site and close to the linea alba, and without viscera obstruction. The patient also had no relevant risk factors (e.g., obesity, bladed trocar, prolonged operation time, wound infection, postoperative complications, etc.) mentioned previously. Moreover, no consensus has been reached on whether the fascial defect after drainage tube removal at the 5 mm port site requires suturing[11]. The exact mechanism of DSH in our case is uncertain according to current research.

Indeed, we propose the classification of DSH into three types according to the onset time of hernia and the removal status of the drainage tube. Specifically, the first type occurs several hours to several days after the surgical procedure without drainage tube removal, which is characterized by a visceral hernia to the free space between abdominal wall and drainage tube or visceral incarceration to the side hole of the drainage tube. The contents generally consist of omentum, small bowel, mesentery, and appendix[11,17,18]. The second type occurs immediately or several hours to several days after removal of the drainage tube, with viscera (e.g., small bowel, omentum, appendix, fallopian tube, and gallbladder) incarceration to the residual cavity at the drainage port in most cases[19-23]. The third type can develop several weeks to several months or later after surgery, which features local abdominal distension at the drainage port, with or without visceral incarceration[15,24]. The incidence of the third type has been reported to be almost twice that of the other two types[1].

Moreover, the potential risk of each type of DSH was summarized in our study following in-depth analysis of the current literature. The predominant cause of the first type is a port size larger than the drainage tube, producing additional space between the tube and abdominal wall. Viscera such as small bowel and mesentery may be herniated to the hiatal region with a sudden increase in intra-abdominal pressure when the patient suffers acute pain, cough, nausea, and vomiting[11,18]. Besides, due to the larger quantity or size of the side holes of the tube, a huge-caliber tube may contribute to bowel obstruction. In such circumstances, there may be a higher risk of incarceration or attachment of small bowel and mesentery to the side holes, resulting in bowel canal angulation. In addition, the suction
effect after air decompression without clamping the tube is another vital reason for DSH[17]. The second type occurs partly due to aggressive tube extraction. Severe pain may raise intra-abdominal pressure and squeeze the small bowel to herniate to the remnant cavity at the drainage site. In these cases, high abdominal pressure is an essential cause in the development of DSH [22]. Other risk factors that affect fascia healing, such as malnutrition, obesity, metabolic diseases (e.g., diabetes mellitus), and chemotherapy, may also contribute to DSH [23]. For the third type, the unstitched fascial defect and co-existence of some disorders that may affect the healing of fascial tissue and the gradually increased intra-abdominal pressure may promote the formation of DSH. Therefore, possible reasons for DSH in our patient might be the uncontrolled chronic bronchitis that caused frequent coughing leading to high intra-abdominal pressure, as well as the unstitched fascial defect at the drainage site. As a result, it is recommended that the 5 mm drain-site fascial defect should be sutured under such conditions and the simultaneous management of comorbidities.

The typical manifestations of DSH are abdominal pain, nausea, vomiting, diffuse or local abdominal distension, as well as obstructed passage of stool and flatus. Significantly, an asymptomatic hernia can also occur in a few people without symptoms except an inconspicuous abdominal mass. An emergency ultrasound, abdominal X-ray, gastrointestinal radiography and abdominal CT scan should be scheduled to confirm DSH. Abdominal contrast-enhanced CT scanning is particularly crucial to display the position of the visceral hernia, and the identification of concurrent bowel canal incarceration, strangulation, and necrosis [26].

When DSH is diagnosed, an emergency operation or an elective surgical approach should be performed according to its classification and the presence of concurrent visceral incarceration. The early-onset DSH (including the first and the second types, as mentioned above), with bowel obstruction as the primary manifestation, usually requires immediate exploratory surgery. There is a need to perform fascial defect closure as well as standard bowel resection and anastomosis in the case of visceral necrosis. The late-onset DSH (the third type) is frequently accompanied by an abdominal mass alone, without visceral incarceration. The traditional therapeutic choice is elective herniorrhaphy. At present, this operation is still the cure for DSH. A retrospective study [21] on laparoscopic procedures for children revealed that 5/148 had DSH after the operation, three of which were released by sedation. These cases had the potential danger of viscera strangulation. Accordingly, we advocate emergency procedures once visceral incarceration is confirmed in cases of necrosis. In addition, whether a mesh repair is needed depends on abdominal defect caliber, BMI, and the co-existence of other risk factors leading to DSH [27]. For some complex incision hernias, dual-layer sandwich repair for abdominal reconstruction can efficiently reduce the recurrence rate of hernia [28].

