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MINIREVIEWS

Liver injury in COVID-19: Holds ferritinophagy-mediated ferroptosis accountable

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Abstract

Even in patients without a history of liver disease, liver injury caused by coronavirus disease 2019 (COVID-19) is gradually becoming more common. However, the precise pathophysiological mechanisms behind COVID-19's liver pathogenicity are still not fully understood. We hypothesize that inflammation may become worse by cytokine storms caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Elevated ferritin levels can initiate ferritinophagy mediated by nuclear receptor coactivator 4 (NCOA4), which leads to iron elevation, and ferroptosis. In COVID-19 patients, ferroptosis can be restricted to reduce disease severity and liver damage by targeting NCOA4-mediated ferritinophagy. To confirm the role of ferritinophagy-mediated ferroptosis in SARS-CoV-2 infection, further research is required.

Key Words: COVID-19; Liver injury; Ferritinophagy; Ferroptosis; Iron; SARS-CoV-2

Core Tip: Liver injury in patients with coronavirus disease 2019 (COVID-19) has progressively emerged, yet the exact pathophysiological mechanisms to explain liver pathogenicity is presently not fully understood. We hypothesize that cytokine storms caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may promote hyper-ferritinemia, which can further aggravate inflammation. Elevated ferritin levels can trigger nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy, which leads to iron elevation, and ferroptosis. NCOA4-mediated ferritinophagy can be targeted to limit the ferroptosis and, therefore, prevent liver damage and disease severity in patients with COVID-19.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and exhibits a wide range of severity, from mild symptoms to severe presentation and death. Although respiratory symptoms are more frequent, signs of hepatic involvement have gradually come to light[1-4]. Aside from respiratory complications, the most common complication of SARS-CoV-2 infection is liver injury, which has been reported in up to 50% of cases[5-7]. Expanding prove shows a close relationship between anomalous liver function and the severity and mortality of the illness[8,9]. Derangement of alanine aminotransferase/aspartate aminotransferase levels is a key indicator of liver damage in COVID-19, accompanied by marginally elevated bilirubin levels, which are commonly used to diagnose hepatic injury such as acute hepatitis, steatosis, portal inflammation, granulomas, thrombotic bodies, and biliary pathology[10-12]. The raised liver catalysts are not only associated with severe disease and longer disease duration, but also common in the early stage of the COVID-19 pandemic[13]. However, the precise cause of liver damage is still unclear[14,15].

SARS-COV-2 INFECTION-ACTUATED LIVER INJURY IN COVID-19

The following potential mechanisms have been suggested that may be responsible for hepatic injury: SARS-CoV-2 causing direct harm to hepatocytes and biliary epithelium, indirect damage prompted by an exaggerated cytokine storm, and/or drug-incited hepatoxicity[10]. Patients with COVID-19 may experience liver dysfunction as a direct result of viral infection. A previous study showed the liver pathology of SARS patients and found SARS-associated coronavirus in liver tissues, suggesting that hepatic impairment was caused by viral infection in the liver[16]. Angiotensin converting enzyme 2 (ACE2) has recently been discovered as the SARS-functional CoV's host cell receptor, facilitating the entry of SARS-CoV-2 into cells[17-20]. The spike (S) protein of SARS-CoV-2 may also be broken down by transmembrane protease serine 2 (TMPRSS2), which makes it easier for the virus to fuse with cellular membranes[21]. Although they are expressed in many organs, including the liver, ACE2 and TMPRSS2 are expressed at varying amounts in different cell types, with cholangiocytes expressing them at a higher level than hepatocytes[22,23]. It has been demonstrated that hepatocyte and cholangiocyte organoids are receptive to SARS-CoV-2 infection[24]; however, *in vivo* confirmation of this phenomenon is still pending[25]. Ultrastructural and histological analysis have shown that hepatocytes exhibit a characteristic SARS-CoV-2 infected lesion[26]. In-depth proteomic analysis of autopsy tissue recently produced new data that showed little evidence of virus replication in the liver[27]. Additionally, an autopsy of a COVID-19 patient demonstrated that the liver tissue was free of viral inclusions[28]. Direct viral damage to the liver is not considered to be the main culprit when multiorgan problems such cardiopulmonary insufficiency, renal impairment, systemic inflammatory status, and the use of several medicines are taken into account. Consequently, the mechanism of liver damage by SARS-CoV-2 infection remains unknown.

SYSTEMIC INFLAMMATION-RELATED LIVER DYSFUNCTION IN COVID-19

Although the majority of COVID-19 patients experience a moderate early disease onset, some patients' conditions quickly worsen and they may experience multiple organ failure as a result of an inflammatory "cytokine storm"[29,30]. Tumor necrosis factor-α, interleukin(IL)-2, IL-6, IL-7, IL-18, granulocyte-colony stimulating factor, interferon-γ, monocyte chemotactic protein 1, macrophage inflammatory protein 1 alpha, interferon-inducible protein-10, and ferritin are examples of inflammatory cytokines that are exuberantly released during an inflammatory cytokine storm[9,30]. Patients with severe disease had significantly higher peripheral blood levels of the aforementioned variables than patients with mild disease[31,32]. Hypercytokinemia that is deadly or fulminant may set off a series of events that damage the liver[33]. In patients with COVID-19, lymphopenia and high C-reactive protein levels may operate as independent predictors of hepatic damage, which may be caused by an inflammatory cytokine storm [34]. Through the activation of killer T cells and toll-like receptors (TLRs), SARS-CoV-2 can directly produce a number of proinflammatory signals[35]. Following SARS-CoV-2 infection, activated T lymphocytes attack the infected cells, causing them to die and become necrotic until there are no more T lymphocytes left. TLRs, chemicals associated with damage, that are generated by infected dead cells,

can intensify the inflammatory signals. Failure to control viral and bacterial infections caused by T-lymphocyte depletion results in the activation of various inflammatory signaling pathways that activate macrophages thereby causing subsequent inflammatory reactions. In addition to the lungs, this vicious cycle can harm numerous organs, including the liver. Furthermore, it has been observed that COVID-19 patients show hepatic impairment due to a severe cytokine storm rather than the direct cytopathogenic effects of SARS-CoV-2 itself[36-39]. Patients with COVID-19 are more likely to have a number of hepatic illnesses, such as non-alcoholic fatty liver disease, liver cirrhosis, hepatocellular carcinoma, hepatitis B, and hepatitis C[36,40,41].

HYPER-FERRITINEMIA IN COVID-19 AND LIVER INJURY

It has been established that hyperferritinemia is a distinctive symptom of severe COVID-19[42]. The severity and poor prognosis of patients with COVID-19 have been directly associated with ferritin levels [33]. Although the liver significantly contributes to the levels of circulating serum ferritin in COVID-19, proximal tubule cells of the kidney and splenic macrophages are also two potential biological sources. Hepatocytes not only actively secrete ferritin[43], but also release ferritin after hepatic cell death[44]. Furthermore, by producing iron in enterocytes and macrophages, the important iron-regulatory hormone hepcidin may raise intracellular ferritin levels[45]. Majority of patients had inflammation-dependent elevation of hepcidin levels to varying degrees in severe illnesses with hyperinflammation [46]. The severity of COVID-19 is associated with elevated serum hepcidin levels[46,47]. Interestingly, SARS-CoV-2 can imitate hepcidin without triggering an inflammatory response by causing ferroportin blockage, which results in high ferritin levels[48].

IRON OVERLOAD IN LIVER INJURY CAUSED BY COVID-19: INTERMEDIATION OF FERRITINOPHAGY

The body's main organ for storing iron is the liver. According to growing evidence, lytic cell death processes like necroptosis, pyroptosis, and ferroptosis cause intense inflammatory reactions by releasing cellular components and permeating cell membranes. This results in the activation of hepatic stellate cells (HSCs) and the recruitment of immune cells[49]. It is without dispute that both hereditary and acquired iron in excess contribute to liver damage. Due to the active mobilization of cellular iron caused by the stimulation of ferritinophagy, ferroptosis may be used to evaluate excess iron. However, unrestrained free iron is harmful to the liver, promoting the development of hepatic disorders and producing serious side effects[49].

The most important cellular iron storing protein is ferritin. The liver is the primary organ for storing iron as a ferritin complex and plays a crucial role in maintaining iron homeostasis. It has been proven that excessive iron conditions may lead to liver damage. Different types of liver disorders are largely caused by iron-catalyzed oxidative damage[50,51]. The release of free iron from the broken hemoglobin and ferritin catabolism may cause COVID-19-related iron excess. High blood levels of free iron may result from ferritin, losing some of its internal iron content[52]. Ferritin abundance is a major determinant of iron homeostasis, as proved by the fact that iron deposits produced by ferritin result in a weakly labile iron pool. Contrarily, the release of iron into the labile iron pool, as a result of ferritin depletion, increases vulnerability to ferroptosis[53]. Studies have hypothesized that ferroptosis in fibroblasts and cancer cells is influenced by the selective autophagic turnover of ferritin (ferritinophagy) [54]. Ferritin's cargo receptor, nuclear receptor coactivator 4 (NCOA4), attaches and transports it to autophagosomes for ferritin breakdown and iron release[55,56]. Ferritinophagy has previously been shown to have important roles in the pathological processes of neurodegeneration, cancer, ischemia/reperfusion injury, and urinary tract infections[57], however, its possible involvement in COVID-19 remains unknown[58]. For the past 4 years, ferritinophagy has been involved in physiology and pathology process of liver, including hepatic insulin resistance[59], hepatocyte senescence[60], ferroptosis in hepatic stellate cells[61-63], hepatocellular carcinoma[64,65] and liver fibrosis[66] (Supplementary Table 1).

In COVID-19 patients, iron depletion or chelation has been suggested as a possible antiviral treatment to guard against severe inflammatory reactions and tissue damage by sequestering iron and inhibiting the generation of oxygen radicals and lipid peroxidation[67]. Poonkuzhi *et al*[68] mentioned that deferasirox administered orally, along with intravenous deferoxamine made iron chelation therapy effective for COVID-19 victims. A case-control study showed that iron chelators which reducd iron intake could be considered a therapeutic goal of COVID-19[69]. Additionally, the iron chelator and lactoferrin can block SARS-CoV-2 receptor binding for entrance into host cells[70,71].

FERRITINOPHAGY-MEDIATED FERROPTOSIS IN LIVER INJURY CAUSED BY COVID-19

Excess intracellular iron can produce reactive oxygen species (via Haber-Weiss and Fenton processes), reactive nitrogen species, and reactive sulfur species by reacting with molecular oxygen[72]. Redox injury favors mitochondrial malfunction, leading to ferroptosis, various tissue damages, and eventual fibrosis[73]. A new genetically encoded form of programmed cell death called ferroptosis is caused by iron-dependent lipid peroxidation[74]. Opportunities for diagnosis and treatment have been created by further functional understanding of ferroptosis' role in liver fibrosis development[74,75]. Artesunate reduces liver fibrosis by modulating the ferroptosis signaling system, according to a recent publication by Kong *et al*[66]. Additionally, Sui *et al*[76] demonstrated that by controlling the ferroptosis signaling pathway, magnesium isoglycyrrhizinate reduces liver fibrosis and HSC activation. Moreover, for artemether to reduce liver fibrosis and HSC activation brought on by carbon tetrachloride, p53-dependent induction of ferroptosis is required[77]. For artemether to effectively treat hepatic fibrosis *via* the ferroptosis pathway, iron regulatory protein 2 is necessary. Moreover, by inhibiting lipid peroxidation and glutathione depletion, ferrostatin-1, deferoxamine, and vitamin E may have a protective impact on hepatocytes[78].

Iron is abundant in HSCs, which is necessary for ferroptotic cell death[62]. Presumably, ferroptosis encourages the onset and progression of liver fibrosis. It has been found that liver fibrosis caused by acetaminophen in mice is amplified by excessive hepatic iron deposition and ferroptosis, which can be reversed by ferrostatin-1[79,80]. Ferroptosis was also shown by Zhou *et al*[81-83] to be a kind of autophagy-dependent cell death. Numerous studies have suggested that autophagy controls cellular iron homeostasis and the production of reactive oxygen species, thereby acting as an upstream mechanism in the activation of ferroptosis[81-83]. According to Wang *et al*[84], ferric citrate, a ferroptosis stimulant, potently causes ferroptosis in murine primary hepatocytes and bone marrow-derived macrophages, which prevents the healing of liver injury. Chen *et al*[85] proposed that ferroptosis caused by reactive oxygen species contributes to liver damage caused by COVID-19.

Notably, a number of recent investigations have shed light on controlled cell death and underlined the significance of autophagy as an emerging mechanism of ferroptosis[86,87]. Multiple routes, including ferritinophagy, which is NCOA4 dependent, may be involved in the molecular mechanisms [54]. Thus, during ferroptosis, ferritinophagy promotes iron accumulation and free radical damage. Dihydroartemisinin, according to Du *et al*[88], reduces leukemia cells' ability to proliferate and causes ferroptosis by degrading ferritin under the control of autophagy. Moreover, Kong *et al*[66] demonstrated that artesunate reduced HSC ferroptosis caused by ferritinophagy. Notably, the activation of ferritinophagy is required for the RNA-binding protein, embryonic lethal vision-like protein 1, to regulate ferroptosis in HSCs[62]. New diagnostic and therapeutic ways to control HSC survival and death in liver fibrosis may be provided by further investigations of the post-transcriptional regulating mechanisms of ferroptosis. However, as hepatocytes die, ferritin is further released. Due to the mutual stimulation of ferritin and hepatocyte destruction, a vicious cycle is created that continuously worsens liver damage.

CONCLUSION

In light of this, we speculate that cytokine storms caused by SARS-COV-2 infection can encourage hyper-ferritinemia, exacerbating inflammation. Elevated ferritin levels can cause ferroptosis, cell death, and liver damage by inducing NCOA4-mediated ferritinophagy. Therefore, in COVID-19 patients, ferroptosis can be addressed to reduce liver damage and disease severity by limiting ferroptosis (Figure 1). To validate the role of ferritinophagy-mediated ferroptosis in SARS-CoV-2 infection, further research is required. Drug designing to target hepatic cells ferritinophagy-mediated ferroptosis would be a novel approach in the treatment of COVID-19-induced liver injury.

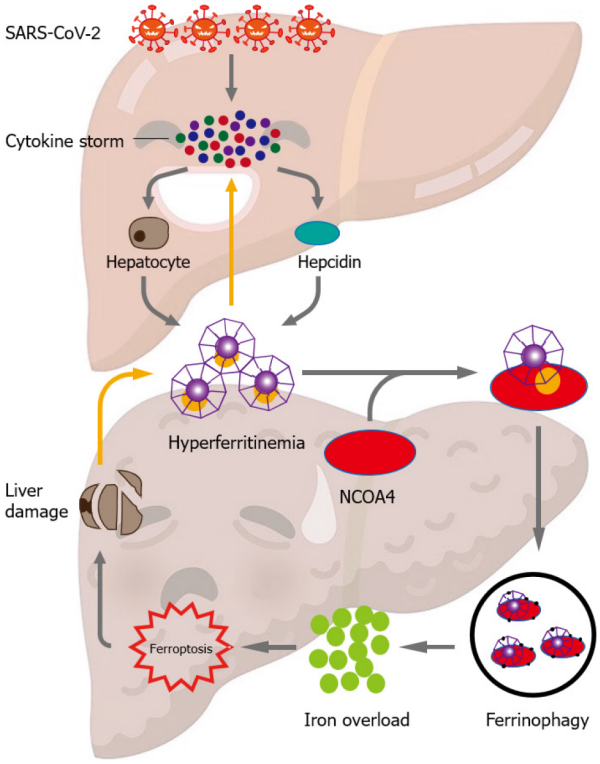

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Figure 1 Proposed mechanism of ferritinophagy-mediated ferroptosis in severe acute respiratory syndrome coronavirus 2 infection-induced liver injury. High levels of inflammation characterized by cytokine storms are caused by severe acute respiratory syndrome coronavirus 2 infection. These cytokine storms cause hyper-ferritinemia by stimulating hepatocytes to secrete ferritin and upregulate hepcidin levels, which further amplifies inflammation. The nuclear receptor coactivator 4 binds to ferritin and delivers it to autophagosomes for ferritin degradation and iron release. Ferroptosis is generated by the excess of intracellular iron, consequently resulting in liver injury. The death of hepatocytes further releases ferritin. Thus, the mutual promotion of ferritin and hepatocyte damage generates a vicious loop that constantly heightens liver injury.

FOOTNOTES

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MINIREVIEWS

Amebic liver abscess by *Entamoeba histolytica*

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Abstract

Amebic liver abscesses (ALAs) are the most commonly encountered extra-intestinal manifestation of human invasive amebiasis, which results from *Entamoeba histolytica* (*E. histolytica*) spreading extraintestinally. Amebiasis can be complicated by liver abscess in 9% of cases, and ALAs led to almost 50000 fatalities worldwide in 2010. Although there have been fewer and fewer cases in the past several years, ALAs remain an important public health problem in endemic areas. *E. histolytica* causes both amebic colitis and liver abscess by breaching the host's innate defenses and invading the intestinal mucosa. Trophozoites often enter the circulatory system, where they are filtered in the liver and produce abscesses, and develop into severe invasive diseases such as ALAs. The clinical presentation can appear to be colitis, including upper-right abdominal pain accompanied by a fever in ALA cases. Proper diagnosis requires nonspecific liver imaging as well as detecting anti-*E. histolytica* antibodies; however, these antibodies cannot be used to distinguish between a previous infection and an acute infection. Therefore, diagnostics primarily aim to use PCR or enzyme-linked immunosorbent assay to detect *E. histolytica*. ALAs can be treated medically, and percutaneous catheter drainage is only necessary in approximately 15% of cases. The indicated treatment is to administer an amebicidal drug (such as tinidazole or metronidazole) and paromomycin or other luminal cysticidal agent for clinical disease. Prognosis is good with almost universal recovery. Establishing which diagnostic methods are most efficacious will necessitate further analysis of similar

clinical cases.

Key Words: Amebic liver abscess; *Entamoeba histolytica*; Polymerase chain reaction; Enzyme-linked immunosorbent assay; Percutaneous catheter drainage; Amebicidal drug

Core Tip: Amebic liver abscesses are the most commonly encountered extraintestinal manifestation of human invasive amebiasis, which results from *Entamoeba histolytica*. It breaches the host's innate defenses and invades the intestinal mucosa. Trophozoites enter the circulatory system and are filtered in the liver and produce abscesses. The diagnostics primarily aim to use PCR or enzyme-linked immunosorbent assay to detect *Entamoeba histolytica*. Medical treatment of amebic liver abscesses is possible using an amebicidal drug and a luminal cysticidal agent. Prognoses are generally good. Elucidating the detailed pathogenesis and establishing which diagnostic methods are most efficacious will necessitate further analyses of similar clinical cases.

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INTRODUCTION

General information on amebic liver abscess

Worldwide the most commonly encountered manifestation of invasive extraintestinal amebiasis in humans is amebic liver abscesses (ALAs), which occur when *Entamoeba histolytica* (*E. histolytica*) spreads extraintestinally[1-5]. In 9% of cases, liver abscesses develop as a complication of amebiasis, and in 2010, ALAs led to a total of nearly 50000 fatalities[6,7]. Though cases have declined in number in recent years, ALAs are still a major public health issue within endemic areas[8]. ALA patients may present with what appears to be colitis, with pain in the upper right abdomen and sometimes accompanied by a fever; however, asymptomatic infections may also occur[1,9]. Hepatitis E virus infection and amebiasis are endemic in India and coexisting acute hepatitis E and ALA has also been reported[10]. The aim of this review was to share the general information of ALA and its pathogenesis, examinations, diagnosis, treatment, complications, prognosis, and prevention.

General information on amebiasis

E. histolytica is an anaerobic parasitic invasive enteric protozoan, and infections of *E. histolytica* correlate to high mortality and morbidity rates[11,12]. Each year, this protozoan causes 40000-100000 deaths, ranking only behind malaria in patient mortality[13-15]. According to a previous report, invasive amebiasis develops in fewer than one-tenth of patient infections[11]. The geographic distribution of amebiasis has worldwide amplitude and a high rate of incidence, and it remains a public health concern in low- and middle-income developing countries in the tropics, particularly in environments that are crowded and lacking in adequate sanitation and clean water due to the oral-fecal route of pathogen transmission (including ingestion of food or water that contains cysts from this protozoan)[6,16-19]. On the other hand, this pathogen is only rarely seen in wealthier countries but is epidemiologically growing; in particular, recent immigrants from endemic regions (or travelers returning from a long-term stay in an endemic region) have a greater risk of developing amebiasis[6,20-22].

Maintaining a high index of suspicion is recommended for amebiasis regarding other groups that are at greater risk, such as men who have sex with men, people with acquired immunodeficiency syndrome or HIV, immunocompromised hosts such as patients with cirrhosis, or people who reside in group homes or mental health facilities[6,23]. In particular, relatively large numbers of cases have been reported in Japan in individuals infected with HIV-1, and it was found that these individuals commonly suffered from subclinical amebiasis[24]. In addition, asymptomatic individuals infected with HIV-1 who have a high anti-*E. histolytica* titer run a risk of invasive amebiasis, most likely as a result of subclinical amebiasis exacerbation[24].

In the Western world, the low overall prevalence, as well as the fact that the latency period between infection by the underlying pathogen and clinical symptom onset may be lengthy, creates a risk of

delaying diagnosis of amebiasis and thus inadequate treatment[20]. Additionally, pregnancy has also been found to be an invasive amebiasis risk factor; management of pregnant patients becomes especially complex[20]. Mortality due to amebiasis is primarily the result of extraintestinal infections, with the most common of these being ALAs[25].

PATHOGENESIS

The route of transmission of *E. histolytica* that leads to ALA has yet to be thoroughly elucidated; broadly, after *E. histolytica* breaches the host's innate defenses, it causes liver abscess and amebic colitis by invading the intestinal mucosa[8,26]. Often, trophozoites enter the circulatory system. They are then filtered in the liver and produce abscesses and can develop further into severe invasive diseases, such as ALAs[27]. On the other hand, conditions of immune-compromised individuals and/or momentaneous immune modulation in humans have been reported to increase both bacterial and viral activities/infections and related diseases[28-31]. ALA may arise following an impairment of the anti-*E. histolytica* immune system, and the immune evasion is a typical mode of action of pathogens in humans.

Regarding its molecular mechanism, *E. histolytica* uses the virulence factor Gal/GalNAc lectin in order to invade the host tissue; this molecule not only protects against ALAs but also induces an adherence-inhibitory antibody response[3]. In addition, *E. histolytica* has a pair of low-molecular-weight protein tyrosine phosphatase (LMW-PTP) genes, *EhLMW-PTP1* and *EhLMW-PTP2*, which are expressed through cysts, cultured trophozoites, and clinical isolates[32]. There is a single amino acid sequence difference, at position A85V, between the proteins EhLMW-PTP1 and EhLMW-PTP2[32]. Both of these genes are expressed in cultured trophozoites, particularly *EhLMW-PTP2*; trophozoites that are recovered from ALAs show downregulated EhLMW-PTP1 expression[32].

In an *in vitro* study, the compound linearolactone, as isolated from *Salvia polystachya,* demonstrated antiparasitic activity against *E. histolytica* through the production of reactive oxygen species and was able to induce apoptosis-like effects in trophozoites of *E. histolytica* through intracellular reactive oxygen species production, which affected the structure of the actin cytoskeleton[33]. Therefore, linearolactone served to more actively reduce ALA development[33]. Furthermore, calreticulin is a highly conserved protein in the endoplasmic reticulum and serves in an important capacity in regulating vital cellular functions[34]. In patients with acute phase ALAs, interleukin levels (interleukin-6, interleukin-10, granulocyte colony stimulating factor, and transforming growth factor β1) were higher, while resolution phase ALA patients had higher levels of interferon gamma detected[34].

Entamoeba dispar is a separate amoeba species that annually infects 12% of the global population, and it has been classified as "noninvasive" in the past[17]. However, this amoeba has been isolated from patients suffering from symptomatic non-dysenteric colitis, and DNA sequences from this species have been both detected and genotyped in samples from dysenteric colitis patients as well as samples from ALA patients, suggesting that this amoeba may play some role in human large intestine and liver lesion development[17].

EXAMINATIONS

It is difficult to distinguish ALA from pyogenic liver abscesses using only clinical, laboratory, and radiological findings[35,36]. In order to diagnose the various ALA-related complications, computed tomography (CT) scans serve as an ideal tool[37]. As a result, serologic *E. histolytica* tests are a necessary part of accurate evaluations of liver abscesses within high-risk groups[35,36]. On the other hand, in a study to use CT findings to determine different morphological types of ALA and to determine any differences in their clinical features, ALAs were found to have three distinct CT morphological types, each varying in terms of its laboratory and clinical features[38].

Type I abscesses (representing 66% of the total) have walls that were either absent or incomplete as well as peripheral septa and edges that are ragged and exhibit enhancement that is both irregular and interrupted[38]. Here, we show a CT from our institution of a 44-year-old woman with a type I abscess (Figure 1). Clinically, these abscesses had an acute presentation alongside severe disease. Laboratory parameters were significantly deranged, and they had higher incidences of rupture with higher rates of admission to inpatient care and/or intensive care[38]. In a large majority of type I abscesses (81%), disease severity prompted percutaneous drainage to be carried out immediately[38].

Type II abscesses (representing 28% of the total) have complete walls with both peripheral hypodense halo and rim enhancement. Type III abscesses (representing 6% of the total) demonstrate walls but without enhancement[38]. The type II and III abscesses feature delayed presentations, with near-normal laboratory findings and mild to moderate disease[38]. On the other hand, whether ALA patients are infected with HIV cannot be determined through the clinical characteristics alone. Even in the absence of HIV symptoms, it is advisable to routinely test ALA patients for HIV[39].

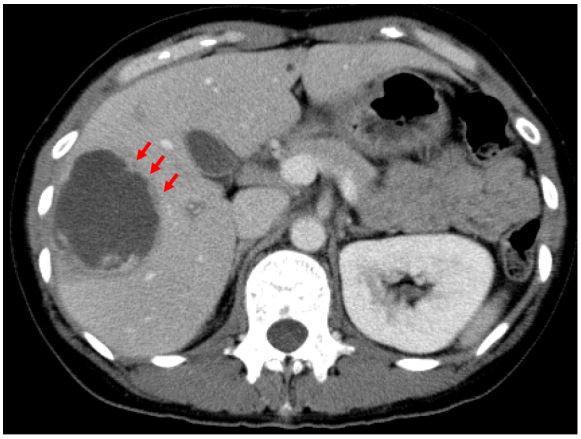

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Figure 1 Computed tomography of a 44-year-old woman with a type I abscess. The axial computed tomography image illustrates the non-enhancing and ragged edge of the abscess in the absence of a definite wall, peripheral septa, and ragged edges; these edges exhibited both irregular and interrupted enhancement (arrows).

DIAGNOSIS

Despite the rarity of ALAs, a high index of suspicion should be maintained by physicians working with patients who have presented with synchronous lesions of the colon and liver, particularly because in recent years travel has increased to regions where they are endemic[40]. Crucial predictors of ALAs include habitual alcohol consumption and low socioeconomic status[25]. A number of diagnostic tools are available for diagnosis; if there is a suspicion of amebiasis, testing yield can be maximized through a combination of stool testing and serology[6]. Diagnosis relies on nonspecific liver imaging and on detecting anti-*E. histolytica* antibodies, which cannot be used to distinguish between acute and previous infections[5,21]. Therefore, diagnostics must focus primarily on detecting *E. histolytica* using PCR or enzyme-linked immunosorbent assay[1]. Among these options, a parallel analysis using indirect enzyme-linked immunosorbent assay with crude soluble antigen together with excretory-secretory antigen for ALA serodiagnosis improved the overall amebic serology efficacy compared to either assay on its own[41].

Recently, the XEh Rapid® IgG_4-based rapid dipstick test for rapid detection of ALAs (based on detecting the anti-*E. histolytica* pyruvate phosphate dikinase IgG_4 antibody) demonstrated high diagnostic specificity in infected patients (97%-100%), with diagnostic sensitivity varying between 38% and 94%[42]. The various evaluation process-related difficulties have been discussed elsewhere; nonetheless, it has demonstrated promise for development into a point-of-care test, especially for settings that have relatively restricted resources, and consequently further investigation to confirm its sensitivity as a diagnostic is warranted[42]. On the other hand, one valuable antigen for amebiasis serodiagnosis is the C-terminal region of the intermediate subunit of *E. histolytica* galactose- and N-acetyl-D-galactosamine-inhibitable lectin[43]. The newly developed immunochromatographic kit, which uses fluorescent silica nanoparticles coated with the C-terminal region of the intermediate subunit of *E. histolytica* galactose- and N-acetyl-D-galactosamine-inhibitable lectin prepared in *Escherichia coli*, has proven beneficial for rapid amebiasis serodiagnosis[43].

Ultrasound is currently the criterion standard for liver abscess diagnoses[14]. Acute abdominal pain can be the result of a variety of diseases, but even in non-endemic Western countries parasitic abscess should not be overlooked as a potential diagnosis[14]. Contrast-enhanced ultrasound is a promising new technique, with the potential for greater accuracy in recognizing liver abnormalities, including abscesses; however, definition of differential diagnoses will require retrospective population-wide studies[14].

It is difficult to definitively diagnose ALAs because sensitive point-of-care molecular tests are not readily commercially available[44]. A diagnostic study was performed in order to compare the available methods for *E. histolytica* laboratory diagnoses in pus samples, stool samples, and blood samples taken from patients who had radiological and/or clinical diagnoses of ALA with loop-mediated isothermal amplification. The results found that loop-mediated isothermal amplification had significantly greater sensitivity (88%) then reverse transcriptase PCR (64%) as well as outstanding specificity (100%)[44]. On the other hand, in ALAs, cell-free circulating *E. histolytica* DNA can be detected in serum in ALAs, which could prove beneficial for not only positive diagnosis but also the efficacy of follow-up treatments[21]. Additional innovative detecting methods have been developed for *E. histolytica*, and stool samples were analyzed using PCR-denaturing gradient gel electrophoresis in order to distinguish between pathogenic *E. histolytica* (pathogenic) and non-pathogenic *Entamoeba dispar*[45]. The PCR amplification target was a relatively small region (228 bp) of the *adh112* gene, which was selected for

greater test sensitivity[45]. These results, validated by nested PCR-restriction fragment length polymorphism, would imply that PCR-denaturing gradient gel electrophoresis may have promise as a tool to distinguish between *Entamoeba* infections and contribute to the determination of a specific course of treatment for *E. histolytica* patients, thus obviating unnecessary treatment of patients who have been infected with *Entamoeba dispar*, which is non-pathogenic[45].

Additionally, diagnosis is possible through abdominal ultrasound and echography-guided liver puncture[46]. If liver abscess fluid bacterial cultures remain negative, amebic abscess should be considered as a possibility, even if the patient has no personal history of tropical or subtropical travel [1]. In culture-negative cases, 16S rRNA abscess fluid analysis plays a part in improved microbiological diagnoses[35].

TREATMENT

ALAs can be treated medically. Percutaneous catheter drainage (PCD) is required in only 15% of cases [5,47]. They generally respond well to treatment using metronidazole, alongside drainage if indicated[2,4,48]. In uncomplicated cases, it is advisable to avoid surgical drainage[48].

Safe, effective complex abscess decompression has been enabled through surgical drainage with preoperative CT and intraoperative ultrasonography[48]. In particular, liver abscesses in the caudate lobe can be accessed without major complications *via* different percutaneous drainage routes, despite its deep location and the fact that it is surrounded by large blood vessels[4]. Thus, PCD or percutaneous needle aspiration (PNA) could be regarded as a first-line therapy for caudate lobe amebic abscess management, in adjunct to medical therapy[4]. Following substantial reduction or cessation of PCD output along with clinical recovery, treating physicians may be concerned with residual collections on radiological evaluations[49]. However, both the significance and prevalence of such collections remain unknown, and it is subsequently unclear what approach should be taken in order to tackle them. On the other hand, PCD removal can be expedited successfully in ALAs, even when residual collections are present[49]. In pediatric patients, PNA and drain placement were both found to be effective as ALA treatments, though PNA had greater efficacy[50].

On the other hand, ultrasound-guided PCD has been found to be both safe and effective as a treatment method for ruptured ALAs, including free ruptures with diffuse intraperitoneal fluid collections. For ruptured ALAs, PCD is also recommended as the first line of therapy[51]. At present, metronidazole on its own as well as PNA and PCD play unclear roles in treating uncomplicated ALAs [52]. Compared to metronidazole on its own, PNA results in earlier resolution of both pain and tenderness in patients suffering from medium to large ALAs[52]. On the other hand, PCD is preferable for larger ALAs[52]. However, further efforts to generate more accurate and reliable data are needed due to therapeutic dilemmas caused by discrepancies in randomized controlled trials[52]. In addition, the literature seems to be conflicting on the topic with proponents of both percutaneous methods and laparoscopic drainage[4,53]. Given the rarity of amebiasis, the rarity of the complication itself, and the possibility that PCD may prove ineffective due to viscosity of the abscess content, catheter dislocation *etc*, a step-up approach would be advisable in that case.

The indicated treatment is to use an amebicidal drug such as metronidazole or tinidazole as well as paromomycin or another luminal cysticidal agent for clinical disease[1,6,54]. Treatment involves oral administration of 500-750 mg of metronidazole (or another nitroimidazole if necessary), three times daily, for 7-10 d[55]. As an alternative option, 2000 mg of tinidazole can be administered orally on a daily basis for 3 d[55]. However, in 40%-60% of patients, the parasites persist within the intestine. Therefore, nitroimidazole treatment should always be followed with a luminal agent such as a 7-d regimen of 500 mg of paromomycin three times a day or a 20-d regimen of 650 mg of iodoquinol three times a day[55].

The drug of choice for treating ALAs is often metronidazole, a common antibacterial and antiprotozoal drug; though it has long been preferred, it is also associated with a number of different adverse effects in some clinical situations, including intolerance[54,56,57]. The mechanisms of resistance to metronidazole, as well as mutagenic potential, have previously been described[23]. Though ordinarily safe, under rare circumstances this drug is capable of causing serious central nervous system disturbances. In particular, metronidazole neurotoxicity as well as characteristic bilateral symmetrical cerebellar dentate hyperintensities have been shown on brain magnetic resonance imaging[58]. However, neurotoxicity is not dependent on dose, and with discontinuation of the drug it can be fully reversed[57,58]. Additionally, it is still unknown what effects, if any, the drug has when used by pregnant or lactating patients (and consequently in breastfeeding infants)[54].

The efficacy of nitazoxanide has been demonstrated in invasive intestinal amebiasis treatment; however, a study has shown that in uncomplicated ALAs nitazoxanide has efficacy comparable to metronidazole and enjoys the advantages of both superior tolerability and simultaneous luminal clearance, leading to a lower likelihood of recurrence[54].

In comparison to metronidazole, tinidazole has an earlier clinical response, a shorter course of treatment, a more favorable rate of recovery, and a higher tolerability; consequently, for ALAs

tinidazole can be considered preferable to metronidazole[56]. The recommended treatment for asymptomatic infections is a luminal cysticidal agent, in order to reduce the chances of either invasive disease or transmission[6].

For surgical treatment, a laparoscopic approach imposes the least physical burden resulting from the laparotomy[46]. According to the latest research results, ubiquitin Ehub antibodies are induced solely in patients with ALA or other invasive amoebiasis, and the antibody response is mainly to the glycoprotein, indicating that the glycans are immunodominant[59]. Therefore, Ehub glycan inhibitors hold potential as an amoebiasis treatment through selective damage to trophozoites[59].

COMPLICATIONS

In rare cases, abscesses can rupture into the peritoneum, pericardium, or pleura, or into the hilum of the bile duct; they may also lead to septic emboli[2]. Thromboses of the hepatic vein and the inferior vena cava are uncommon ALA complications (though well documented) and are generally attributed to the inflammation and mechanical compression that accompany larger abscesses[60]. With ALAs, the combination of portal vein thrombosis and hepatic vein thrombosis is a common occurrence, frequently manifesting as segmental hypoperfusion in the portal venous phase and indicating ischemia[61]. When events such as these are detected using CT, they may indicate a more severe disease that demands more aggressive management, including percutaneous drainage[61]. However, there has been one report of a left hepatic ALA in a patient who had no clear source of infection, initially presenting with a left portal vein thrombosis[22].

In rare cases, hepatic artery aneurysms can complicate amebiasis in hepatic abscess patients[13]. In addition to the significant harm caused by the disease, particularly in developing countries, there is only sporadic case report data available, which suggests that there may be an underreporting bias[13]. Further studies are necessary in order to further elucidate vascular involvement in this setting of parasitological interest[13]. Furthermore, intrahepatic pseudoaneurysms due to ALAs are exceptionally uncommon. There are only a handful of published reports[62]. In every known symptomatic case, the treatment was embolization of the hepatic artery; consequently, the natural course of the disease remains poorly understood, as do the effects of abscess drainage on outcomes[62]. On the other hand, according to one report regarding symptomatic intracavitary intrahepatic pseudoaneurysms as a result of an ALA, an ultrasound-guided abscess PCD caused the intrahepatic pseudoaneurysms to spontaneously resolve[62]. Recently, there has been a case reported of ALA copresenting with coronavirus disease 2019. Based on pathophysiological similarities, coinfection with both of these could affect the clinical course of the patient[18].