We believe that precautionary measures and strategies are available to prevent and reduce the occurrence of DSH based on the risk factors mentioned above. The first issue is to be more prudent regarding routine abdominal drainage. The purpose of surgical drainage is to decrease liquid (e.g., ascites, blood, inflammatory exudates, etc.) accumulation and remove gastrointestinal juice in the case of anastomotic fistula. Surgical drainage can potentially induce all types of postoperative complications, such as intra-abdominal or wound infection, adhesions, bowel canal erosion, aggravated abdominal pain, respiratory suppression, bleeding, anastomotic ruptures, etc. [29]. Improper placement of drainage, however, can lead to the formation of DSH to some extent. Therefore, it is recommended that the necessity and harm of abdominal drainage in clinical practice should be seriously considered. Nowadays, an increasing number of experts recommend irregular insertion of abdominal drainage tubes with the application of laparoscopic techniques and innovation of surgical procedures, especially in laparoscopic gynecological surgery and laparoscopic cholecystectomy [1,15,17]. Secondyl, it is recommended that there should be reasonable consideration regarding the selection and insertion position of the drainage tube. Insertion of surgical drainage should be avoided at the ≥10 mm trocar site to eliminate the free space between the abdominal wall and the tube. The residual unstitched huge fascial defect after tube removal is prone to causing visceral incarceration [11]. Therefore, it is advisable to insert the tube into the pelvic cavity to keep it away from the small intestine. In addition, a Z-shaped or oblique insertion can avoid a straight tunnel, thus reducing intra-abdominal viscera bulging [15,18,30]. In addition, it is better to use tubes with a smaller caliber, fewer and diminutive side holes if needed. Simultaneously, in order to prevent the suction effect, the drainage tube should remain clamped until the completion of air decompression [17]. Thirdly, a more scientific practice is advisable to remove the drainage tube. Aggressive drain extraction inevitably aggravates wound pain and increases intra-abdominal pressure, as well as the rate of visceral injury and bleeding. Therefore, it is better to remove the drainage tube gradually, rather than aggressively. It is strongly recommended to conduct a clockwise or counterclockwise rotation of the tube until free from the adhesion before removal of the drainage tube. In addition, sedation and angesia should be considered in some cases [21]. Fourthly, fascial defects should be sutured appropriately after removal of the drainage tube, especially defects ≥10 mm in diameter. Fascial defect closure at the 8 mm drain site would also be beneficial to patients. There are various available approaches used for suturing, such as a single intermittent suture, continuous suture, purse-string suture and total layers suture [12,15]. However, no consensus has been reached at present with regard to whether the drainage site of 5 mm in diameter should be closed. The group supporting no-closure assumed that the incidence of hernia at the 5 mm port site was extremely low with no requirement for closure [31].
operative times and excessive manipulation could expand the fascial incisions, which, in turn, increased the occurrence rate of hernia[32]. In our opinion, patients may benefit from fascia closure at the 5 mm drainage site when such patients have one or more risk factor(s) for DSH. Lastly, the overall management of comorbidities is of crucial importance. Hernias may still occur in some cases, even if the fascia at the port site has been sutured. These people, in general, have co-existing disorders that may affect healing of the fascial incision or increase the intra-abdominal pressure, such as chronic obstructive pulmonary diseases, diabetes mellitus, malnutrition, constipation, obesity and benign prostatic hyperplasia[25]. Strategically, multidisciplinary treatment may benefit the formulation of an individualized treatment schedule that is convenient for whole-process supervision of the physical condition of patients. Collectively, a comprehensive and profound understanding of the risk factors for DSH and the application of adequate precautions are thought to decrease the incidence of DSH to a minimum.

CONCLUSION

DSH is rare in the clinical setting. There is a need to pay enough attention to its disastrous complications. Unnecessary placement of a drainage tube should still be eliminated despite the reduced application of intra-abdominal drain placement with the advent of minimally invasive surgery, and an overall understanding of the complications of postoperative drainage. However, drainage is still needed after surgery for patients with infections and those who are prone to fistulas. In such circumstances, it is recommended that inserting a drainage tube at the ≥ 10 mm trocar site should be avoided and advisable, scientific, and practical measures taken to manage intra-abdominal drains. In addition, it is of great significance to have a better understanding of the risk factors for DSH, and complete closure of fascial defects at the drainage site for those high-risk groups, in order to decrease the incidence of DSH.