PROGNOSIS

There are highly varied infection outcomes for amebiasis due to the protozoan parasite *E. histolytica*[63]. Prognosis is favorable, and there is near-universal recovery[5]. A study of the relationship between the genotypes of parasites and amebic infection outcomes found a significant association with disease outcomes related to single nucleotide polymorphisms (both non-synonymous and synonymous) within the protein 2 (*kerp2*) locus, which is rich in both lysine and glutamic acid[63]. An incomplete linkage disequilibrium value has also been found to exist at the *kerp2* locus, with potential recombination events and significant values for population differentiation[63]. At the *kerp2* locus, disease-specific single nucleotide polymorphisms, potential recombination events, and significant values for population differentiation are present, indicating that the host continuously exerts selection pressure on the parasite on the *kerp2* gene and its gene products; this could potentially serve as a way to determine the outcome of disease caused by *E. histolytica* infections[63].

Additionally, in isolation from asymptomatic carriers, *E. histolytica* is closer, phylogenetically, to species that cause human liver abscesses, and they exhibit potential interpopulation recombination[63]. Individuals who experience persistent asymptomatic infections of *E. histolytica* could have a greater likelihood of future ALA development, and asymptomatic people who live in areas where it is endemic should always be mandated to undergo close investigations[63]. On the other hand, potentially valuable predictors of recurrent ALA include the presence of resistance genes (*nim*) and *Prevotella* in the abscess fluid, accompanied by elevated levels of matrix metalloproteinase-9 and large abscess size (11 cm × 10.8 cm); recurrence rates were 8.9%[64].

PREVENTION

Despite the knowledge that has been gained and the scientific advances that have been made, there are still no effective treatments to prevent this infection[65]. The extended duration of subclinical *E.*

histolytica infection makes it difficult to control this disease not only in individual amebiasis patients but also epidemiologically[24]. Anti-*E. histolytica* testing targeting individuals who are at greater risk could prove beneficial in early subclinical amebiasis diagnosis, and earlier treatment of infected patients could halt invasive amebiasis from developing, thus preventing community transmission[24].

The compound curcumin can demonstrate anti-amebic effects within the liver, which would suggest that administering curcumin daily could help to significantly decrease infection incidence rates[65]. Immunization using a chimeric vaccine (using the recombinant protein PE Δ III-LC3-KDEL3) was successful in preventing invasive amebiasis, avoiding acute proinflammatory response, and rapidly activating a protective response. Ultimately, this recombinant protein induced increased serum levels of IgG[3]. Additionally, in order to proactively eliminate the disease, it would be beneficial to have greater awareness among at-risk members of the public[8].

CONCLUSION

The aim of this minireview was to highlight the pathogenesis of and difficulty of diagnosing ALAs. Methods of pathogenesis and accurate diagnosis have yet to be determined. However, accurate diagnoses can be achieved through newer molecular biological techniques, and these can lead to appropriate management of infections due to this organism. Future studies should ideally aim to elucidate pathogenesis and determine more effective diagnoses for effective ALA management.

FOOTNOTES

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MINIREVIEWS

Living with liver disease in the era of COVID-19-the impact of the epidemic and the threat to high-risk populations

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Abstract

The cardinal symptoms of severe acute respiratory syndrome coronavirus 2 infection as the pandemic began in 2020 were cough, fever, and dyspnea, thus characterizing the virus as a predominantly pulmonary disease. While it is apparent that many patients presenting acutely to the hospital with coronavirus disease 2019 (COVID-19) infection have complaints of respiratory symptoms, other vital organs and systems are also being affected. In fact, almost half of COVID-19 hospitalized patients were found to have evidence of some degree of liver injury. Incidence and severity of liver injury in patients with underlying liver disease were even greater. According to the Centers of Disease Control and Prevention, from August 1, 2020 to May 31, 2022 there have been a total of 4745738 COVID-19 hospital admissions. Considering the gravity of the COVID-19 pandemic and the incidence of liver injury in COVID-19 patients, it is imperative that we as clinicians understand the effects of the virus on the liver and conversely, the effect of underlying hepatobiliary conditions on the severity of the viral course itself. In this article, we review the spectrum of novel studies regarding COVID-19 induced liver injury, compiling data on the effects of the virus in various age and high-risk groups, especially those with preexisting liver disease, in order to obtain a comprehensive understanding of this disease process. We also provide an update of the impact of the new Omicron variant and the changing nature of COVID-19 pathogenesis.

Key Words: Liver injury; Hepatobiliary injury; COVID-19; SARS-CoV-2; High-risk

populations; Liver disease

Core Tip: The severe acute respiratory syndrome coronavirus 2 virus primarily produced respiratory symptoms in patients; subsequently, its effects on the hepatobiliary system were previously overlooked. New emerging studies on the effects of coronavirus disease 2019 (COVID-19) on the hepatobiliary system show that the association is significant and warrants further review. In this article, we review the existing data and present a comprehensive understanding of hepatobiliary injury in COVID-19 in those with underlying liver disease and in special populations, such as pregnancy, obesity, diabetes, and racial minority groups. Most of our reviewed populations are at increased risk of liver injury and mortality from COVID-19.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic continues to threaten the health of our communities with new emerging variants and surges in rates of infection. As the virus continues to transform and mutate, the effects severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has on various organ systems can change as well. Thus, the importance of understanding its effects on not only the respiratory system, but also extrapulmonary organ systems, becomes greater. One of the least studied systems in terms of the short- and long-term effects of COVID-19 infection is the hepatobiliary system. In this article, we review the spectrum of novel literature on hepatobiliary injury in COVID-19 and explore its relationship with various preexisting liver pathologies and special populations. Although it is a daunting task to summarize and interpret all the medical literature on this subject, we aim to provide a comprehensive review in order to address important questions regarding the effect of the virus on the liver as well as the effect of comorbid hepatobiliary conditions on mortality in COVID-19. We hope to aid clinicians and patients in gaining a better understanding of this devastating virus.

APPROACH

Articles were obtained by searching PubMed, CrossRef, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/), and Google Scholar databases using the keywords listed in the appendix. The abstracts were reviewed to assess if they met the inclusion and exclusion criteria to be included in the review. To be included in the review, the articles must have been about COVID-19 and hepatobiliary disease and must have been written in English. Case reports were excluded from the study.

Ultimately, we identified 56 articles that met the inclusion criteria. These articles were analyzed and summarized in this review. The hepatobiliary diseases reviewed in this article include liver cirrhosis, sclerosing cholangitis (SSC), autoimmune hepatitis (AIH), non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) syndromes, post-liver transplantation, and hepatitis B (HBV) and hepatitis C (HCV) co-infections. Special populations include patients who had the following characteristics- pregnancy, obesity, racial minorities, and diabetes.

PATHOPHYSIOLOGY AND TYPES OF LIVER INJURY IN COVID-19

The pathophysiologic effects of COVID-19 on the hepatobiliary system are still under debate. However, there have been studies that have evaluated the possible mechanisms of injury, both direct and indirect as illustrated in Figure 1. Direct viral injury of hepatobiliary damage is evidenced by liver biopsy findings of ballooned hepatocytes, acidophilic bodies, and lobular inflammation. Three plausible mechanisms can explain the pathophysiology of direct liver injury caused by SARS-CoV-2. The first

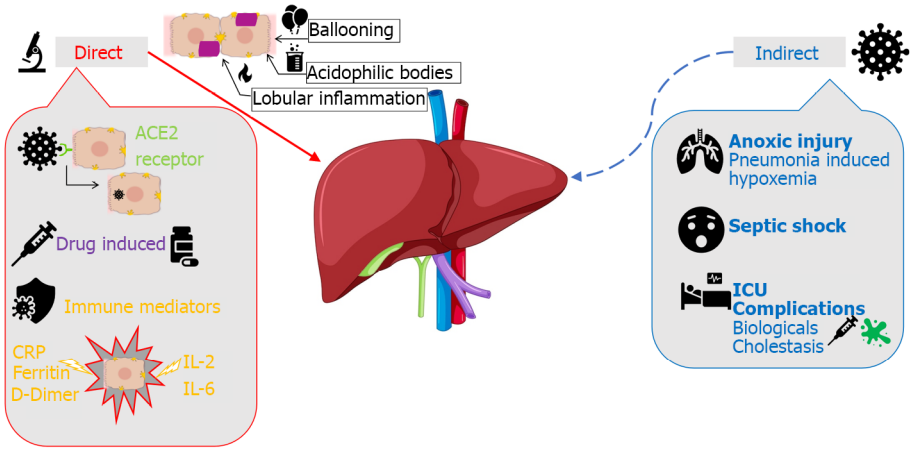

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Figure 1 Severe acute respiratory syndrome coronavirus 2 and its pathophysiological effects on the hepatobiliary system. ACE2: Angiotensin-converting enzyme 2; IL: Interleukin; CRP: C-reactive protein; ICU: Intensive care units.

mechanism is initiated by viral binding to angiotensin-converting enzyme 2 (ACE2) receptors on target cells of epithelial cholangiocytes and hepatocytes as a means of entry into these cells[1]. Viral entry and replication within these cells leads directly to cytotoxicity. The second mechanism is primarily immune-mediated. Immune dysfunction accompanying COVID-19 disease progression, including both lymphopenia or immune system upregulation, can independently lead to hepatic cytotoxicity[1]. Severity can be correlated with the degree of elevation in inflammatory biomarkers such as C-reactive protein, ferritin, D-dimer, interleukin (IL)-6, and IL-2[2]. The third mechanism involves drug-induced liver injury from common drugs used in COVID-19 management. Specifically, the COVID-19 medications with known hepatotoxic effects include ritonavir, remdesivir, chloroquine, tocilizumab, and ivermectin[2].

The hepatobiliary system can also be affected indirectly through the downstream effects of COVID-19 infection. Patients with severe hypoxia and hypoxemia from COVID-19 pneumonia can sustain anoxic injury of major extrapulmonary organs, including the liver[3]. Sepsis with hypotension can also cause liver injury due to poor perfusion. Additionally, critically ill patients (*i.e.*, patients requiring Intensive Care Unit admission) are more prone to liver dysfunction as they may require life-saving hepatotoxic drugs, such as high-potency antibiotics, amiodarone, propofol, antiepileptics, and parenteral nutrition. These patients may experience cholestasis due to inflammatory cytokines that can impair bile acid secretion and absorption. SARS-CoV-2 can also cause reactivation of existing metabolic liver or biliary disease *via* immunologic processes or drugs. Biologic drugs used in COVID-19 treatment, such as tocilizumab and baricitinib, can lead to HBV reactivation. SARS-CoV-2 may also exacerbate cholestasis in those with underlying cholestatic liver disease.

DELTA *VS* OMICRON VARIANTS OF COVID-19

Since the start of the COVID-19 pandemic in early 2020, we have learned of emerging SARS-CoV-2 variants with predominance during different periods of time. Understanding the differing hepatobiliary effects of individual variants is of great importance as new surges of the virus are often brought on by the emergence of a new variant, and viral characteristics among the variants differ. According to the Centers of Disease Control and Prevention data, the dominant variant from March 2021 to June 2021 was the Alpha variant, with a drift to the Delta variant from June 2021 to December 2021[4]. Omicron variant predominance occurred during December 2021 and continues to this day as various sub-variants of Omicron have emerged. Our literature search revealed only two studies focused on the liver injury caused by different variants of COVID-19. In a prospective cohort study by Deng *et al*[5], 157 SARS-CoV-2 infected patients on hospital admission were enrolled, of which 77 patients were infected with Delta variant and 80 patients were infected with Omicron variant[5]. Mild liver injury was found in 23.4% of Delta-infected patients and 18.8% of Omicron-infected patients. In contrast, cholangiocyte injury was found in 76.5% of Delta-infected patients and 83.3% of Omicron-infected patients. While the numbers are staggering, there is no significant difference in this group's rates of hepatobiliary injury. In a study by Jang[6], no difference in liver injury was noted between Delta and Omicron variants[6]. They do note that the prevalence of the COVID-19 vaccine during the Omicron variant-dominant era may likely play a role in this. However, there is insufficient data on the isolated effects on the hepatobiliary system of the different variants, and further study of this subject is warranted.

CO-MORBID HEPATOBILIARY CONDITIONS: LIVER CIRRHOSIS

The interplay between COVID-19 and liver cirrhosis has yet to be precisely characterized. On review of data gathered from the National COVID Cohort Collaborative (N3C), 30-d survival of COVID Positive/Non-Cirrhotic patients *vs* Positive/Cirrhotic patients had statistically significant differences wherein Positive/Cirrhotic Patients had 2.38 times mortality hazard at 30 d[7]. Moreover, data gathered from SECURE-Cirrhosis and COVID-Hep registries suggest an association between increased mortality and rates of mechanical ventilation with higher Child-Pugh classes. Specifically, Class A was associated with a 1.9 odds ratio of death, Class B with 4.14, and Class C with 9.32. Of note, patients who survived acute COVID-19 infection returned to baseline mortality associated with liver cirrhosis alone[8].

Overall, the data suggest underlying liver cirrhosis and chronic liver disease (CLD) are risk factors for severe COVID-19 infection and death. To further stratify these patients, increasing severity of underlying liver disease as characterized by Child-Pugh class is associated with an increased risk of morbidity. The underlying immunologic processes that can perhaps explain this phenomenon may be found in the decreased T cell response to vaccination in cirrhotic patients, as well as a > 50% reduction in Cluster of Differentiation 8 response to omicron infection that has been noted in patients with cirrhosis when compared to patients without cirrhosis, which puts this population at even higher risk of severe disease[9,10].

CO-MORBID HEPATOBILIARY CONDITIONS: SSC

There is a subset of COVID-19 patients with liver injuries who may also be at increased risk of developing SSC secondary to infection with SARS-CoV-2, generally evidenced by elevated bilirubin in the setting of typical imaging or endoscopic retrograde cholangiopancreatography findings. Several case reports and case series have suggested the possibility of a connection between COVID-19 infection and the development of SCC[11-13]. One multicenter retrospective study of 127 patients diagnosed with SSC identified 16.7% of the patients as having a recent COVID-19 infection[14]. In a recent retrospective study published in the *Journal of Hepatology* by Hartl *et al*[15], researchers compared liver injury parameters between patients admitted for COVID pneumonia *vs* those admitted for non-COVID pneumonia[15]. They found that patients with CLD and COVID-19 pneumonia had increased rates of prolonged and progressive cholestasis and cholestatic liver failure. Additionally, in their study, 15.4% of patients with CLD (10/65) developed SSC in COVID pneumonia compared with 4.6% (3/65) in patients with CLD and non-COVID pneumonia ($P < 0.05$). Patients with NASH/NAFLD were also at increased risk of developing SSC after COVID-19. These results suggest a connection between COVID-19 infection and the development of SSC. Additional studies are needed to elucidate the pathophysiology and mechanism for this phenomenon.

CO-MORBID HEPATOBILIARY CONDITIONS: AIH

AIH is an immune-mediated disorder of unclear etiology. Triggers include infections, medications, and toxins. Upon review of selected articles, an increased incidence of AIH following COVID-19 vaccination was noted. A retrospective meta-analysis by Chow *et al*[16] found that a rare adverse event which presented as AIH -like syndrome was seen after receiving COVID-19 vaccinations[16]. A total of 32 cases of COVID-19 vaccine-induced AIH-like syndromes were identified. These patients typically presented with jaundice (81%), and approximately 19% of patients were asymptomatic and presented with elevated liver enzymes detected during routine blood work. Antinuclear antibody was positive in 56% of patients and anti-smooth muscle antibody was positive in 28%. The prognosis of AIH secondary to COVID-19 vaccination is excellent, and complete resolution was seen in 97% of patients, of which 75% had received steroids.

Subsequently, upon further literature review, a case series showed an association between COVID-19 infection and the development of AIH[16]. Potential antigenic cross-reactivity exists between SARS-CoV-2 and human tissue, which increases the possibility of development of autoimmune disease after COVID-19 infection. The study showed that antibodies against the spike protein S1 on SARS-CoV-2 had a high affinity for human tissues (transglutaminase, Myelin basic protein)[16]. In previously published case reports, most patients who developed these antibodies were female, aged 35 to 80. One particular case report we reviewed involved a 61-year old female with underlying history of Hashimoto's thyroiditis and hypertension who developed AIH 1 mo after administration of the Pfizer/BioNTech BNT162b2 vaccine. She presented with a constellation of symptoms including: malaise, anorexia, nausea, and scleral icterus for two weeks. The patient has no history of liver disease or alcohol abuse, nor has used any hepatotoxic drugs or supplements. She was diagnosed with mild COVID-19 infection 8 mo prior and received the Pfizer/BioNTech BNT162b2 vaccine one month prior. Laboratory studies were significant for alanine aminotransferase (ALT) 455 IU/mL [upper limit of normal (ULN) 55 IU/mL]; aspartate aminotransferase 913 IU/mL (ULN 34 IU/mL); gamma glutamyl transferase 292

IU/mL (ULN 36 IU/mL); alkaline phosphatase 436 IU/mL (normal range: 40–150 IU/mL); total bilirubin 11.8 mg/dL (ULN 1.2 mg/dL); direct bilirubin 9.18 mg/dL (ULN 0.5 mg/dL) along with positive anti-nuclear and anti-smooth muscle antibody titers. Upon diagnosis, the AIH patient was given prednisone and had complete resolution of her liver function abnormalities. Most patients presenting with AIH post COVID-19 vaccinations had similar age, presentation, and laboratory values as the case discussed above. This particular case used a simplified AIH score to diagnose the patient. The use of such a scoring system would prove to be efficacious in patients presenting with AIH symptoms post- COVID-19 vaccination[17].

Individuals with preexisting AIH and interactions with COVID-19 infection were another population that was reviewed. A retrospective multicenter cohort study in Europe and the Americas studied the severity of COVID-19 infection in patients with CLD with and without preexisting AIH[18]. To limit bias, the patients with AIH were compared to a propensity score–matched cohort of COVID-19 patients without AIH but with CLD. The study included 110 AIH patients, of which 80% were female, with a median age of 49. Twenty-nine percent of the patients with AIH already had features of liver cirrhosis prior to the COVID-19 infection. They observed new-onset liver injury in 37.1% of the patients and found that continued use of immunosuppressants during COVID-19 was associated with a lower rate of liver injury at an odds ratio of 0.26 (95%CI: 0.09-0.71, $P = 0.009$)[18]. However, the use of antivirals was associated with new-onset liver injury with an odds ratio of 3.36 (95%CI: 1.05-10.78, $P = 0.041$)[18]. Interestingly, there was no difference in the rates of severe COVID-19 and all-cause mortality between AIH and non-AIH CLD patients. Based on this study, the maintenance of immunosuppressive therapy in COVID-19 patients with AIH did not increase the severity of COVID-19 disease but lowered the rate of new-onset liver injury. This is in contrast to the use of antiviral agents that have been found to be associated with new-onset liver injury[18]. However, caution should be exercised in describing a causal relationship between these factors, as an exact mechanism has yet to be fully explored.