FOOTNOTES

Author contributions: Deng C acquired and interpreted the clinical data; Su J reviewed the literature and drafted the manuscript; Yin HM made substantial contributions to the conception and design of the work; all authors read and approved the final manuscript.

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Synchronized early gastric cancer occurred in a patient with serrated polyposis syndrome: A case report

Ying-Ze Ning, Guan-Yi Liu, Xiao-Long Rao, Yong-Chen Ma, Long Rong

**Abstract**

**BACKGROUND**

Serrated polyposis syndrome (SPS) is a relatively rare disease that is characterized by multiple serrated lesions/polyps. Very little is known regarding the extra-colonic cancers associated with SPS. The genetic basis of the process remains unknown.

**CASE SUMMARY**

A 67-year-old male patient initially presented with belching and abdominal distension for a year as well as diarrhea for over 2 mo. The patient underwent colonoscopy and was diagnosed with serrated polyposis syndrome. Half a year later, a gastroscopy was performed during the postoperative re-examination to screen for other lesions of the upper gastrointestinal tract. An elevated lesion was detected in the anterior wall of the gastric antrum. Curative en bloc resection of the lesion was achieved via endoscopic submucosal dissection. The pathological result was high-grade dysplasia with focal intramucosal carcinoma. Exome sequencing was performed for the patient and five gastric cancer-associated variants (methylenetetrahydrofolate reductase, metaxin 1, coiled-coil domain containing 6, glutamate ionotropic receptor delta type subunit 1, and aldehyde dehydrogenase 1) were identified.

**CONCLUSION**

This paper reports a case that presented with both SPS and early gastric cancer. Genetic mutations that were potentially responsible for this condition were sought by exome sequencing.

**Key Words:** Serrated polyposis syndrome; Early gastric cancer; Gene mutation; Endoscopy; Exome sequencing; Case report
Core Tip: Serrated polyposis syndrome (SPS) is a relatively rare disease. Very little is known regarding the extracolonic cancers associated with SPS. The genetic basis of the process remains unknown. Here, we report a case that presented with SPS and synchronized early gastric cancer. Genetic mutations that were potentially responsible for this condition were sought by exome sequencing.

INTRODUCTION

Serrated polyposis syndrome (SPS), previously known as hyperplastic polyposis, is a relatively rare disease that is characterized by multiple serrated lesions/polyps (SL/Ps), mainly in the proximal colon [1]. An increasing body of evidence suggests that patients with SPS have an increased risk of colorectal cancer (CRC) but the genetic basis of the process remains unknown [2]. Also, very little is known regarding the extracolonic cancers associated with SPS. To understand the molecular basis of SPS, it is important to identify the corresponding disease-causing genes. Because whole-exome sequencing can almost cover the entirety of protein-coding regions in the genome, which contains approximately 85% of disease-relevant mutations, it can serve as a powerful tool for cost-effective disease mechanistic research [3].

This paper reports a patient with SPS and synchronized early gastric cancer (GC) treated with endoscopic submucosal dissection (ESD), along with some potential causative mutations found in exome sequencing.

CASE PRESENTATION

Chief complaints
A 67-year-old male patient initially presented with belching and abdominal distension for a year as well as diarrhea for over 2 mo.

History of present illness
The patient had no history of present symptoms.

History of past illness
The patient had a history of hypertension that was well controlled with medication.

Personal and family history
No personal or family history of SPS or cancers was reported.

Physical examination
Physical examination was unremarkable.

Laboratory examinations
Since the patient was Helicobacter pylori negative, the diagnosis of H. pylori infection-related GC was excluded.

Imaging examinations
The patient underwent colonoscopy and found multiple flat and sessile polyps located throughout different segments of the colon and ranging from 5 to 20 mm in diameter. More than 10 polyps were removed and pathological examination confirmed most polyps to be sessile serrated lesions (SSLs) and 4 as tubular adenoma, all without severe dysplasia (Figure 1A). The diagnosis of SPS was established. Half a year later, a gastroscopy was performed during the postoperative re-examination to screen for other lesions of the upper gastrointestinal tract. An elevated lesion was detected in the anterior wall of the gastric antrum (Figure 1B).