CO-MORBID HEPATOBILIARY CONDITIONS: NAFLD/NASH

The United States is currently experiencing the COVID-19 pandemic, while also suffering from an epidemic of NASH. Many common comorbid conditions, such as type 2 diabetes mellitus, chronic obstructive pulmonary disease, hypertension, and cardiovascular disease, have been widely studied and shown to play a role in COVID-19 mortality. Metabolic syndromes like NAFLD and its sequelae, NASH, should also be considered among these comorbid conditions as their prevalence is rapidly rising. Liver injury and subsequent fibrosis caused by the accumulation of fat in the liver could exacerbate the cytokine storm associated with SARS-CoV-2 infection, possibly leading to poor outcomes in these patients[19]. This can be evidenced by the presence and degree of liver injury with poorer outcomes in the NAFLD/NASH population compared with the general population infected with SARS-CoV-2. In our literature search, we found five studies that have evaluated the effect of underlying NAFLD on COVID-19- induced liver injury and mortality. The first is a prospective cohort study that concluded that NAFLD diagnosis was not associated with worse outcomes in patients hospitalized with COVID-19 [20]. However, the NAFLD group of patients had a higher average C-reactive protein level compared with the non-NAFLD group, suggesting that there was a more pronounced inflammatory response in the NAFLD group. The second study used the NAFLD fibrosis score (NFS) in 86 patients with COVID-19 and underlying NAFLD to determine its association with COVID-19 mortality[21]. 44.2% of these patients had advanced liver fibrosis, according to the NFS. It was shown that there was a statistically significant association ($P < 0.05$) between advanced NFS score and severe illness from COVID-19 in these patients compared with the general population. Through a pooled analysis, the third study found that NAFLD was associated with an increased risk of severe COVID-19, even after adjusting for obesity as a possible confounder[19]. The fourth study used Fibrosis-4 index (FIB-4) scores of a cohort of 310 patients with confirmed COVID-19 infection and NAFLD to determine their association[22]. The authors concluded that the severity of COVID-19 illness was markedly increased among patients with NAFLD and intermediate to high FIB-4 scores. Using large-scale TSMR analyses and genome-wide meta-analysis of the United Kingdom biodata bank, the last study determined that there was no causal relationship between NAFLD, serum ALT, grade of steatosis, NAFLD Activity Score, and fibrosis stage with severe COVID-19[23]. The emergence of the NAFLD epidemic and the scale of the COVID-19 pandemic greatly emphasize the importance of understanding these conditions together through further studies.

CO-MORBID HEPATOBILIARY CONDITIONS: LIVER TRANSPLANTATION

Patients with solid organ transplants are a special population to be considered in the setting of COVID infection due to their immunosuppressant medications. Of particular interest to our review are patients who have undergone liver transplantation. While limited in quantity, data reviewed from COVID-Hep, SECURE-Cirrhosis registries suggest that transplant recipients faced an approximately 37.5% fatality

rate[24]. However, another Spanish prospective cohort study found that these patients had similar fatality rates to control groups[25]. Overall, these differences in study findings suggest poor statistical power as data on these populations is not readily available.

SPECIAL POPULATIONS: PREGNANCY

Liver dysfunction affects approximately 3% of all pregnant women and has been linked to premature delivery, low birth weight, and stillbirth[26]. Recent literature suggests that the incidence of more severe liver disease in pregnancy, such as acute fatty liver of pregnancy and hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome, is higher than previously reported[27]. This is further complicated by the increased incidence of liver disease in pregnancy patients with concurrent COVID-19 infection. Possible mechanisms of liver injury in these patients include multiorgan microvascular injury, sequelae of a genetic mitochondrial fatty acid oxidation disorder, or a purely immunological process[28]. An immunologic process wherein elevated IL-6 and tumor necrosis factor-alpha could contribute to endothelial dysfunction and genetic polymorphisms of toll-like receptor 4 and, in turn, could dysregulate maternal inflammatory processes, may explain or partially explain the observation[29]. Understanding this process is important in understanding the possible effect of COVID-19 as an inciting or confounding factor for liver injury during the peripartum period. In a 2020 double cohort study, Chai *et al*[30] discussed SARS-CoV-2 virus affinity for ACE2 on cholangiocytes, resulting in subsequent dysfunction of liver regeneration and immune responses[30]. COVID-19 infection has been reported to increase the risk of pregnancy complications such as eclampsia, preeclampsia, and HELLP syndrome [31]. In a retrospective study, Deng *et al*[32] reported a 29.7% prevalence of liver injury in pregnant women who were infected with SARS-CoV-2[32]. A meta-analysis also showed significantly increased odds of developing HELLP syndrome in pregnant patients with COVID-19 compared to those who did not have COVID-19 infection[33]. The pathophysiology of the effect of COVID-19 on liver function is still unclear but may be linked to an immunologic process, as mentioned above. The studies reviewed in our literature search almost unanimously concluded that there is an increased incidence and severity of maternal and fetal complications amongst pregnant women with COVID-19.

SPECIAL POPULATIONS: OBESITY

Obesity is a known independent risk factor for COVID-19. Metabolic syndrome is associated with poor outcomes related to liver injury in COVID-19. We reviewed six articles concerning liver injury in obese patients with COVID-19. While there were many articles on the effect of metabolic syndrome on liver injury in COVID-19, many did not study the isolated role of obesity in liver injury from COVID-19. Ultimately, we had three articles that met our inclusion criteria in this review. A retrospective analysis of COVID-19 patients admitted to a hospital in Northern Italy revealed that 18.6% of the obese COVID-19 patients had liver injuries[34]. These numbers appear to be higher in those with underlying metabolic syndrome, especially those with NAFLD, due to an inflammatory mechanism of injury, as discussed earlier in this article. Mechanisms of liver injury in obese patients with COVID-19 may derive from the adipocytes themselves and/or from secondary syndromes of obesity. Adipocytes have similar functions to immune cells and produce inflammatory mediators, which in conjunction with the cytokine storm from SARS-CoV-2, may contribute to superimposed direct injury of the liver and other organs[35]. Sleep apnea syndrome caused by obesity can lead to hypoxia and subsequent anoxic injury to the liver[36]. However, more studies need to be conducted on this subject to definitively note the role of obesity in liver injury in COVID-19 patients. The effects of the environmental and habitual changes, including social distancing, sedentary lifestyles, and school and work closures brought out by the pandemic must also be taken into account. According to a retrospective study by Gwag *et al*[37] of school-aged children in Korea, the proportion of children who were overweight or obese increased from 24.5% at the COVID-19 pandemic baseline to 38.1% 1 year later[37].

SPECIAL POPULATIONS: RACIAL DISPARITIES

COVID-19 affects certain racial groups differently, especially within the Hispanic and African American communities. There were various studies that explored the effects and aftermath of the COVID-19 infection in diverse groups. A microsimulation study was done to estimate individual risks using data collected from the Health and Retirement Study, Panel Study of Income Dynamics, Centers for Disease Control and Prevention, and the Center for Medicare and Medicaid Services[38]. The study used the future elderly model and the future adult model and had a target population of United States individuals aged 25 years and older who had COVID-19 through March 13, 2021. The study found that Black and Hispanic persons greater than or equal to 65 years of age had a disproportionate share of the

mortality burden, though they had a lower age-adjusted life expectancy. The study showed Hispanic men aged 65 years or older lost an average of 2.5 times more quality of life years *per* capita compared to similarly aged white men. Hispanic men aged 25 to 64 lost three times more quality of life years than other men in the same age group[38].

A recent cohort study across twenty-one American institutions involving over nine hundred United States adults with CLD and polymerase chain reaction confirmed COVID-19 showed that Hispanic Americans (25.5%) and African Americans (31.4%) were disproportionately affected[39]. These two racial minorities comprised over half (56.9%) of the hospitalized group compared to the racial majority of Non-Hispanic Whites (33.8%). The most likely root cause is multifaceted. Hispanic CLD patients were not only majority female (50.4%) but also happened to be the youngest on average. African American CLD patients had a significant prevalence of hypertension (70.1%)[39]. These findings were also evident in another retrospective study which showed that African Americans had a statistically significant increased risk (odds ratio: 2.69) of hospital admission with underlying NAFLD and COVID-19[40]. Another study in New Mexico indicated that Native Americans (NA) had an 11-fold increase in the risk of COVID-19 related hospitalizations compared to Non-Hispanic Whites, in which 77% of NAs had underlying CLD[41]. One variable to consider would be differences in socioeconomic variables amongst the Hispanic and African American groups in this study. White Americans tended to have higher rates of private insurance, while the majority of African and Hispanic Americans were enrolled in Medicaid/Medicare. White American patients tended to reside in single-family homes with an average of 1-2 residents, while Hispanic patients tended to live in multi-family homes with 5+ residents on average. In this study, both African and Hispanic Americans, on average, lived in lower-income households. The same socioeconomic discrepancy that affected Hispanics and African Americans was paralleled in the Native American population, such as crowded homes, lower-income households, and increased comorbidities such as diabetes and CLD[41].

Analyzing these studies suggests that various socioeconomic factors put certain minority groups with CLD at increased risk of contracting COVID-19 and subsequently requiring hospitalization. Over time, further studies need to be conducted to accurately assess the life years lost with each racial group in patients with CLD and COVID-19 infection.

SPECIAL POPULATIONS: DIABETES

Several studies have shown an association between diabetes and increased risk of COVID-19 severity and increased in-hospital mortality[42]. Other studies have also found evidence that diabetic patients who contract COVID-19 are at increased risk for liver injury. In a retrospective cohort study by Phipps *et al*[43], 16.7% of patients with diabetes developed elevated transaminases greater than two times the upper limits of normal[43]. Another study by Kumar *et al*[44] showed that up to 73.3% of COVID-19 patients with diabetes developed liver injuries[44]. Another recent study by Singh and Khan observed that many diabetic patients who contracted COVID-19 also have pre-existing liver disease (48% of the total of 2780 patients)[45]. This study reveals a complex relationship between patients with diabetes with pre-existing liver injury and the development of acute liver injury from COVID-19 infection.

CO-INFECTION

Since the first reported case in December 2019, the understanding and treatment of COVID-19 has experienced numerous developments. Immunosuppressants and steroids have become the leading modalities of treatment after our understanding of the pathogenesis and patient outcomes related to the cytokine-mediated immune response from the virus has evolved. However, the use of immunosuppressants and steroids to treat COVID-19 becomes a double-edged sword as patients under treatment experience reactivation of underlying chronic HBV and HCV virus infection[46]. An American study estimated that the mortality of known liver disease patients with COVID-19 was 12% compared to 4% in COVID-19 patients with no liver disease[45]. Simultaneously, a United Kingdom National Health Science study estimated that CLD was a risk factor in hospitalized COVID-19 patients with a hazard ratio (HR) of 2.39 (95%CI: 2.06-2.77)[47].

CO-INFECTION: HBV

The World Health Organization (WHO) estimates that there are 296 million individuals living with the HBV. Recent studies show that concurrent HBV and COVID-19 infections have led to worse outcomes for patients due to the increased risk of developing acute-on-chronic liver failure. One small retrospective study of 105 patients in China concluded that the increase in mortality among liver injury patients was 28.57% *vs* 3.30% in non-HBV COVID-19 positive patients[48]. Another study involving

HBV-Core antibody-positive patients showed that the risk of a hepatitis flare (ALT > 80 U/L) increased with corticosteroid 20 mg dose (HR: 2.19, $P = 0.048$) and 40 mg dose (HR: 2.11, $P = 0.015$) respectively [49]. The American Association for the Study of Liver Disease currently recommends that patients who are COVID positive and develop an acute hepatitis flare should undergo treatment promptly with antivirals[24]. A recently published clinical case review suggested that all RNA-positive COVID-19 individuals be screened for HBV markers prior to starting any treatment regiments as both may have compounding effects. If the patient is HBV surface antigen-positive, they should be prophylactically treated with entecavir and tenofovir (Disoproxil and Alafenamide) for 12 mo with routine HBV DNA testing every 3 mo. Those who are HBV surface antigen-negative or HBV core antibody negative should be viewed as low risk and monitored for any reactivation and subsequently treated with nucleotides [50].

CO-INFECTION: HCV

It's estimated that there are roughly 58 million people worldwide with chronic HCV. Since its discovery in 1989; routine testing and screening have become standard practice for any procedure involving blood transfusion, blood products donation, and assessment of high-risk individuals, such as prisoners, drug users, and health care workers. WHO estimates that roughly 70% of acute HCV infections will continue onto chronic HCV infections, while 30% will spontaneously resolve within six months. Chronic HCV is highly concerning as patients develop liver cirrhosis, liver failure, and hepatocellular carcinoma, which leads to approximately 290000 deaths worldwide in 2019[51]. Antiviral treatment has a 95% cure rate; however, the limiting factor is the lack of proper access to diagnosis and treatment. Preliminary results from an International Registry showed that patients with decompensated cirrhosis and COVID-19 had additional liver function deterioration leading to a mortality rate of 43%-63%[52]. Therefore, a recent Italian Joint Association statement called Alliance against Hepatitis recommends starting joint HCV/COVID-19 screening, allowing for prompt HCV treatment[53]. However, if the patient is COVID-19 positive, it is recommended that direct-acting antivirals for treating chronic HCV be deferred until they test negative for the COVID-19 vital antigen *via* nasopharyngeal swab[54].

All these factors will need to be studied further to assess if the WHO Global Hepatitis initiative to eliminate viral hepatitis globally by 2030 is still feasible. One annual global model outcome study involving 110 nations concluded that a single-year delay in viral hepatitis elimination led to an additional 44800 deaths due to Hepatocellular Carcinoma and 72300 hepatic-related deaths over the next 10 years[55]. With the onset of the COVID-19 pandemic, healthcare systems have drastically reduced the critical screening protocols for viral hepatitis, thus leaving more patients undiagnosed with hepatitis. However, with the recent policy and healthcare system changes, the mass-testing and telemedicine infrastructure stemming from the COVID-19 pandemic could ultimately help to curb viral hepatitis.

FUTURE DIRECTIONS OF RESEARCH

In our review of current literature, it appears that a complex relationship exists between COVID-19 and the development of hepatobiliary injury. However, a clear causative relationship remains unclear, and higher quality studies are required to better characterize the relationship between COVID-19 and its effects on the hepatobiliary system. Future research must answer the question of whether hepatobiliary comorbid conditions lead to worsening liver injury in COVID-19 patients or COVID-19 infections lead to acute and chronic liver injury regardless of underlying comorbidities. For example, a future study design can compare COVID-19 patients with mild, moderate, and severe CLD with patients with no prior diagnosis of CLD and determine the rates of liver injury in each group to assess if a linear relationship exists between CLD and the development of liver injury in COVID-19 patients.

Another significant area of research that may provide valuable insight into viral pathology is differentiating the effects of COVID-19 variants on hepatobiliary injury to help clinicians and researchers predict the pathophysiology of future variants and sub-variants. A simple clinical query into the difference in the development of liver injury in patients infected with the delta variant compared to those infected with the omicron variant could be conducted to provide more insight.

Additionally, further studies are necessary to determine the contribution of co-morbid conditions to the difference in morbidity and mortality observed between ethnic minorities and their White American counterparts. Future studies should consider including racial ethnicities/minorities when analyzing liver injury due to COVID infection.

CONCLUSION

Since the beginning of the COVID-19 pandemic, many studies have been conducted to characterize and understand the effects of this virus. Aside from causing derangements in the respiratory system, the virus appears to have the ability to affect multiple organ systems. As case reports, case series, and multiple high-quality studies have emerged, mounting evidence shows a relationship between COVID-19 infection and the development of liver injury and hepatobiliary-related disease entities. A general concept of the possible pathways from COVID-19 infection to liver injury has been described[1,2]. However, it remains unclear which pathophysiologic pathway is the predominant mode through which COVID-19 infection leads to liver injury.

Perhaps not surprisingly, multiple studies have linked patients with pre-existing hepatobiliary conditions such as cirrhosis of the liver, NASH/ NAFLD syndromes, AIH, and liver transplant recipients as being at increased risk for developing acute and chronic liver injury from COVID-19 infection. Similarly, patients with obesity, diabetes mellitus, and pregnancy have also been shown to be predisposed to liver injury from COVID.

One interesting finding in recent COVID-19 research is the discovery of a relationship between COVID-19 infection and the development of SSC. While most studies have been case reports and case series, our review showed that some recent high-quality studies have added supporting evidence to this potential relationship. Specifically, recent studies have suggested that patients with CLD who develop severe COVID-19 are also at increased risk of developing SSC[15].

Our review further suggests that racial disparities exist between minorities (African Americans, Hispanics, NA) and White Americans in terms of morbidity and mortality due to COVID-19 infection. Although the underlying reason is complex and multifactorial, some studies have shown that minority populations are more likely to have comorbid hepatobiliary conditions, obesity, and diabetes that predispose them to acute and chronic liver injuries. Further studies are needed to characterize this complex relationship, and to describe the contribution of social determinants of health to the development of severe COVID disease and liver injury.

FOOTNOTES

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MINIREVIEWS

Cortical bone trajectory screws in the treatment of lumbar degenerative disc disease in patients with osteoporosis

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Abstract

Lumbar degenerative disc disease (DDD) in the elderly population remains a global health problem, especially in patients with osteoporosis. Osteoporosis in the elderly can cause failure of internal fixation. Cortical bone trajectory (CBT) is an effective, safe and minimally invasive technique for the treatment of lumbar DDD in patients with osteoporosis. In this review, we analyzed the anatomy, biomechanics, and advantages of the CBT technique in lumbar DDD and revision surgery. Additionally, the clinical trials and case reports, indications, advancements and limitations of this technique were further discussed and reviewed. Finally, we concluded that the CBT technique can be a practical, effective and safe alternative to traditional pedicle screw fixation, especially in DDD patients with osteoporosis.

Key Words: Lumbar degenerative disc diseases; Cortical bone trajectory screw; Anatomy; Biomechanics; Indications; Clinical trials and case reports; Advancements

Core Tip: Some reviews in the literature have provided information that contributes to the anatomy, surgical technique, and biomechanics of cortical bone trajectory screws. However, the aim of this review is to report the recent clinical trials and case reports, indications, advancements and limitations of this technique. We concluded that the cortical bone trajectory technique can be a practical, effective and safe alternative to traditional pedicle screw fixation, especially in degenerative disc diseases patients with osteoporosis.