Methods of genetic analysis
Total genome DNA from peripheral blood was extracted using the cetrimonium bromide/sodium
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Figure 1 Narrow-band imaging magnified observation. A: The first colonoscopy removed over 10 polyps and the diagnosis of serrated polyposis syndrome was established. A flat polyp with a size of 1.0 cm × 0.8 cm was observed in the ascending colon. The surface of the polyp was cloudy and the boundary was not clear. Type II open-shape pit pattern was seen by narrow-band imaging magnified observation after indigo carmine acetic acid staining; B: An elevated lesion was detected in the anterior wall of the gastric antrum at the gastroscopy. Upon white light endoscopy, a type IIc lesion approximately 1.2 cm × 1.0 cm in size could be seen in the anterior wall of the gastric antrum, with a small amount of white fur attached to the surface. Narrow-band imaging magnified observation showed the dividing line and the enlarged and irregular gland. No obvious abnormal blood vessels were found.

dodecyl sulfate method. Gene libraries were constructed and paired-end sequencing was performed using the Illumina® HiSeq platform. Statistics was mapped with a reference genome using Burrows-Wheeler Alignment software (parameters: mem-t4-k32-M) and the duplicates were removed by Picard. Individual single nucleotide polymorphism (SNP) variations were detected using the Genome Analysis Toolkit. Subsequently, annotation of the detected SNPs was performed using SnpEff.

Results of genetic analyses
To explore the molecular characteristics of the patient, sequencing analysis was performed. Exome sequencing identified 3111 nonsynonymous single nucleotide variants in the exon region. These genes were filtered by the mutation data in ClinVar, COSMIC v90 and previous genome-wide association study reports. Five GC-associated variants (methylenetetrahydrofolate reductase [MTHFR], metaxin 1 [MTX1], coiled-coil domain containing 6 [CCDC6], glutamate ionotropic receptor delta type subunit 1 [GRID1], and aldehyde dehydrogenase 1 [ALDH2]) were identified, as shown in Table 1. Additionally, a cross check for genes that has been reported as causative of SPS or relating to the serrated pathway was performed. The BRAF V600E and KRAS G12D mutations, common hotspot mutations in SPS, were not found.

FINAL DIAGNOSIS
The pathological result of the lesion in the gastric antrum was high-grade dysplasia with focal intramucosal carcinoma.
Table 1 Details of five gastric cancer-associated variants

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chr</th>
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<th>SIFT/Polyphen_2/MT</th>
<th>Pathways</th>
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<td>MTX1</td>
<td>1</td>
<td>exon1:c.T187A:p.S63T</td>
<td>-</td>
<td>Metabolism of proteins</td>
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Chr: Chromosome; D: Deleterious; P: Possibly deleterious.

TREATMENT

Curative en bloc resection of the lesion was achieved via endoscopic submucosal dissection (ESD).

OUTCOME AND FOLLOW-UP

The lesion in gastric antrum was considered to be curatively resected. No recurrence was observed on her last esophagogastroduodenoscopy surveillance 1 year after surgery.

DISCUSSION

SL/Ps include hyperplastic polyps, traditional serrated adenoma, and SSLs. SPS was redefined by World Health Organization (WHO) in 2019 and its diagnosis is based on the cumulative number of serrated lesions in a patient who meets one of the two following WHO criteria: ≥ 5 SL/Ps proximal to the rectum, all ≥ 5 mm in size and including ≥ 2 Larger than 10 mm; or > 20 SL/Ps of any size distributed throughout the colon, with ≥ 5 proximal to the rectum. The true prevalence of SPS is likely under-recognized and not diagnosed because of the need to keep track of the cumulative lifetime number of SL/Ps in a patient. To monitor for risk of malignant progression, endoscopic surveillance is recommended for all patients every 1 year to 3 years; however, suitable monitoring schedules remain controversial.

SL/Ps are currently recognized as the precursors of CRC and SPS has been considered a high-risk condition for CRC. However, there are only a few reported cases of SPS patients having extracolonic malignancies and the association between SPS and extracolonic cancer risk in various studies are not consistent. In their American cohort, Jasperson et al. found 12 of 51 SPS patients (24%) had a history of extracolonic tumors, but none were found to have gastric lesions. Hazewinkel et al. reported 9 of 105 SPS patients (8.6%) from five medical centers in Europe, which did not significantly differ from the expected number of the general population, but the cancer-specific risk was not estimated. A Korean study reported the diagnosis of stomach cancer in 2 of 30 SPS patients (6.7%) via esophagogastroduodenoscopy, suggesting that Asian patients with SPS require screening of the upper gastrointestinal tract.

In the present case, the stomach lesion was detected in the postoperative re-examination 6 mo after the diagnosis of SPS. As gastroscopy was not performed when the sessile serrated lesions were removed from the colon, the condition of any GC at that time cannot be confirmed. This emphasizes the importance of upper gastrointestinal tract screening in SPS patients.

To date, some molecular signatures of the serrated pathway of CRC formation have been described, including BRAF and KRAS mutations, microsatellite instability and CpG island methylator phenotype. However, the molecular processes of tumorigenesis are still largely unknown, let alone the molecular characteristics of synchronized cancers. Having sequenced the exosome of the patient’s peripheral blood, five variants (MTHFR, MTX1, CCDC6, GRID1, and ALDH2), which are reportedly related to GC, were identified. MTHFR encodes a key enzyme in the folate metabolism pathway, with MTHFR polymorphisms having a functional impact on metabolism. ALDH2, encoding tissue alcohol metabolizing enzymes, can influence acetaldehyde levels in the stomach, which increase the risk of GC through a variety of mechanisms.
tumor necrosis factor-induced cell death[11]. MTX1 is overexpressed in GC tissue compared with paired normal tissues, and patients with higher MTX1 expression experience a poorer prognosis[12]. CCDC6, which is recognized as the target gene of microRNA-149-5p (miR-149-5p) and miR-19b-3p[13], inhibits cell proliferation and the epithelial-mesenchymal transition and facilitates cell apoptosis[14]. Although the glutamate receptor GRID1 exclusively functions in the central nervous system, recent evidence suggests that GRID1 may also be involved in multiple kinds of malignant processes during the progression of cancer[15]. As the annotation information of SPS-related genes is limited, we could only first identify the mutations that are reportedly closely related to GC. Considering the characteristics of this patient, these five mutations are presumably associated with both GC and SPS. The mechanism by which these genes affect the pathogenesis of GC and SPS remains to be determined.

Here, exome sequencing was performed for a patient with SPS and synchronized early GC. Although a single patient is not sufficient to identify potential genetic characteristics of SPS, the findings still add to the body of knowledge on the molecular mechanism underpinning SPS with synchronized GC. Further validation experiments using resected specimen are necessary to clarify the effect of mutations on GC and SPS.

CONCLUSION
In conclusion, this paper reports a case that presented with both SPS and early GC. Genetic mutations that were potentially responsible for this condition were identified by exome sequencing. Further studies are needed regarding the extracolonic cancer risk of SPS patients.

FOOTNOTES

Author contributions: Ning YZ wrote the manuscript; Liu GY and Rao XL collected the data; Ma YC analyzed the data; Rong L designed the research study; all authors have read and approved the final manuscript.

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Large cystic-solid pulmonary hamartoma: A case report

Xiao-Wan Guo, Xu-Dong Jia, A-Dan Ji, Dan-Qing Zhang, De-Zhao Jia, Qi Zhang, Qiu Shao, Yang Liu

CASE REPORT

Large cystic-solid pulmonary hamartoma: A case report

Xiao-Wan Guo, Xu-Dong Jia, A-Dan Ji, Dan-Qing Zhang, De-Zhao Jia, Qi Zhang, Qiu Shao, Yang Liu

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Abstract

BACKGROUND
It now seems that all pulmonary hamartomas (PHs) are large cystic-solid lesions that are difficult to diagnose. However, few cases of large cystic-solid PHs have been reported. The present case report presents a large cystic-solid PH and provides a literature review of the imaging features, formation mechanism and histopathological basis of PHs.

CASE SUMMARY
A 53-year-old woman with no clinical symptoms underwent a chest computed tomography (CT) examination at our hospital. Nonenhanced CT images revealed a large, flat tumor with multiple air-containing cysts in the left thoracic cavity and a cystic part confined to the medial side of the tumor; the solid part of the tumor showed abundant fat and lamellar soft tissue components. Multiple small blood vessels were detected in the solid part of the tumor on contrast-enhanced CT images. Given the large size of the lesion, the patient elected to undergo surgery. Histological examination revealed PH. A detailed review of the patient’s CT imaging showed that the lesion had a small vascular pedicle to the left lower lobe, which was a clue to its lung tissue histological origin. According to immunohistochemical staining, the confined multiple air-containing cysts were caused by the entrapment of respiratory/alveolar epithelium.