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INTRODUCTION

The incidence of lumbar degenerative disc diseases (DDDs) in the elderly has increased in recent years. The anatomy and curvature of the spine changes significantly with age. Hegazy and Hegazy[1] confirmed the change in morphology and dimensions of lumbar lordosis in aging adults, which suggested that the anatomy and curvature need to be given more attention during surgery[1]. Additionally, osteoporosis is quite common among elderly individuals. Therefore, another key treatment strategy for lumbar DDD in the elderly is the management of osteoporosis. Osteoporosis in the elderly can cause the loosening of internal fixation. A study showed that the rate of pedicle screw loosening in patients with osteoporosis was 12.8% to 25%. Additionally, the risks of proximal and distal junctional kyphosis also increase accordingly[2]. Therefore, the stability of internal fixation in osteoporosis patients should be enhanced during the operation by employing expansive pedicle screws, bone cement screws, or cortical bone trajectory (CBT) screws. Although expansive pedicle screws can increase the intensity of internal fixation, there are clear shortcomings, such as complicated placement, a high screw breakage rate, and limited clinical application. Bone cement screws have also been gradually applied in the treatment of DDD patients with osteoporosis. Zhang *et al*[3] showed that the loosening rate of bone cement screws is less than 4.3%, but intraoperative perfusion of bone cement increased the operation time and radiation exposure. Moreover, bone cement may leak into the spinal canal and blood vessels, leading to serious complications, such as neurological dysfunction and pulmonary embolism [3]. The CBT technique was proposed by Santoni *et al*[4] in 2009. Compared with the traditional technique, the CBT technique increases the contact surface between screws and cortical bone, and all screws used in the CBT technique are surrounded by the cortical bone. Therefore, this technique is more suitable for the treatment of lumbar DDD patients with osteoporosis[4]. Furthermore, in 2014, Mizuno *et al*[5] proposed the combination of this technique with lumbar posterior midline fixation and fusion in midline lumbar fusion (MIDLF) surgery. The CBT technique in MIDLF surgery has been widely used in lumbar DDD, adjacent vertebral diseases and postoperative revision due to its low invasiveness and high safety advantages[6].

ANATOMY AND BIOMECHANICS OF THE CBT TECHNIQUE

The CBT technique is performed at the intersection of the lateral isthmus of the pedicle and the lower edge of the transverse process. The entry point is at 5 o'clock on the left pedicle and 7 o'clock on the right pedicle. The ideal trajectory of placement is along the lower edge of the pedicle with a cranial incline of 25° to 30° and an external incline of 10° to ensure the maximum contact between the screw and cortical bone (Figure 1). Although the shape of the lumbar pedicles varies in different segments, the trajectory of placement remains unchanged. Four cortical bone surfaces are contacted using the standard CBT technique in the lumbar spine, namely, the isthmus, medial wall, lateral wall of the pedicle and anterior lateral wall of the vertebral body[7]. However, CBT screws are usually shorter and thinner than conventional pedicle screws. Matsukawa *et al*[8] measured the diameter and length of CBT in the adult lumbar spine using computed tomography (CT) and concluded that the diameter of the trajectory ranged from 6.2 ± 1.1 mm (L1) to 8.4 ± 1.4 mm (L5). The length of the trajectory at each vertebra was 36.8 ± 3.2 mm (L1), 38.2 ± 3.0 mm (L2), 39.3 ± 3.3 mm (L3), 39.8 ± 3.5 mm (L4), and 38.3 ± 3.9 mm (L5)[8]. Therefore, the biomechanical stability of the CBT technique has become a popular topic in research. Kojima *et al*[7] found that the bone CT value around CBT screws was four times higher than that around traditional pedicle screws, which indicated that the bone-screw interface strength of the CBT technique was greater[9]. Li *et al*[10] also showed that the CBT technique had better fatigue resistance stability, especially in osteoporotic vertebrae[10]. However, the CBT technique is less effective against lateral bending and rotation than the conventional pedicle screw technique, which may result in a lower

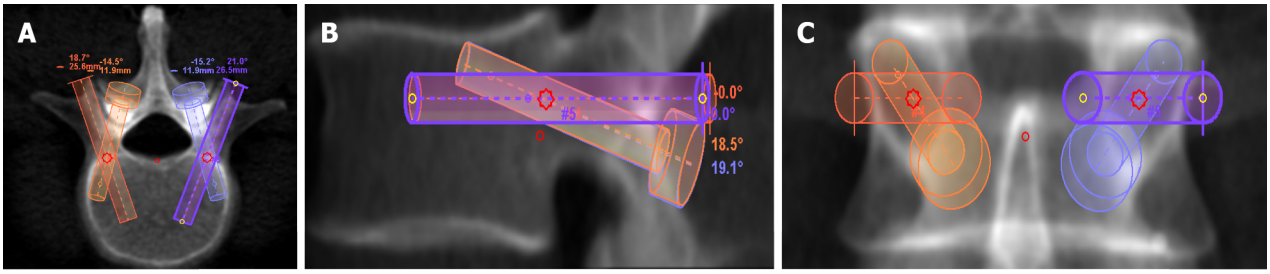

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Figure 1 Comparison of the cortical bone trajectory screw with the traditional pedicle screw trajectory. A: Axial view; B: Lateral view; C: Anteroposterior view.

interbody fusion rate using CBT screw fixation than that using traditional pedicle screw fixation[11,12]. Therefore, a transverse connection could be used to improve the anti-lateral bending and anti-rotational stability during CBT screw placement.

CBT TECHNIQUE IN LUMBAR DDD

As the CBT technique is applied closer to the posterior midline than the traditional pedicle screw technique, vertebral muscles and adjacent segment joints are less harassed; therefore, the CBT technique has many advantages, including less blood loss and fatty infiltration, a shorter hospital stay and a lower incidence of adjacent segment degeneration (ASD). Additionally, the trajectory of the CBT technique is away from important nerve and vascular tissues, which further decreases the risk of injury. The CBT technique combined with MIDLF surgery is minimally invasive and safer and has been widely used in the treatment of lumbar diseases. Studies have shown that the CBT technique combined with MIDLF in the treatment of DDD patients with osteoporosis can achieve similar clinical decompression effects to those of the traditional pedicle screw technique combined with transforaminal lumbar interbody fusion (TLIF) technology[13]. Mizuno *et al*[5] proposed that CBT screws combined with MIDLF in the treatment of patients with single-level lumbar spondylolisthesis achieved good clinical outcomes. Lumbar decompression, fixation and fusion can be completed by the CBT technique at the same time, which is in line with the concept of minimally invasive surgery. Takenaka *et al*[14] compared the CBT technique and the traditional pedicle screw technique combined with lumbar posterior interbody fusion (PLIF) in the treatment of lumbar DDD. They concluded that the operation time, intraoperative blood loss, postoperative drainage volume, bed rest time and postoperative hospital stay time in the CBT technique group were significantly lower than those in the traditional pedicle screw technique group. CBT screws combined with PLIF surgery can achieve a more minimally invasive treatment effect for DDD patients with osteoporosis[14]. Kasukawa *et al*[15] compared the clinical efficacy of CBT and conventional pedicle screw internal fixation in TLIF. They concluded that the CBT technique can achieve better clinical results, smaller incisions and faster postoperative recovery than the conventional pedicle screw technique.

CBT TECHNIQUE IN LUMBAR REVISION SURGERY

Recently, the incidence of failed back surgery syndrome and ASD has increased with the extensive application of spinal internal fixation, leading to a high proportion of lumbar revision surgeries[16]. In revision surgery, the exposure risk of the nerve structure and blood vessels is significantly increased due to hypertrophic scar tissue and unclear spinal anatomy. Another advantage of the CBT technique is the reduction in exposure risk in revision surgery. During revision surgery, the internal fixation of the original operation usually needs to be replaced when the adjacent segment is decompressed and fixed. However, the replacement of internal fixation can not only increase the operation time and surgery risk but also result in more blood loss. Therefore, decompression, fixation and fusion on the adjacent segments without removing the internal fixation of the original surgery has become a key technique for the treatment of ASD. The CBT technique, which has a unique entry point and trajectory, can complete screw placement, decompression and fusion of adjacent segments through a small incision while retaining the original internal fixation, thereby avoiding extensive dissection and reducing the operation time and risk. In addition, the CBT technique can be used to place two groups of screws in the same vertebral body[17]. A study by Takata *et al*[18] showed that the CBT technique combined with MIDLF in lumbar revision surgery has the advantages of less soft tissue injury, fewer postoperative complications and better stability of internal fixation compared with traditional revision surgery[18].

CLINICAL TRIALS AND CASE REPORTS OF USING THE CBT TECHNIQUE

We performed an online database search on PubMed using the terms "cortical bone trajectory", "clinical trials", and "case reports". Only papers published in English until June 10, 2022 were reviewed. Finally, seventeen articles were identified and included in Table 1[3,9,18-32]. There were thirteen retrospective cohort studies, two retrospective cohort comparative studies, and two prospective cohort studies. Most studies in this table indicated that the CBT technique offered good clinical outcomes with shorter incision length.

INDICATIONS FOR THE CBT TECHNIQUE

CBT screw fixation not only provides more stable internal fixation strength for patients with osteoporosis but can also be combined with a variety of minimally invasive procedures to reduce the risk of injury and intraoperative exposure. Especially for patients with obesity or diabetes, the application of CBT screw fixation can significantly reduce the incidence of postoperative complications. The following indications for CBT screw fixation were determined by comprehensive analysis of the anatomical characteristics, biomechanical characteristics and technical advantages of the CBT technique: (1) Lumbar disc degenerative diseases, especially combined with osteoporosis; (2) Obesity and high iliac crest; (3) ASD after traditional pedicle screw placement; (4) Salvage screw placement after failure of traditional pedicle screws; (5) Diseases mainly characterized by the destruction of the anterior and middle columns of the vertebral body, such as lumbar tuberculosis and intervertebral space infection; (6) Thoracolumbar fracture; and (7) Lumbar scoliosis correction and internal fixation with osteoporosis. However, CBT screw fixation is not suitable for bone destructive diseases with the absence of isthmus or spinal deformity characterized by rotation.

ADVANCEMENTS OF THE CBT TECHNIQUE

Although CBT screws are widely used in a variety of lumbar diseases, placing CBT screws is extremely demanding. Freehand techniques have a risk of exiting nerve root injury and lead to a high failure rate during screw placement. Because the anatomical entry point is hard and not evident, the placing instruments can easily slip and cause pedicle, isthmus and upper endplate injuries during surgery. The failure rate of the freehand placement technique is as high as 33.1%[33]. Second, the entry point and trajectory of the CBT technique are different from those of traditional screw placement. Surgeons cannot rely on tactile feedback to place screws, which will inevitably increase the amount of intraoperative X-ray exposure and operation time. To reduce complications and ensure screw placement safety and accuracy, researchers have begun to use 3D-printed guide plates, navigation, and robots to assist in CBT screw placement. The 3D-printed guide plate, navigation and robot-assisted placement of CBT screws successfully compensated for the disadvantages of freehand screw placement and improved the safety and accuracy of CBT screw placement for internal fixation. Marengo *et al*[34] used a 3D-printed guide plate to assist in the placement of CBT screws, and they concluded that 85.2% of the screw entry points were within 2 mm of the planned entry points. Buza *et al*[35] compared the surgical effects of MIDLF assisted by the Mazor spinal robot and free-hand MIDLF and found that the Mazor spinal robot improved the accuracy of CBT screw placement with less intraoperative blood loss and shorter hospital stays and operation times. Le *et al*[36] compared the free-hand CBT screw technique with the CBT screw technique assisted by the Tianji orthopedic surgery robot and found that the robot-assisted CBT screw technique reduced the incidence of adjacent segment facet joint injury. The accuracy of robot-assisted CBT screw placement was higher than that of the freehand group, and the acceptable screw placement in the robot-assisted group was 98.3%, which was significantly higher than that in the freehand group (84.5%). Additionally, the blood loss, operation time and radiation exposure dose of the robot-assisted group were significantly lower than those of the freehand group. Three-dimensional navigation technology is used to assist and monitor the trajectory of CBT screws in real time, which maximizes the contact between screws and the cortical bone interface and reduces the risks of screw placement (Figure 2). Navigation-assisted CBT screw placement can reduce the incidence of superior facet joint injury[17]. Khan *et al*[37] compared the accuracy of CBT screw internal fixation in the treatment of lumbar DDD with osteoporosis using a 3D guide plate, navigation and freehand[37], and they concluded that the accuracy rate of screw placement in the 3D-printed guide group and the navigation group was 100%. The accuracy rate of screw placement in the freehand group was only 87.5%. Although the application of spinal robotic and three-dimensional navigation technology has significantly improved the accuracy of CBT screw placement, there are still some shortcomings in this technology. Systematic errors are related to the patient's position change, image registration errors and screw skidding. Additionally, the angle and position of the screw may be shifted during implantation due to differences in surgeons' experience and learning curves. Therefore, it is necessary to probe the trajectory and perform intraoperative fluoroscopy to confirm the accuracy and safety of CBT screws as in the

Table 1 Clinical trials and case reports of the cortical bone trajectory screw fixation

Ref.	Country/region	Study design	Number of cases	Indication	Technique	Revision surgery	Accuracy	Outcomes	Fluoroscopy X-ray dose	Complications	Incision length
Crawford CH 3rd *et al*[19], 2019	United States	RCCS	56	Spondylolisthesis and foraminal stenosis	Navigated CBT-pedicle screw (29) traditional open TLIF (27)	NA	NA	Lower ODI and less back pain in navigated CBT group	NA	Late reoperations for adjacent segment disease were significantly greater in the traditional open TLIF group	NA
Hsu *et al* [20], 2020	Taiwan	ROS	12	Thoracolumbar osteoporotic compression fracture	Short-segment CBT instrumentation with vertebroplasty	None	NA	The average blood loss and VAS scores were significantly improved; the average sagittal Cobb angle significantly increased from 15.4° preoperatively to 18.8° postoperatively	NA	None	NA
Noh *et al* [21], 2021	South Korea	ROS	200	Spinal stenosis, spondylolisthesis, degenerative disc diseases	Open surgery with CBT screw instrumentation	5 cases with adjacent segment disease	NA	Symptom and quality of life significantly improved after surgery	NA	5 cases with ASD, 1 case with screw loosening, 8 cases with dura tear	NA
Takata *et al* [18], 2014	Japan	ROS	6	Degenerative spondylolisthesis	Hybrid CBT-pedicle screw	NA	NA	Mean operative time 175.8 min. Blood loss 70–200 mL	NA	One had a mild infection after surgery	Around5-6 cm, shorter than that of the conventional PS
Zheng *et al* [22], 2022	China	RCCS	48	Traumatic thoracolumbar fractures without neurologic defects (type A)	Percutaneous CBT (PCBT 24) OPPS 24	No	NA	VAS scores improved after operation. Blood loss and hospital stay were better in PCBT group	NA	No complications in PCBT group, four cases with complications in OPPS group	PCBT group was better than OPPS group
Petrone *et al*[23], 2020	Italy	ROS	238	Degenerative lumbosacral disease	First group: 43 cases without CT planning-Second group: 158 cases with CT planning. Third group: 37 cases with 3D printed guide	NA	Screws entirely within the cortex of the pedicle were 78.9%, 90.5% and 93.9% in the three groups	All patients' symptoms improved after surgery mean operation time was 187, 142 and 124 min in the three subgroups	NA	The total amount of complications were 4.2% (16.3%, 3.8%, 0.0% respectively)	NA
Dayani *et al*[24], 2019	United States	POS	22	Lumbar degenerative disease and spinal instability	Early experience (first 11 patients) late experience (last 11 patients)	NA	Early experience phase: 66.7% (4/6) of medial pedicle breaches; 100% of lateral vertebral body breach	Late phase: greater efficiency	NA	Incidence of complications decreased in the late phase	NA

Marengo *et al*[25], 2018	GER	ROS	101	Degenerative lumbo-sacral disease	CT planning	32 patients (31.6%)	NA	Symptom and quality of life improved after surgery; mean procedural time 187 min; mean hospital stay 3.47 days; mean blood loss 383 mL	1.60 mg cm2	4 screws misplaced; 1 wound infection; 1 pseudmeningocele	NA
Chen *et al* [26], 2018	Taiwan	ROS	6	Lumbar adjacent segment disease	C-arm guidance	Revision surgery:6 cases	NA	Symptom and quality of life improved after surgery	NA	No post-operative complication	NA
Orita *et al* [27], 2016	Japan	POS	40	Degenerative spondylolisthesis or lateral lumbar disc herniation; stenosis	Percutaneous CBT (pCBT 20); traditional PPS arms (20); C-arm fluoroscope guidance	NA	NA	Clinical outcome regarding LBP and lower limb pain improved with no significant difference between the two groups	Shorter duration of fluoroscopy in PCBT group	No complications	Shorter incision length in PCBT group
Snyder *et al*[28], 2016	United States	ROS	79	Degenerative lumbosacral disease	Navigation guide	Revision surgery: 20 cases (25.3%)	NA	Mean length of stay was 3.5 days; mean operative blood loss was 306.3 mL	NA	9 complications (8.9%) including hardware failure, pseudarthrosis, DVT, pulmonary embolism, epidural hematoma, wound infection. No complications by misplaced screws	NA
Mai *et al* [9], 2016	United States	ROS	22	Lumbar spine disease	NA	NA	NA	NA	NA	Screw loosening: 2 intra-operative dural tear: 1. Both a pedicle fracture and screw loosening: 1	NA
Ninomiya *et al*[29], 2016	Japan	ROS	21	Degenerative spondylolisthesis	Conventional PS (10) CBT (11). C-arm fluoroscope guidance	NA	NA	Symptom and quality of life improved after surgeryboth techniques showed good slip reduction	NA	NA	NA
Elmekaty *et al*[30], 2018	Sweden	ROS	59	Lumbar spondylolisthesis	MIS-PLF: 22; MIS-TLIF: 15; MIDLF: 22	NA	NA	MIDLF: shorter operation time, less bleeding amount, lower values of CRP and CK than the other two techniques; symptom and quality of life of all the patients improved after surgery	NA	Screw loosening. MIS-PLF: 10%. MIS-TLIF: 7.14%. MIDLF: 4.76%	MIDLF with a small, single posterior midline incision (3.5 cm)
Zhang *et al* [3], 2021	China	ROS	52	Lumbar tuberculosis	CBT group: 27. PS group: 25	NA	NA	All patients achieved good clinical outcomes; incision pain in CBT group is better than PS group on the 1st day and 3 rd day after surgery	NA	All patients have no intraoperative complications	NA
Wochna *et al*[31], 2018	United States	ROS	71	Traumatic thoracolumbar fractures	ORIF PS: 39; MIS PS: 20; CBT: 12	NA	NA	EBL was 337.50 mL for CBT, 184.33 mL for MIS,	NA	1 case of construct failure; 1 case of incisional site	NA

								and 503.33 mL for ORIF; LOS was 4.06 days fewer for CBT compared to ORIF		infection in the PS group; but none were found in the CBT group	
Laratta *et al*[32], 2019	United States	ROS	134	Degenerative spondylolisthesis mechanical collapse with foraminal stenosisdegenerative scoliosis adjacent segment disease	Navigation with intraoperative CT	Revision surgery: 26.9%	Accuracy rate was 98.3%. The accuracy within 1 mm of error was 99.2%	NA	NA	Lateral breaches: 3 (0.5%); medial breaches: 7 (1.1%)	NA

ROS: Retrospective cohort study; RCCS: Retrospective cohort comparative study; POS: Prospective cohort study; TLIF: Transforaminal lumbar interbody fusion; PS: Pedicle screw; CBT: Cortical bone trajectory; LBP: Lower back pain; PLF: Posterolateral fusion; MIDLF: Midline lumbar fusion; MIS: Minimally invasive spine; EBL: Estimated blood loss; LOS: Length of stay; ORIF: Open reduction internal fixation; OPPS: Open posterior pedicle screw.

conventional pedicle screw placement technique.

LIMITATIONS OF THE CBT TECHNIQUE

Although CBT screws combined with the MIDLF technique have been widely used in clinical practice, relevant studies are still lacking. (1) The screws used in various biomechanical studies have different specifications, so the results have not been uniformly concluded; (2) Most clinical studies are retrospective case studies with small sample sizes and short follow-up times. Therefore, long-term, large-sample and prospective studies are still needed to further reveal the long-term complications and long-term fusion rate; (3) CBT screws are mostly used in patients with short-segment lumbar DDD. For patients with long segments, lumbar DDD and thoracic disease are rarely reported and need further research; and (4) To date, research on the corresponding relationship between the degree of osteoporosis and the choice of internal fixation methods is limited. The focus of further studies should be the correlation between the degree of osteoporosis and various internal fixation enhancement techniques to ensure the best selection of the internal fixation under different degrees of osteoporosis.

CONCLUSION

CBT can be used as a practical and effective alternative to traditional pedicle screw fixation. It has obvious advantages in the treatment of lumbar DDD, especially in patients with osteoporosis under strict mastery of the indications and contraindications.

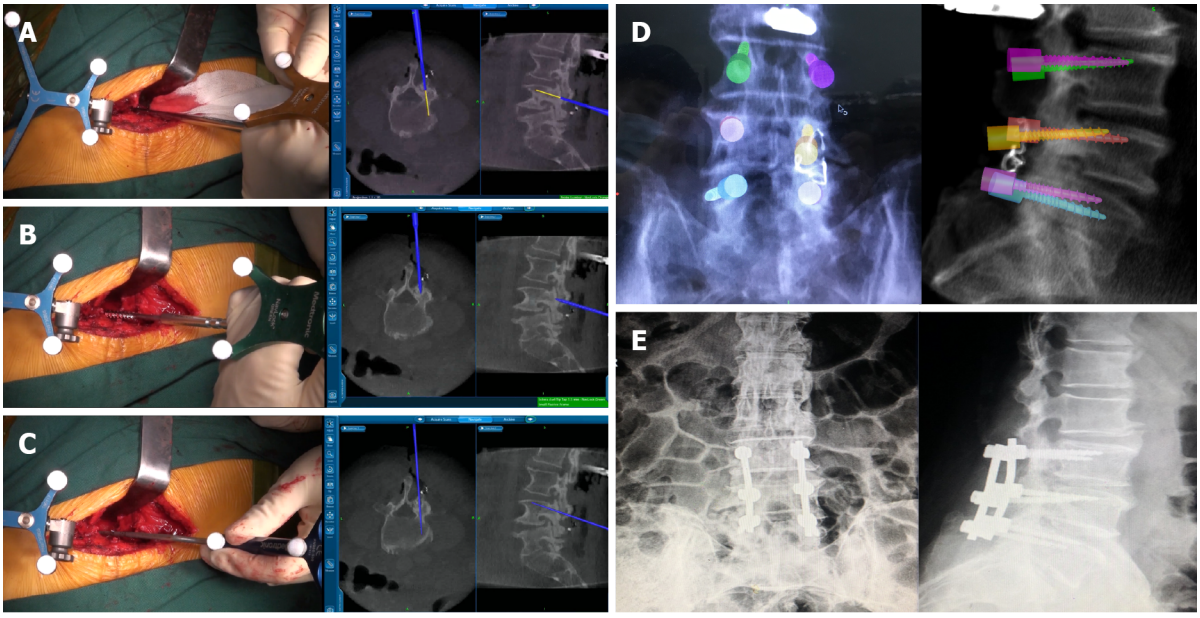

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Figure 2 Implantation of the cortical bone trajectory screw assisted by the navigation system. A: Feeling the entry point of the cortical bone trajectory (CBT) screw in L4 with the assistance of the navigation system; B: Awl of the CBT screw in L4 with the assistance of the navigation system; C: Tapping of the CBT screw in L4 with the assistance of the navigation system; D: Fluoroscopy showed the placement of CBT screws during the surgery; E: X-ray showed the implantation of CBT screws after surgery.

FOOTNOTES

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MINIREVIEWS

Probiotics for preventing gestational diabetes in overweight or obese pregnant women: A review

Ya-Fang Deng, Li-Ping Wu, Yan-Ping Liu

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Abstract

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host. Specific probiotics or probiotic foods can be used to reduce the risk of diseases associated with aberrant gut microbiota composition. The incidence of gestational diabetes mellitus (GDM) has increased annually with the proportion of overweight and obese people. Overweight or obese pregnant women are at high risk of GDM and have obvious changes in gut microbiota compared with normal-weight pregnant women. Specific probiotics or probiotic foods may alter gut microbiota in overweight or obese pregnant women and inhibit the expression of inflammatory factors, consequently resulting in weight loss and reduced insulin resistance. This review discusses the mechanism of probiotics on GDM, as well as the dose, method and duration of probiotics use, and summarizes current evidence on probiotics in improving glucose metabolism and other maternal and infant outcomes in overweight/obese pregnant women.

Key Words: Probiotics; Gut microbiota; Diabetes, Gestational; Overweight; Obesity, Maternal

Core Tip: The occurrence and progression of gestational diabetes mellitus (GDM) are associated with intestinal microbiota disorder. Probiotics modulate the gut microbiota, which can decrease lipopolysaccharide-containing microbiota in the gut and plasma lipopolysaccharides, and inhibit expression of inflammatory factors, thereby reducing insulin resistance, modulating glucose metabolism, and preventing GDM, especially in high-risk groups such as overweight/obese pregnant women. This review provides up-to-date evidence on the effects of probiotics in preventing GDM and improving glucose metabolism and other maternal and infant outcomes in overweight/obese pregnant women, and discusses the mechanism of probiotics on GDM, and the dose, method, and duration of probiotics use.

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INTRODUCTION

Probiotics are defined by the Food and Agriculture Organization of the United Nations/World Health Organization (WHO) as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host[1]. Probiotic supplementation is well tolerated and safe even in pregnant women and their children[2-5]. However, adverse effects such as stomach ache, flatulence, dystocia, amniotic fluid reduction, Crohn's disease, and headache have been reported[3,6,7]. Gastrointestinal symptoms are the most common adverse effects[3]. An increased risk of pre-eclampsia, including superimposed, has been reported after probiotic administration, in systematic reviews and meta-analyses[8-10]. However, a systematic review and meta-analysis in 2021 indicated that adverse effects associated with probiotic and prebiotic use do not pose any serious health concerns to mothers or infants[2]. As dietary adjuncts, specific probiotics or probiotic foods can be used to reduce the risk of diseases associated with aberrant gut microbiota composition, increased intestinal permeability, or altered immunological or metabolic balance[11].

The human gut microbiota is engaged in multiple interactions affecting host health during the host's entire lifespan, modulating key processes in metabolism, inflammation and immunity[12,13]. Koren *et al* [14] indicated that host-microbial interactions that affect host metabolism can occur and may be beneficial in pregnancy. During pregnancy, the gut microbiota plays a crucial role in metabolic dysfunction[15]. Maternal status is associated with alterations in the compositions and diversity of the intestinal microbiota community during gestation[15]. Maternal metabolic disorders can influence the long-term health of mothers and their offspring[15]. The composition of the gut microbiota is significantly altered in pregnant women with gestational diabetes mellitus (GDM), pre-eclampsia, abnormal placental growth, and obesity compared with healthy pregnant women[15,16]. Scientific probiotic and prebiotic supplements have positive effects on mothers and their offspring.

GDM is the diagnosis of diabetes in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation[17], and is a common complication in pregnant women that can negatively affect pregnancy outcomes and short- and long-term maternal and child health[18]. Pre- or early-pregnancy overweight or obese pregnant women are at high risk of GDM[6,19]. As the proportion of overweight and obese people has increased, the incidence of GDM has also increased annually[20,21]. WHO recommends the following international body mass index cutoff for adults[22]: Overweight = 25.0-29.9 kg/m^2 and obese ≥ 30 kg/m^2, but standards vary from country to country. A narrative review indicated that the body weight condition might be the critical factor for the effects of probiotics on GDM [23].

Current research on the use of lifestyle interventions to prevent GDM is contradictory, particularly the efficacy of prevention, which differs among obese pregnant women[24]. Some reviews or meta-analysis[25-27] showed that probiotics may reduce blood glucose level in pregnant women and prevent GDM, especially in high-risk groups including overweight or obese pregnant women[10], excessive weight gain during pregnancy, and abnormal gut microbiota[11]. Therefore, probiotics might be a new strategy for preventing GDM. We review the mechanism of probiotics on GDM, as well as the dose, method, and duration of probiotics administration, and summarize current evidence on probiotics in preventing GDM or improving glucose metabolism and other maternal and infant outcomes in overweight/obese pregnant women.

MECHENISM OF PROBIOTICS ON PREVENTING GDM IN OVERWEIGHT/OBESE PREGNANT WOMEN

Intestinal microorganisms perform many important functions; one of which is participation in metabolic processes such as the production of short-chain fatty acids (SCFAs)[28]. SCFAs mediate the transmission of signals between the microbiome and the immune system and are responsible for maintaining balance in the anti-inflammatory reaction, such as propionic and n-butyric acids produced in the large intestine by gut bacteria[29]. The level of propionic acid decreases with the course of pregnancy, while obese women have an increased level, which is associated with many metabolic adaptations[29]. Szczuko *et al* [29] showed that propionic and linear caproic acid levels can be critical in maintaining lower anthropometric parameters during pregnancy. Pregnancy stages alter the gut microbiota community structure [29]. Reduced numbers of *Bifidobacterium* and increased numbers of *Staphylococcus*, *Enterobacteriaceae*, and *Escherichia coli* were detected in overweight compared with normal-weight pregnant women[30,31]. Meanwhile, fecal *Bacteroides* and *Staphylococcus* concentrations were significantly higher and bifidobacterial counts were less in infants of overweight mothers during the first 6 mo of life compared with nonobese mothers[13]. Obese (high-fat feeding) can increase lipopolysaccharide-containing microbiota in the gut and plasma leading to a state of chronic low-grade systemic inflammation that is casually linked to insulin resistance (IR)[32,33]. A systematic review by Shirvani-Rad *et al*[34] indicated that the probiotic products could be of benefit to managing obesity when using them as an adjunct therapy at high dose.

The incidence of GDM is obviously associated with changes in the gut microbiota (increased levels of *Enterobacteriaceae* and *Enterococcus* and decreased levels of *Bifidobacteria* and *Lactobacillus*)[11,35,36]. Mokkala *et al*[37] reported that an interaction between GDM status and intervention was observed in women without GDM, which means that the evolution of the gut microbiota throughout pregnancy is influenced by GDM and dietary intervention. Specific gut microbiota species do not differ between women with and without GDM and gut microbiota is neither involved in the incidence of GDM nor differs according to GDM status. Intestinal microbiota disorder during pregnancy may interact with various pathways such as IR, chronic inflammatory reaction, endotoxemia, and energy metabolism[38]. Chronic inflammatory reaction increases IR, deceases insulin-like growth factor binding protein (IGFBP), disrupts the function of pancreatic β cells and insulin secretion, which can cause and promote progression of GDM[39]. New means to stabilize the microbial balance during pregnancy could benefit maternal health[40]. Pregnant women may benefit from gut microbiota targeted dietary supplementation[37].

The use of probiotic microorganisms to prevent and treat intestinal dysbiosis, leading to an increase in SCFAs in the colon, seems to be an important direction for further research[28]. Isolauri *et al*[11] showed that probiotics could balance the properties of aberrant endogenous microbiota, and regulate intestinal permeability and the secretion of proinflammatory mediators to control systemic and local inflammatory status and energy efficiency, which could be the underlying mechanisms of probiotics in GDM. Overweight and obese women without GDM, particularly those receiving the fish oil + probiotics combination, manifested changes in relative abundance of bacterial species over the pregnancy in a randomized controlled trial (RCT) in 2021[37]. Halkjær *et al*[41] also found that multistrain probiotics consisting of *Streptococcus thermophilus* DSM 24731, *Bifidobacteria*, and *Lactobacilli* can modulate the gut microbiota and increase α-diversity in obese pregnant women, but a larger study population is needed to determine pregnancy effects after probiotic supplementation. When the abundance of these key species began to decline, a collapse in symbiosis was observed, reflected in a deterioration in host metabolic health[42]. A systematic and meta-analysis of RCTs found that probiotic supplements reduce the level of fasting plasma glucose (FPG) and improve insulin, IR, and insulin sensitivity, especially for GDM and healthy pregnant women[42]. However, for overweight or obese pregnant women, a network meta-analysis in 2019 showed that interventions that aim to prevent GDM, such as physical exercise programs, and administration of metformin, vitamin D, and probiotics are not effective[43]. Therefore, we wondered whether probiotics may modulate the abundance of gut microbiota in overweight/obese pregnant women, which could decrease both the proportion of lipopolysaccharide-containing microbiota in the gut and plasma lipopolysaccharides[11], and they also inhibit the expression of inflammatory factors, thereby reducing IR, modulating glucose metabolism, and preventing GDM.

SPECIES, DOSE, METHOD, AND DURATION OF PROBIOTICS

Most of the probiotic properties are species- and strain-specific[11]. The properties of each probiotic strain should be well defined and cannot be extrapolated to other strains[44]. Sánchez *et al*[44] stated that it is necessary to scientifically demonstrate the efficacy of the strain in conferring a health benefit on the host, but this effect does not have to be linked to any specific mechanism of action. The most common probiotic species include *Bifidobacterium*, *Lactobacillus paracasei*, *Streptococcus thermophilus* and *Lactobacillus rhamnosus* (*L. rhamnosus*), which are also part of the normal human microbiome[45]. The main probiotics used in studies contained *Bifidobacteria* and *Lactobacilli*. It has been proven that

Bifidobacteria can encompass degradation of nondigestible carbohydrates, protect against pathogens, produce vitamin B, antioxidants, and conjugate linoleic acids, and stimulate the immune system[46]. Strains of *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* have a long history of safe and effective use as probiotics, but *Roseburia spp.*, *Akkermansia spp.*, *Propionibacterium spp.*, and *Faecalibacterium spp.* show promise for the future[47]. As another dominant genus of intestinal microbiota, *Blautia* plays some part in metabolic diseases, inflammatory diseases, and biotransformation[48]. There is a disparity in association of *Blautia* with human diseases (less in sufferers of diabetes/obesity, but more in inflammatory bowel disease)[48]. Because of the probiotic properties, the effects of different species or strains probiotics should be explored.

The dose, method, and duration of probiotics has varied among studies. The dose may have a major influence on the effect of probiotics administration. A 12-wk RCT in 81 obese postmenopausal women showed that significant favorable changes (mostly large or medium effects) in the evaluated parameters, including waist, total cholesterol, low-density lipoprotein, and insulin in the high-dose [10^{10} colony forming units (CFU)/d] and low-dose (2.5×10^9 CFU/d) groups by receiving lyophilisate powder containing several species of live probiotic bacteria[49]. The high-dose, low-dose, and placebo groups showed significant differences in lipopolysaccharide levels, glucose, insulin, and homeostasis model assessment of IR (HOMA-IR)[49]. Using the multispecies probiotic Ecologic® Barrier favorably in a dose-dependent manner can have beneficial effects[49]. The meta-analysis by Zheng *et al*[50] indicated that the dose or CFU of a probiotic is an important factor in the efficacy of probiotic supplementation on metabolic health in pregnant women, and a dose > 10^7 CFU probiotic counts can show beneficial effects. For overweight/obese pregnant women, the dose of probiotic may be not less than 10^9 CFU/d[3,6,41,51].

Diet is a principal driver of gut fermentation and therefore can influence functionality of the indigenous microbiota[47]. The combination of dietary probiotics and probiotic supplements might reduce the risk of GDM and larger birth size because of the synergy between a probiotic-rich diet and probiotic supplements[37,52,53]. Luoto *et al*[53] studied the safety and efficacy of perinatal probiotic-supplemented dietary counseling (additionally intensive dietary counseling complying with current recommendations at every study visit provided by a nutritionist, combined with conventional food products with favorable fat and fiber contents for use at home) in normal weight pregnant women. The intervention group (probiotics + diet) had a reduced frequency of GDM compared with the diet/placebo and control groups. However, probiotics combined with diet in overweight/obese pregnant women for the prevention of GDM were not investigated in that study. Mokkala *et al*[37] indicated that overweight and obese women without GDM may benefit from dietary modulation through gut microbiota modulation.

Specific probiotics or probiotic foods were mainly administered orally in ice-stored probiotic capsules or probiotic yogurt, and one study reported that two participants stopped taking the capsules because they were difficult to swallow[41]. Asgharian *et al*[6] showed some beneficial effects on glucose metabolism in overweight and obese pregnant women by using probiotic yogurt, whereas no significant differences were found in other studies provided with probiotic capsules[3,41,51,54,55]. A review reported daily consumption of 200 g yogurt containing *Lactobacillus gasseri* (10^8 CFU/g) for 12 wk significantly reduced abdominal obesity[39]. According to a study by Homayoni *et al*[56], foods are better carriers of probiotics than supplements are. In the study by Lindsay *et al*[55], obese pregnant women were required to take probiotics after meals, which may have reduced the possibility of adverse gastrointestinal symptoms. Other similar studies did not report the specific time of probiotic supplementation. Some researchers recommended the administration of probiotic capsules with a glass of cold water or milk (avoiding acidic or hot drinks), to keep the strain active[7].

The cointervention of multiple alive bacteria strains on preventing and treating metabolic diseases could be a promising method of treatment[23]. Prebiotics are defined in 2017 as "a substrate that is selectively utilized by host microorganisms conferring a health benefit," which is a popular dietary approach to the modification of the gut microbiota to improve host health[47,57]. Prebiotics such as inulin-type fructans and arabinoxylan oligosaccharides can be consumed to increase the number of *Bifidobacteria* and cause butyrogenic effects in the human colon, which are the result of crossfeeding interactions between *Bifidobacteria* and butyrate-producing colonic bacteria[46]. Butyrate is an essential metabolite in the human colon, as it is the preferred energy source for the colonic epithelial cells, and contributes to the maintenance of the gut barrier functions, and has immunomodulatory and anti-inflammatory properties[46]. Butyrate and propionate regulate glucose metabolism by stimulating the process of intestinal gluconeogenesis[29]. Personalized nutrition and precision medicine are beginning to influence the application of probiotics and prebiotics[58]. Synbiotics are a mixture comprising live microorganisms and substrates selectively utilized by host microorganisms that confers a health benefit on the host, which is better than prebiotics alone[59]. Studies also showed that probiotics and prebiotics (synbiotics) were used to modulate the maternal gut microbiome composition, which might enhance probiotic survival and growth better than probiotics alone[39,52]. A narrative review by Li *et al*[23] reported that novel food-processing strategies like enzyme-modified prebiotics and probiotic-fermented natural foods have been developed to enhance the beneficial effects on alleviating metabolic diseases.