CONCLUSION
This case shows the imaging manifestations of a large PH. Heightened awareness of its formation mechanism and histopathological basis may alert radiologists to...
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consider this diagnosis in their daily workflow.

Key Words: Lung; Lung benign lesion; Hamartoma; Computed tomography; Case report

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Core Tip: We describe a large pulmonary hamartoma (PH) and its preoperative computed tomography (CT) imaging features, including multiple air-containing cysts, a rich blood supply and a vascular pedicle. The CT imaging features, formation mechanism, and histopathological basis of a large PH are summarized in this case report.

INTRODUCTION

Pulmonary hamartoma (PH) has been defined as a mesenchymal tumor consisting of varying combinations of cartilage, fibrous tissue, fat, smooth muscle, and respiratory epithelium derived from entrapped adjacent lung tissue\[1\]. It is the most common benign neoplasm and usually presents as solitary nodules in the lung. However, PH can show unusual characteristics and can be clinically and radiologically challenging to diagnose preoperatively. In addition, PHs larger than 10 cm and containing multiple air-containing cysts are rare. In this case report, we present a rare case of a large PH with multiple air-containing cysts. We aim to increase the awareness of its formation mechanism, histopathological basis, and computed tomography (CT) imaging features through a literature review. This diagnosis should be considered in the daily workflow to improve the accuracy of the preoperative diagnosis of this disease.

CASE PRESENTATION

Chief complaints
A 58-year-old woman who had never undergone a chest CT examination had a CT scan as part of a routine physical examination. Her medical history was negative for any symptoms of discomfort.

History of present illness
The patient’s history was unremarkable.

History of past illness
The patient underwent a hysterectomy for myoma 4 years prior. The patient had hypertension for 10 years, but her blood pressure was stable under drug control.

Personal and family history
No personal and family history.

Physical examination
No abnormal positive indications were found in physical examination.

Laboratory examinations
The blood biochemistry results were normal. Pulmonary function testing, arterial blood gas evaluation and electrocardiogram results were normal.

Imaging examinations
Initial nonenhanced chest CT images revealed a well-defined tumor with multiple air-containing cysts confined to the medial side of the tumor, and the solid part of the tumor showed abundant fat and lamellar soft tissue components. The tumor was well defined except for a locally unclear boundary with the left lower lung lobe (Figure 1A and B). Further contrast-enhanced chest CT examination showed
Figure 1 Computed tomography images of a large cystic-solid pulmonary hamartoma in a 53-year-old woman. A and B: Nonenhanced chest computed tomography (CT) images show a well-defined tumor on the left diaphragm; C and D: Contrast-enhanced chest CT images show the blood supply of the tumor (solid arrow).

multiple small blood vessels in the solid part of the tumor, and several blood supplies to the tumor were detected coming from the left lower lobe (Figure 1C and D).

FINAL DIAGNOSIS
The final diagnosis after histological confirmation was a large PH (Figure 2).

TREATMENT
Single-hole exploratory video-assisted thoracoscopic surgery was performed. There was no adhesion between the tumor and the lung tissue, except for a thin vascular pedicle connecting the tumor to the left lower lobe. The pedicle was dissected, and the tumor was completely removed. Gross examination showed a soft and flat-shaped tumor measuring 14.5 cm × 11.0 cm × 2.5 cm in size (Figure 2A). The multiple cystic components within the tumor were confined to one side, and the diameter of the cysts ranged from 1 cm to 3.5 cm.

OUTCOME AND FOLLOW-UP
Electron microscopy suggested that the well-developed epithelium lacked significant cytological atypia in the cystic part. Other parts had mesenchymal components, including fat, connective tissue and smooth muscle (Figure 2B-E). Immunohistochemical staining of the tumor was consistent with the components of normal lung tissue. Smooth muscle cells were observed in the tumor (SMA +) and were positive for desmin. Ciliated respiratory epithelium that lined clefts tested positive for thyroid transcription factor-1, napsin A and cytokeratin 7, and basal cells located within these epithelia tested positive for S-100, which indicated that these epithelia represented entrapped bronchioles and alveolar walls. Immunostaining with HMB45 was negative. The proliferation index Ki67 was low (< 5%). The patient recovered well after surgery, and no obvious abnormality has been found by chest CT examination at annual follow-ups thus far.
DISCUSSION