At present, all studies on the use of probiotics in overweight/obese pregnant women start from the second or third trimester of pregnancy. The commencement of probiotics in the first trimester would be

important to explore in future research, but Callaway *et al*[51] believes that this poses practical difficulties in routine clinical practice. Xie *et al*[10] showed that longer duration (≥ 8 wk) of probiotics had a more significant preventive effect on GDM. Whether and which species, dose, method, and duration of probiotics administration will affect the prevention of GDM or improve glucose metabolism and maternal and infant outcomes remain to be further explored.

EFFECTS OF PROBIOTICS ON GLUCOSE METABOLISM IN OVERWEIGHT/OBESE PREGNANT WOMEN

A few studies have used probiotics in overweight/obese women in the second and third trimester of pregnancy to reduce FPG at 24-28 wk of gestation and the incidence of GDM (the diagnostic criteria for GDM vary among different studies). The results of these studies on FPG are inconsistent, and no significant differences on the incidence of GDM between the groups were observed (Table 1). Lindsay *et al*[55] reported that probiotic capsules (*L. salivarius* UCC118) in obese pregnant women at 24-28 wk gestation do not reduce maternal fasting glucose or the incidence of GDM, and longer administration may be required for any probiotic effect to be exerted. The probiotics [*L. rhamnosus* and *B. animalis* subsp. *lactis* (BB-12)] used in the SPRING prospective double-blind randomized trial also did not prevent GDM in 433 overweight and obese pregnant women, who started taking probiotic capsules from 20 wk gestation to delivery[51]. However, they noted a higher fasting glucose level in the probiotics group. Although they used identical probiotics to Luoto *et al*[53], dietary counseling may have played a key role. However, Asgharian *et al*[6] showed that probiotic yogurt [*Lactobacillus acidophilus* (*L. acidophilus*) La5 and *Bifidobacterium lactis* Bb12, 5×10^{10} CFU/d] provided from 24 wk gestation to delivery decreased FPG and 2 h PG oral glucose tolerance test at 28 wk gestation in overweight and obese women, which may be related to the species of probiotic bacteria and the viable count in probiotic yogurt. Different strains of probiotics (*Lactobacilli* and *Bifidobacteria*) may also affect the results. Halkjær *et al*[41] provided multistrain probiotics that increased the gut microbiota diversity in obese pregnant women, but there was no significant difference in GDM and gestational weight gain (GWG). Further studies in different settings with a larger number of participants are recommended. Pellonperä *et al*[3] reported that fish oil and/or probiotics during pregnancy did not lower the risk of GDM or improve glucose metabolism in 439 overweight and obese women. In high-risk pregnant women, Shahriari *et al*[7] provided probiotic capsules containing a mixture of *L. acidophilus* LA1, *Bifidobacterium longum* sp54 cs, and *Bifidobacterium bifidum* sp9 cs, and the results showed that probiotics supplementation from the first half of the second trimester up to 24 wk of pregnancy did not reduce the risk of GDM. Further studies should focus on the effect of probiotics on the incidence of GDM in high-risk pregnant women.

The effect of probiotics on preventing GDM in overweight or obese pregnant women has been the subject of debate in current systematic reviews and meta-analysis[9,10]. The study by Chu *et al*[9] found that there were no significant differences between probiotics and placebo on GDM and suggested that probiotics were not a promising approach to prevent GDM and promote the health of subsequent generations. However, the latest meta-analysis carried out in China reported that probiotics can effectively prevent GDM in overweight and obese pregnant women[10]. As the number, sample size and quality of studies have been limited, more well-designed large trials are needed for better meta-analyses.

IR during pregnancy is the pathogenetic basis of GDM, and increased levels of microinflammatory factors are one of the main manifestations of IR[18]. Related studies measured HOMA-IR and C-peptide as secondary outcomes[3,55], which increased from early to date pregnancy in all intervention groups, and there were no significant differences between the different groups. From the same RCT as Pellonperä *et al*[3], Houttu *et al*[60] measured high-sensitivity C-reactive protein (hsCRP), matrix metalloproteinase (MMP)-8, phosphorylated insulin-like growth factor binding protein-1 (IGFBP-1), IGFBP-1 and vaginal MMP-8 in the different intervention groups and in all of the overweight/obese pregnant women. IGFBP, which may affect the development of GDM, differed significantly between women with or without GDM. The increased level of microinflammatory factors is one of the main manifestations of IR, which is mainly a chronic inflammatory reaction centered on the release of proinflammatory factors such as interleukin-6 and tumor necrosis factor α[18]. Glycoprotein acetylation (GlycA) is a composite nuclear magnetic resonance biomarker of systemic inflammation, including α1-acid glycoprotein, touchglobin, α1-antitrypsin, α1-antichymotrypsin and transferrin[61,62]. Mokkala *et al*[63] indicated that GlycA reflects gut microbiome diversity and is more accurate than hsCRP in reflecting metabolomic profile. Thus, proinflammatory factors, IGFBP and GlycA can be added as indicators to observe IR.

Administration of specific probiotics from the second and third trimester of pregnancy can enrich the diversity of gut microbiota in obese pregnant women, but the effect on reducing fasting blood glucose in overweight/obese pregnant women is still controversial and no positive findings on preventing the incidence of GDM were observed in these trials. As a result of strain specificity, different strains, dose, method, and duration of diverse probiotic species, as well as the influence of combining dietary

Table 1 Use of probiotics in the prevention of gestational diabetes and infant outcomes in overweight and obese pregnant women

Ref.	Participant	Strain	Dosage	Administration method	Administration duration	Sample size	Results
Lindsay *et al*[55], 2014	BMI 30.0-39.9 kg/m^2	*Lactobacillus salivarius* UCC118	10^9 CFU/d	Probiotic or placebo capsules refrigerated after a meal	24-28 wk gestation	175 (IG: 63; CG: 75)	FPG (probiotic: 4.60 mmol/L; placebo: 4.69 mmol/L, P = 0.391). Insulin (probiotic: 15.63 mU/L; placebo: 16.88 mU/L, P =0.16). HOMA2-IR (probiotic: 3.26; placebo: 3.53, P = 0.16). C-peptide (probiotic: 3.32 ng/mL; placebo: 3.37 ng/mL, P = 0.184). Total cholesterol (probiotic: 6.33 mmol/L; placebo: 6.60 mmol/L, P = 0.571). Total GWG (probiotic: 11.1 ± 6.2 kg *vs* placebo: 9.4 ± 5.6 kg, P = 0.479). PE (probiotic: 4.8%; placebo: 2.7%, P = 0.09)
Asgharian *et al*[6], 2020	Pre- or early-pregnancy BMI ≥ 25 kg/m^2	*Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12	100 g/d (5×10^8 CFU/g)	Probiotic or conventional yoghurt refrigerated	24 wk of gestation until delivery	130 (IG: 64; CG: 64)	FPG (probiotic yoghurt: 74.8 mg/dL; conventional yoghurt: 77.9 mg/dL, P = 0.008). 1 h OGTT (probiotic yoghurt: 128.0 mg/dL; conventional yoghurt: 136.0 mg/dL, P = 0.071). 2 h OGTT (probiotic yoghurt: 103.9 mg/dL; conventional yoghurt: 115.5 mg/dL, P = 0.002). GDM (probiotic yoghurt: 9%; conventional yoghurt: 17%, P = 0.184). Preeclampsia (probiotic yoghurt: 2%; conventional yoghurt: 0, P = 0.997). Preterm birth (probiotic yoghurt: 5%; conventional yoghurt: 13%, P = 0.077). Cesarean delivery (probiotic yoghurt: 52%; conventional yoghurt: 35%, P = 0.695). Total bilirubin on days 3-5 after birth (probiotic yoghurt: 9.1 mg/dL; conventional yoghurt: 11.3 mg/dL, P < 0.001). Treatment for hyperbilirubinemia (probiotic yoghurt: 36%; conventional yoghurt: 59%, P = 0.001). Phototherapy for hyperbilirubinemia (probiotic yoghurt: 16%; conventional yoghurt: 42%, P = 0.001)
Callaway *et al*[51], 2019	BMI > 25 kg/m^2	*Lactobacillus rhamnosus* (LGG) and *Bifidobacterium animalis* subsp. *lactis*(BB-12)	10^9 CFU/d	Probiotic or placebo capsules	Recruitment (12-20 wk of gestation) until birth	433 (IG: 207; CG: 204)	GDM (probiotic: 18.4%; placebo: 12.3%, P = 0.184). FPG (probiotic: 79.3 mg/dL; placebo: 77.5 mg/dL, P = 0.049). PE (probiotic: 9.2%; placebo: 4.9%, P = 0.09). 28 wk diastolic BP (probiotic: 66.4 mmHg; placebo: 65 mmHg, P = 0.070). Excess weight gain (probiotic: 32.5%; placebo: 46%, P = 0.01). SAG < 10^{th} percentile (probiotic: 2.4%; placebo: 6.5%, P = 0.042)
Pellonperä *et al*[3], 2019	BMI ≥ 25 kg/m^2	*Lactobacillus rhamnosus* HN001 and *Bifidobacterium animalis* subsp. *lactis* 420	10^{10} CFU/d	Probiotic or placebo capsules refrigerated	13.9 ± 2.1 wk of gestation until 6 mo postpartum	439 (fish oil + placebo: 109; probiotics + placebo: 110; fish oil + probiotics: 109; placebo + placebo: 110)	-GDM (fish oil + placebo: 32.5%; probiotics + placebo: 28.4%; fish oil + probiotics: 36.9%; placebo + placebo: 36.9%, P = 0.59). Insulin (fish oil + placebo: 8.0 mU/L; probiotics + placebo: 5.5 mU/L; fish oil + probiotics: 6.6 mU/L; placebo + placebo: 6.4 mU/L, P = 0.16). HOMA2-IR (fish oil + placebo: 0.98; probiotics + placebo: 0.65; fish oil + probiotics: 0.80; placebo + placebo: 0.75, P = 0.12). SAG < 10^{th} percentile (fish oil + placebo: 7.6%; probiotics + placebo: 7.3%; fish oil + probiotics: 8.7%; placebo + placebo: 9.8%, P = 0.93)
Okesene-Gafa *et al* [4], 2020	BMI ≥ 30 kg/m^2	*Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB12	6.5×10^9 CFU	Probiotic or placebo capsules	Recruitment (12-17 wk) until birth	230 (IG: 115; CG: 115)	Excess weight gain (probiotic: 82.4%; conventional: 73.4%, P = 0.08). GDM (probiotic: 26.7% *vs* placebo: 27.5%, P = 0.80). Birthweight (probiotic: 3684 g *vs* placebo: 3504 g, P = 0.08)
Halkjær *et al*[41], 2020	BMI ≥ 30 and < 35 kg/m^2	Probiotic mixture Vivomixx® (*Streptococcus thermophilus* DSM 24731,	450×10^9 CFU/d	Probiotic or placebo capsules refrigerated	14-20 wk of gestation until delivery	50 (IG: 25; CG: 24)	Total GWG (probiotic: 12.7 ± 5.3 kg *vs* placebo: 13.1 ± 5.8 kg, P = 0.82). Intervention period weight gain (probiotic: 10.2 ± 3.4 *vs* placebo: 10.0 ± 4.2, P = 0.87). Birthweight (probiotic: 3608 g *vs* placebo: 3640 g, P = 0.82). GDM

		bifidobacteria and lactobacilli)					(probiotic: 16% *vs* placebo: 8%, $P = 0.67$)
Shahriar *et al*[7], 2021	High-risk pregnant women for GDM including BMI > 25 kg/m^2	Mixture of *Lactobacillus acidophilus* LA1, *Bifidobacterium longum* sp54 cs, and *Bifidobacterium bifidum* sp9 cs	500 mg/d, 9.6×10^9 CFU	Probiotic or placebo capsules with a glass of water or milk (acidic or hot drinks were avoided)	14 wk of pregnancy up to 24 wk	542 (IG: 241; CG: 266)	GDM (probiotic: 41.9% *vs* placebo: 40.2%, $P = 0.780$). PE (probiotic: 17.8%; placebo: 17.3%, $P = 0.87$)

BMI: Body mass index; CFU: Colony forming unit; CG: Control group; FPG: Fasting plasma glucose; GDM: Gestational diabetes mellitus; GWG: Gestational weight gain; HOMA-IR: Homeostasis model assessment of insulin resistance; IG: Intervention group; OGTT: Oral glucose tolerance test; PE: Preeclampsia; SGA: Small for gestation age.

counseling on their interventional effects should be extensively studied in the future. We suggest that further studies should increase the sample size and study population, provide comprehensive details of the study design, and be conducted in more high-risk GDM groups.

Table 1 summarizes the effects of probiotics on GDM in studies conducted in overweight and obese pregnant women. GDM is diagnosed by the criteria of the International Association of The Diabetes and Pregnancy study Group in the table.

EFFECTS OF PROBIOTICS ON OTHER MATERNAL AND INFANT OUTCOMES IN OVERWEIGHT/OBESE PREGNANT WOMEN

Taking probiotics can modulate the diversity of gut microbiota in obese pregnant women, and may even affect infants' gut microbiota, which may have a positive impact on their growth and health[11,64]. The previous research mentioned noted that probiotics may reduce GWG, the mean neonatal total serum bilirubin (TSB) on days 3-5 after birth and small for gestation age (SGA) infants in overweight/obese pregnant women, while other outcomes were not significantly different.

Maternal outcomes

Other maternal outcomes besides glucose metabolism include GWG, pre-eclampsia, hypertensive disorders of pregnancy, cesarean delivery, postpartum hemorrhage, and lipid metabolism (cholesterol content). In overweight/obese pregnant women, Callaway *et al*[51] showed lower rates of GWG in women in the probiotics group, but there were no differences in overall weight gain between the groups or weight gain per week. Maternal overweight/obesity and excessive GWG were associated with reduced diversity of gut microbiota[65]. Halkjær *et al*[41] conducted an intention-to-treat and per protocol analysis that showed a lower GWG during the intervention period and increased α-diversity of gut microbiota in the probiotic group compared with the placebo group, although this difference in GWG did not reach significance, possibly because of the small sample size. The administration of probiotics may reduce body weight, although the effect sizes are small[31,66,67]. However, the latest systematic reviews and meta-analyses in 2022 showed that there were no significant differences between probiotics and placebo on excess weight gain in overweight/obese pregnant women[9,10].

The administration of probiotics can reverse alterations or dysregulation of the gut microbiota[68] and decrease both the proportion of lipopolysaccharide-containing microbiota in the gut and plasma lipopolysaccharides. However, there is insufficient evidence to support the role of probiotics in improving blood lipid profile in overweight/obese pregnant women. Lindsay *et al*[55] observed no effect of probiotic intervention on the lipid concentration after administration of probiotics, while the total cholesterol, low density lipoprotein, and triglycerides were lower. Probiotics may be associated with a slight reduction in triglycerides and total cholesterol in treating women with GDM[4]. The increased risk of pre-eclampsia (high-quality evidence) and hypertensive disorders of pregnancy with probiotics reported by Davidson *et al*[8] should be noted. There were few differences between the groups in terms of other outcomes such as cesarean section rate and postpartum hemorrhage.

Neonatal outcomes

Neonatal outcomes in studies that provided probiotics to overweight/obese pregnant women, included macrosomia, SGA, prematurity, jaundice, admission to the neonatal intensive care unit (NICU), and neonatal death within 30 d after birth. Asgharian *et al*[6] analyzed the occurrence of jaundice, treatments used for jaundice and TSB measured on days 3-5 after birth in heel capillary blood, and found that the mean neonatal TSB on days 3-5 after birth and use of all types of treatment, including phototherapy (alone or with other treatments), were significantly lower in the probiotic group than in the conventional yoghurt group. This was the first study to explore neonatal bilirubin level following adminis-

tration of probiotics in overweight/obese pregnant women. Two systematic reviews and meta-analyses showed that probiotics supplement therapy may be effective in treating neonatal jaundice, but the evidence is low certainty and quality[69,70]. Chen *et al*[70] demonstrated that probiotic supplementation is an effective and safe treatment for pathological neonatal jaundice. However, a meta-analysis in 2019 did not recommend routine use of probiotics to prevent or treat neonatal jaundice as limited low-quality evidence indicated that probiotic supplementation may reduce the duration of phototherapy in neonates with jaundice[69]. Large well-designed adequately-powered trials on probiotic supplementation during pregnancy in overweight/obese pregnant women are still needed to identify whether probiotics reduce the occurrence of neonatal jaundice and the mean neonatal TSB level on days 3-5 after birth, and improve the efficacy of phototherapy for jaundice, alone or combined with other treatments. Callaway *et al*[51] found that probiotics have a role in the prevention of SGA, but this requires further investigation in future meta-analyses. Other neonatal outcomes such as microsomia, premature admission to the NICU, and neonatal death were not significantly different between the two groups[3,7,41,51,55].

CONCLUSION

Overweight/obese pregnant women, excessive weight gain during pregnancy, and abnormal gut microbiota are high-risk factors for GDM, and probiotics may be more effective in high-risk pregnant women in preventing GDM by modulating the gut microbiota and inhibiting the expression of inflammatory factors. Current evidence indicates that multiple probiotics may increase α-diversity in obese pregnant women, and probiotics have a positive effect on reducing fasting glucose and GWG in overweight/obese pregnant women and the incidence of SGA, as well as the mean neonatal TSB on days 3-5 after birth. However, probiotics have little effect on other maternal and neonatal outcomes such as GDM, preterm birth and macrosomia. At present, there have been no trials on probiotics in overweight/obese pregnant women in China. More, large, well-designed adequately powered trials are needed to identify the influence of probiotics on maternal and neonatal outcomes in overweight/obese pregnant women in different countries. We suggest the following: (1) Because of the specificity of species and strains of probiotics, future studies should identify the most appropriate probiotics to prevent GDM and other adverse maternal and neonatal outcomes in overweight/obese pregnant women, and enroll more participants at high risk of GDM; (2) Study design should be improved, for example, combining dietary counseling with probiotics intervention may be beneficial in reducing the incidence of GDM; and (3) Large multicenter studies and probiotics administration from early pregnancy should be implemented to determine the optimal dosage, method, and timing of probiotics use.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Effectiveness of microwave endometrial ablation combined with hysteroscopic transcervical resection in treating submucous uterine myomas

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Abstract

BACKGROUND

Hypermenorrhea is characterized by excessive menstrual bleeding that causes severe anemia and interferes with everyday life. This condition can restrict women's social activities and decrease their quality of life. Microwave endometrial ablation (MEA) using a 2.45-GHz energy source is a minimally invasive alternative to conventional hysterectomy for treating hypermenorrhea that is resistant to conservative treatment, triggered by systemic disease or medications, or caused by uterine myomas and fibrosis. The popularity of MEA has increased worldwide. Although MEA can safely and effectively treat submucous myomas, some patients may still experience recurrent hypermenorrhea postoperatively and may require additional treatment.