PH is the most common benign tumor of the lung. It is relatively easy to make a preoperative diagnosis of PH with typical CT imaging findings, such as a well-defined nodule with a size of less than 2 cm, popcorn-like calcification and a fat density component. Large PHs over 10 cm are unusual, and large cystic-solid PHs are even rarer. The final diagnosis of a large cystic-solid PH depends on postoperative pathology. The most common cause of these cysts is entrapped pulmonary epithelium. Although entrapment of the pulmonary epithelium by PH is well known, in our experience, the CT imaging features of this phenomenon have not received sufficient attention. We decided to review the literature on cystic-solid PHs, analyze their CT imaging features, formation mechanism and histopathological basis, and then discuss the sources of the challenges during preoperative diagnosis.

To our knowledge, only eleven cases of cystic-solid PHs have been reported thus far, of which 6 PHs were larger than 10 cm. The reason for the cyst formation is still unclear. Nevertheless, the literature focusing on this issue is sparse. According to the study of Erber et al[2], the entrapment of respiratory epithelium in primary and metastatic intrapulmonary nonepithelial neoplasms is a frequent morphological pattern but to variable extents. Their study involved 38 patients with pulmonary metastases (81%) and 8 patients with primary pulmonary nonepithelial lesions. There are two types of histological distribution of the entrapped pulmonary epithelium. In type one, the entrapped pulmonary epithelium is distributed mainly in the peripheral portion of the tumor, and in type two, the entrapped pulmonary epithelium is found throughout the tumor, albeit to a varying extent. Although the number of patients...
was limited, we thought this conclusion could be extrapolated to more primary and metastatic intrapulmonary nonepithelial neoplasms in the lungs. Because PH is the most common form of primary pulmonary nonepithelial lesions, the same applies to our case. Different types of histological distributions of entrapped pulmonary epithelium produce different CT images. Type one represents the histopathological basis of the cysts in the present case. The entrapped pulmonary epithelium was located at the margin of the tumor and connected to the adjacent lung tissue by a vascular pedicle. In this type, the cysts are dilated bronchioles lined by clear epithelial cells with adjacent spindle cell stroma. It has been speculated that a check-valve mechanism of the bronchioles of the entrapped pulmonary epithelium causes cysts to form[3]. A thin pedicle comprised of blood vessels and bronchioles between the tumor and the left lower lobe was found in the present case during surgery. The present case is the first large cystic-solid PH in which a vascular bronchial pedicle was found during the operation.

The abovementioned type two histological distribution represents the basis of cysts in cystic-solid PH cases where no clear pedicle between the tumor and the lung tissue is found during surgery. The cysts in such PHs are the result of growth coupled with degenerative changes, which ultimately lead to cleft-like spaces or ultimately expand into cysts[4]. Compared with type one lesions, type two lesions showed a mixed distribution of solid and cystic lesions without obvious boundaries on imaging. Such imaging findings of PH significantly increase the difficulty of preoperative diagnosis, and the final diagnosis depends on pathology and immunohistochemistry.

Notably, varying degrees of fluid are observed in the cysts of cystic-solid PHs. According to a previous study[2], glands in the entrapped pulmonary epithelium frequently show a reactive/regenerative appearance. Furthermore, gland size and type vary greatly from small acinar-type glands or micrscopic spaces lined by flattened epithelial cells and containing mucoid secretion to branching leaflet-like papillary spaces. All of the factors mentioned above result in differences in epithelial secretory function. Therefore, in previous case reports, various degrees of fluid were observed in the cysts of cystic-solid PHs: The cysts may be well inflated[5-9] or partially[10] or even completely filled with fluid[10-12].

In addition, through a literature review, we found that the CT image density of cystic-solid PHs can vary from ground glass density to solid density depending on the proportion of the solid part. In some cases, the proportion of solid components in cystic-solid PHs is very low, and cystic-solid PHs show extreme CT imaging, that is, a ground glass nodule appearance[12]. It is difficult to distinguish cystic-solid PHs from adenocarcinomas, which often present as ground glass nodules, and the final diagnosis depends on postoperative pathology. The other extreme case is that if the cystic-solid PH is dominated by the solid part, the cystic part may be too small to be observed on CT imaging[13].

Previous studies have demonstrated a high frequency of rearrangements involving 6p21 or 12q14-15 in PH[14] and HMGI-C and HMGI(Y) protein expression as a consequence of rearrangements involving 6p21 and 12q15[15]. These findings support the view that mesenchymal components of PHs represent neoplastic mesenchymal proliferation rather than neoplasms. Today, even with advancements in medical therapy, pulmonary resection remains the most important treatment measure for patients with PH[16,17]. However, controversy exists about the indication for surgery. For large cysts dominated by cystic-solid PHs, although malignant transformation of PHs is exceptional, prompt surgical resection is the recommended treatment. The main reasons are as follows. First, larger cystic-solid PHs are often located under the visceral pleura, similar to the present case, and separated from the thoracic cavity by only a thin layer of pleura (Figure 2F), so the cystic part is more vulnerable to rupture and can lead to secondary pneumothorax[3,18]. In addition, Secretions into the cysts of cystic-solid PHs are difficult to expel from the lungs and may lead to secondary infection. The patients involved in the present case and in the large cystic-solid PH cases discussed above had very good prognoses with uneventful outcomes after surgery.

CONCLUSION

Due to its epithelial involvement, clinicians and radiologists should be aware that cystic-solid PH is a diagnostic possibility in adults with large intrathoracic cystic-solid tumors. Cysts in PHs can show different features on CT images depending on the type of histological distribution of the entrapped pulmonary epithelium. If large cysts dominating cystic-solid PHs are treated in a timely manner after discovery, the patient will have a good prognosis.

FOOTNOTES

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COVID-19 pandemic and nurse teaching: Our experience

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Abstract

In this letter to the editor, we would like to show in our hospital how our nurse team manage formation during coronavirus disease 2019 pandemic.

Key Words: COVID-19; Anesthesia; Critical care; Nurses; First wave; Training

Core Tip: Coronavirus disease 2019 pandemic in the begging was a great challenge for healthcare workers as there was few non-standardized information in non-trained staff in undesigned areas for critical care attendance. Thus, formation was essential to spread our increasing knowledge of the virus and increase number of trained staff to deal with these specific patients.

TO THE EDITOR

We read with high interest the article by Wang et al[1] showing a protocol of remote training for nurses dealing with coronavirus disease 2019 (COVID-19) patients in intensive care unit (ICU) which combines traditional teaching and the use of new technologies to improve spread and quality of what is taught. In our ICU, joint work between nurses and anesthetists, was key in achieving results during the first wave.
However, a system such as the one proposed by the authors would be useful in the next waves or future pandemics.

During the first wave of the pandemic, almost all health care systems and centers collapsed from all around the world with serious difficulties in logistics, infrastructures, self-sufficiency and human personnel to face high request of health resources\cite{2,3}. To our personal point of view, we consider lack of trained and prepared healthcare workers one of the main factors that contributed to our limited and suboptimal approach to patients at the beginning of this pandemic\cite{4}.

The needs from an infectious disease in which transmission among healthcare personnel has proven to be one of the main routes of contagion urges the creation of programs and protocols as described in this article.

In our case, we faced the first wave in an extreme situation in which, thanks mainly to our nurse team, a new critical care unit came up from an area previously designed for obstetrics and pediatric care and was set up to be completely operational just three hours before our first COVID-19 critical care patient was admitted. Even though it was a huge challenge at first, due to the lack of critical care trained personnel it became necessary to include non-specialized workers in those new and undersigned areas. In our hospital we did not do a protocol as shown in the article commented, which would have been very useful though. Instead, we sought for a balance between inexperienced and experienced nurses in which nurse team leaders taught formation, working skills and leadership.

We believe that online training should not be limited to staff that deals with COVID-19 critical patients and we propose that our working routine should be taught to other healthcare workers less experienced in critical care areas.

One of the biggest challenges we faced in this pandemic was how quickly all healthcare staff needed to adapt to the use of personal protective equipment, a situation completely new but of major importance as a failure in putting on or removing this equipment would be a source of spreading the virus among other patients or workers\cite{5,6}. In our hospital, this task was assigned to our anesthesiologist trainees who took as an example other reference hospital protocols in our country and designed practical workshops designed for teaching all critical care staff. They also taught how to do complex treatment, such as how to intubate and how to prone intubated patients.

To summarize, we agree that these contactless protocols are necessary to standardize our ways of assessing and performing techniques in our critical care patients. We believe this formation should also be extended to physicians.

**FOOTNOTES**

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