AIM

To investigate the efficacy of MEA combined with transcervical resection (TCR).

METHODS

Participants underwent cervical and endometrial evaluations. Magnetic resonance imaging and hysteroscopy were performed to evaluate the size and location of the myomas. TCR was performed before MEA using a hystero-resectoscope. MEA was performed using transabdominal ultrasound. The variables included operation time, number of ablation cycles, length of hospital stay, and visual analog scale cores for hypermenorrhea, dysmenorrhea, and treatment satisfaction at 3 and 6 mo postoperatively. The postoperative incidence of amenorrhea, changes in hemoglobin concentrations, and MEA-related complications were

evaluated.

RESULTS

A total of 34 women underwent a combination of MEA and TCR during the study period. Two patients were excluded from the study as their histopathological tests identified uterine malignancies (uterine sarcoma and endometrial cancer). The 32 eligible women (6 nulliparous, 26 multiparous) had a mean age of 45.2 ± 4.3 years (range: 36–52 years). Patients reported very severe hypermenorrhea (10/10 points on the visual analog scale) before the procedure. However, after the procedure, the hypermenorrhea scores decreased to 1.2 ± 1.3 and 0.9 ± 1.3 at 3 and 6 mo, respectively ($P < 0.001$). The mean follow-up duration was 33.8 ± 16.8 mo. Although 10 women (31.3%) developed amenorrhea during this period, none experienced a recurrence of hypermenorrhea. No surgical complications were observed.

CONCLUSION

Reducing the size of uterine myomas by combining MEA and TCR can safely and effectively treat hypermenorrhea in patients with submucous myomas.

Key Words: Dysmenorrhea; Endometrial ablation techniques; Menorrhagia; Microwaves; Myoma; Uterus

Core Tip: Microwave endometrial ablation may be ineffective in menorrhagia with uterine myomas. Combining transcervical resection and endometrial ablation can help reduce the tumor volume, and cauterization can ensure the effectiveness of this procedure. This can facilitate the pathological evaluation of the excised specimen. The therapeutic effect of this method is considered to be a reduction in the number of uterine myomas. Furthermore, patient satisfaction with this surgical procedure is high.

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INTRODUCTION

Hypermenorrhea is characterized by excessive menstrual bleeding that can cause severe anemia and interfere with everyday life. This condition can restrict women's social activities and decrease their quality of life. Microwave endometrial ablation (MEA) using a 2.45-GHz energy source is a minimally invasive alternative to conventional hysterectomy for treating hypermenorrhea, which is resistant to conservative treatment, triggered by systemic disease or medications, or caused by uterine myomas and fibrosis[1,2]. The popularity of MEA continues to increase worldwide, including that in Japan where the national health insurance program has covered it since April 2012. This procedure has been performed at the International School of Medicine and Welfare Hospital since January 2016, and a previous report has demonstrated that it is reliable and effective in treating hypermenorrhea-induced anemia[3]. Although MEA can safely and effectively treat submucous myomas, some patients may still experience recurrent hypermenorrhea postoperatively and may require additional treatment[4]. Therefore, this study evaluated whether a combination of MEA and transcervical resection (TCR) was effective in treating submucous uterine myomas by reducing the size of uterine myomas in patients with hypermenorrhea, thereby decreasing the possibility of recurrence and additional treatment.

MATERIALS AND METHODS

Study design

The retrospective study protocol was approved by the Ethics Committee of the International University of Health and Welfare Hospital (20-B-399, date: May 7, 2020). All patients provided written informed consent prior to the procedure. Patients were considered eligible if they underwent MEA in addition to TCR for submucous uterine myomas after a primary complaint of hypermenorrhea between January

2016 and June 2020. All patients were followed up for ≥6 mo, and their medical records were reviewed to evaluate their outcomes.

Procedures

All participants underwent cervical and endometrial cytological evaluations as well as histological evaluations, if necessary, to exclude cases of uterine malignancies. In addition, magnetic resonance imaging and hysteroscopy were performed to evaluate the size and location of the myomas, as well as the degree of protrusion into the uterine cavity. The procedure was initiated under general anesthesia in the lithotomy position. The TCR procedure was performed before MEA using a hystero-resectoscope (26-Fr outer sheath; Olympus Corp., Tokyo, Japan), and D-sorbitol (3%) was used as the irrigation solution. Resected tissue specimens undaerwent histopathological examinations in all cases. Therefore, cervical dilatation was performed on the day before surgery using Lamicel (Japan Medtronic Co. Ltd., Tokyo, Japan). MEA was then performed under transabdominal ultrasound guidance using the Microtaze AFM-712 unit (Alfresa Pharma Corp., Osaka, Japan) and a Sounding Applicator (CSA-40CBL-1006200C; Alfresa Pharma Corp., Osaka, Japan) (Figure 1). According to the guidelines, the 2.45 GHz microwave Microtaze device was set to an output power of 70 W for 50-s cycles[5]. Before terminating the MEA, the uterine cavity was evaluated using a hysteroscope to confirm that ablative necrosis at the endometrium did not extend to the internal orifice or endocervix.

Study variables

The variables included operation time, number of ablation cycles, length of hospital stay, and visual analog scale (VAS) scores for hypermenorrhea, dysmenorrhea, and treatment satisfaction at 3 and 6 mo postoperatively. In addition, we evaluated the postoperative incidence of amenorrhea, changes in hemoglobin (Hb) concentrations, and MEA-related complications.

Statistical analysis

Numerical data were reported as mean ± standard deviation (range). All statistical analyses were performed using JMP® software, version 14.2 (SAS Institute Japan Co. Ltd, Tokyo, Japan). Statistical analysis consisted of single-factor ANOVA and multiple parametric comparisons. A P value < 0.05 was considered statistically significant.

RESULTS

A total of 34 women underwent a combination of MEA and TCR during the study period. Two patients were excluded from the study as their histopathological tests identified uterine malignancies (uterine sarcoma and endometrial cancer). Patients who wish to have children were excluded from this treatment since MEA completely destroys the endometrium's functional layers. The patients' characteristics are shown in Table 1. The 32 eligible women (6 nulliparous, 26 multiparous) had a mean age of 45.2 ± 4.3 years (range: 36–52 years). The cases included 10 cases of single myoma (only submucosal fibroids) and 22 cases of multiple myomas (submucosal and intramuscular fibroids) with a mean major axis diameter of 26.3 ± 12.3 mm and a mean protrusion degree of 51.3% ± 11.3%. According to the International Federation of Gynecology and Obstetrics classification of submucosal fibroids, 6 cases presented with Type 1 and 26 cases presented with type 2 fibroids.

The mean procedure duration was 45.5 ± 21.0 min (range: 19–110 min) and involved 7.0 ± 1.3 ablation cycles (range: 5–11 cycles). The mean postoperative hospital stay was 2.5 ± 0.5 d (range: 2–3 d). The patients reported having very severe hypermenorrhea and dysmenorrhea at 10 mo before the procedure, based on average VAS scores of 10/10 for both items. However, the hypermenorrhea scores significantly decreased to 1.2 ± 1.3 (range: 0–5) at 3 mo postoperatively and 0.9 ± 1.3 (range: 0–5) at 6 mo postoperatively (both P < 0.001) (Figure 2A). Similarly, the dysmenorrhea scores significantly decreased to 1.3 ± 1.8 (range: 0–7) after 3 mo and 1.3 ± 1.8 (range 0–5) after 6 mo (both P < 0.001) (Figure 2B). Figure 3 shows that the circulating Hb concentrations improved significantly from 8.7 ± 1.9 g/dL (range: 5.1–12.5 g/dL) preoperatively to 13.5 ± 1.1 g/dL (range: 11.3–15.2 g/dL) postoperatively (P < 0.001). No surgical complications were observed. The patients reported being highly satisfied with the procedure's ability to relieve hypermenorrhea, based on a mean VAS score of 9.5 ± 0.8 (range: 7–10) for satisfaction. The mean follow-up duration was 33.8 ± 16.8 mo (range: 6–60 mo). During follow-up, amenorrhea was reported by 10 patients (31.3%), and there were no instances of hypermenorrhea recurrence.

DISCUSSION

Previous studies have indicated that MEA is an alternative to hysterectomy for patients requiring treatment for hypermenorrhea caused by submucous myomas[1-3]. This procedure has gained popularity in Japan, where the national health insurance program has covered it since 2012. Although

Table 1 Patient characteristics

Characteristics	Values
	mean ± SD (*n* = 32)
Age (years)	45.2 ± 4.3
Pregnancy history (cases)	
Primigravida	6
Multigravida	26
Submucosal uterine fibroid	
Major diameters (mm)	26.3 ± 12.3
Protrusion degree (%)	51.3 ± 11.3
Multiple uterine fibroids (case)	22

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Figure 1 Microtaze AFM-712 generator and sounding applicator (Alfresa Pharma Co, Osaka, Japan).

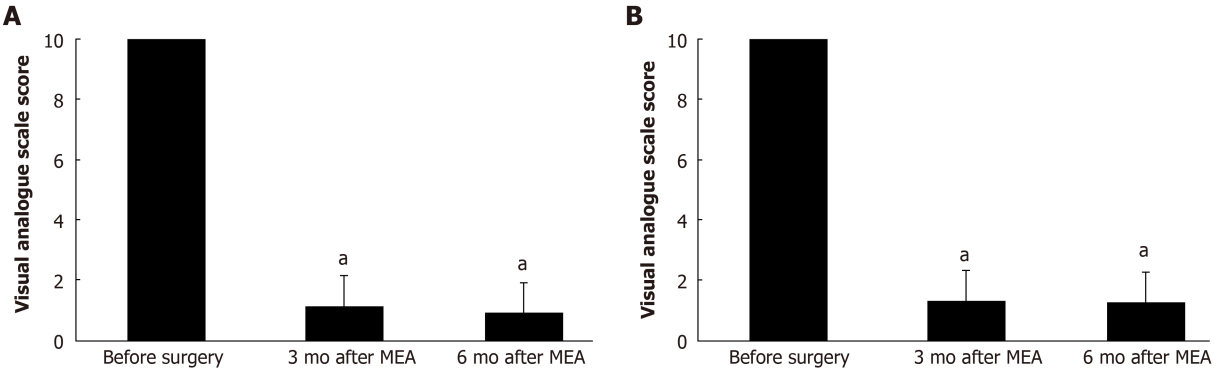

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Figure 2 Changes in the visual analog scale score. A: Hypermenorrhea after microwave endometrial ablation. Values are expressed as the mean ± standard deviation (error bars). [a]*P* < 0.01 relative to the result before surgery; B: Dysmenorrhea after microwave endometrial ablation. Values are expressed as the mean ± standard deviation (error bars). [a]*P* < 0.01 relative to the result before surgery. MEA: Microwave endometrial ablation.

MEA can safely and effectively treat submucous myomas, some patients may experience recurrent hypermenorrhea postoperatively and require additional treatment. This is believed to be caused by endometrial regeneration over time, as the uterine cavity expands because of post-procedural myoma growth. The present study evaluated the efficacy and safety of the combination of MEA and TCR under hysteroscopic guidance for women with submucous myomas. The patients experienced dramatic improvements in their hypermenorrhea symptoms and a significant increase in their circulating Hb

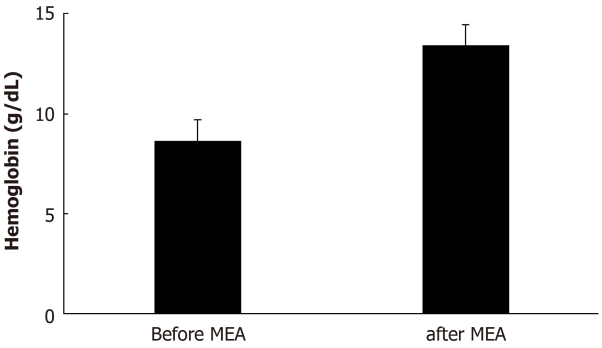

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Figure 3 Comparing blood hemoglobin concentrations before and after microwave endometrial ablation. MEA: Microwave endometrial ablation.

concentrations. Furthermore, none of the women experienced a recurrence of hypermenorrhea during the follow-up period. Submucous myomas deform the uterine cavity, complicating the endometrial ablation process, depending on the shape of the microwave applicator. A resectoscope can be used for pre-ablation excision to improve the outcomes of MEA by smoothing the irregular inner surface, although it is important to be aware of potential issues regarding the scope of myoma resection during this step. Problems are unlikely in patients who have a sufficiently thick residual myometrium, even if the submucous myoma is completely removed. However, excessive thinning is possible if complete myoma resection is attempted. Thus, the Japanese clinical practice guidelines indicate that MEA requires a myometrial thickness of ≥ 10 mm to prevent damage to the surrounding organs[5]. Therefore, the scope of the TCR must be limited to partial resection before MEA if there is a risk of excessively thinning the uterine musculature. We reviewed the patients' TCR procedures and noted that only six patients underwent partial resection, although they experienced no recurrence and reported the same improvements in their clinical symptoms compared with patients who underwent complete resection. The efficacy of the combined procedures can be attributed to the reduction in the fibroid mass and the use of a hysteroscope after MEA to evaluate the uterine cavity and perform cauterization for sites with inadequate ablation.

The levonorgestrel-releasing intrauterine system (LNG-IUS) is another minimally invasive treatment for hypermenorrhea. This system provides promising outcomes, based on a > 50% reduction in menstrual flow (*vs* the preoperative volume) experienced by 84.8% of patients and amenorrhea only occurring in approximately 20% of patients[6]. Based on our findings, the MEA procedure appears to be more effective than the LNG-IUS, although a direct comparison is precluded because we only used subjective VAS ratings to evaluate menstrual flow. Nevertheless, from a long-term perspective, the effects of MEA may be more stable, as only 21% of patients who undergo MEA require another treatment for recurrent hypermenorrhea, while re-treatment is required for 42% of patients who receive the LNG-IUS[6,7]. Furthermore, the LNG-IUS could potentially slip out of place in a uterine cavity that has been deformed by the presence of submucous myomas. Therefore, we suggest that the combination of MEA and TCR is a more effective treatment option for hypermenorrhea caused by submucous uterine myomas. The concurrent use of a resectoscope with MEA permits a histopathological characterization of the lesion, which is not possible if MEA is performed alone. Furthermore, we have previously reported that abnormal findings were observed in endometrial specimens collected *via* total endometrial curettage during MEA, despite these patients having initially negative results for uterine malignancy from cytodiagnostic and histological screening before MEA[8]. The present study also identified two patients with uterine malignancy, which was confirmed based on the histopathological findings from specimens that were excised during the combination of TCR and MEA, despite the preoperative diagnosis being hypermenorrhea caused by submucous uterine myoma. Similarly, histopathological examinations of the TCR specimens can be helpful in identifying uterine malignancies.

It is important to consider the safety of MEA, as complications include heat injury to the pelvic organs, fluid retention in the uterus (because of cervical stenosis or the ablated endometrium), hematometra, pelvic inflammation (*e.g.*, endometritis because of ascending infection), and pyometra[9]. However, we did not detect any of these complications, which may be related to resectoscope usage to evaluate the endometrial lining immediately after MEA. This step allowed for the maximum removal of the necrotic tissue leftover by ablation, and we believe that it can improve the safety of MEA by reducing the rate of complications. Although MEA is not indicated for treating dysmenorrhea and was not originally expected to alleviate its symptoms, some studies demonstrate its effectiveness in treating this condition[10,11]. Our patients reported improvements in dysmenorrhea as soon as their first menses after MEA. We speculate that this was a secondary effect of improvements in hypermenorrhea, as reductions in menstrual volume were accompanied by less severe dysmenorrhea. Thus, MEA might be effective for reducing dysmenorrhea that is associated with hypermenorrhea caused by uterine myomas. Our patients were highly satisfied with MEA, based on an average VAS score of 9.5 ± 0.89 out

of 10 points. Furthermore, most patients continued menstruating, although amenorrhea was reported by 10 patients (31.3%). Thus, we suspect that women with hypermenorrhea may desire a reduction, but not necessarily complete elimination, of menstrual flow while preserving their uterine function. The safety and efficacy of MEA in combination with TCR may also contribute to patient satisfaction. Further studies are needed to consider various issues related to whether a combination of MEA and TCR can effectively treat hypermenorrhea secondary to uterine myomas. For example, hypermenorrhea outcomes should be considered in cases where the fibroids do not protrude into the uterine cavity. Furthermore, long-term follow-up is needed to clarify the hypermenorrhea recurrence rate and time to recurrence. Moreover, screening criteria are needed to identify women who are especially susceptible to hypermenorrhea recurrence. Finally, these studies could also consider novel ablation techniques.

CONCLUSION

The combination of MEA and TCR may safely and effectively reduce the size of uterine myoma and, thus, treat hypermenorrhea caused by submucous myomas.

ARTICLE HIGHLIGHTS

Research background

Hypermenorrhea is characterized by excessive menstrual bleeding that causes severe anemia and interferes with everyday life. This condition can restrict women's social activities and decrease their quality of life. Microwave endometrial ablation (MEA) using a 2.45-GHz energy source is a minimally invasive alternative to conventional hysterectomy for treating hypermenorrhea that is resistant to conservative treatment, triggered by systemic disease or medications, or caused by uterine myomas and fibrosis. The popularity of MEA has increased worldwide. Although MEA can safely and effectively treat submucous myomas, some patients may still experience recurrent hypermenorrhea postoperatively and may require additional treatment.

Research motivation

Although MEA can safely and effectively treat submucous myomas, some patients may still experience recurrent hypermenorrhea postoperatively and may require additional treatment. This study evaluated whether a combination of MEA and transcervical resection (TCR) was effective in treating submucous uterine myomas by reducing the size of uterine myomas in patients with hypermenorrhea, thereby decreasing the possibility of recurrence and additional treatment.

Research objectives

To investigate the efficacy of MEA combined with TCR.

Research methods

Participants underwent cervical and endometrial evaluations. Magnetic resonance imaging and hysteroscopy were performed to evaluate the size and location of the myomas. TCR was performed before MEA using a hystero-resectoscope. MEA was performed using transabdominal ultrasound. The variables included operation time, number of ablation cycles, length of hospital stay, and visual analog scale cores for hypermenorrhea, dysmenorrhea, and treatment satisfaction at 3 and 6 mo postoperatively. The postoperative incidence of amenorrhea, changes in hemoglobin concentrations, and MEA-related complications were evaluated.

Research results

A total of 34 women underwent a combination of MEA and TCR during the study period. Two patients were excluded from the study as their histopathological tests identified uterine malignancies (uterine sarcoma and endometrial cancer). The 32 eligible women (6 nulliparous, 26 multiparous) had a mean age of 45.2 ± 4.3 years (range: 36–52 years). Patients reported very severe hypermenorrhea (10/10 points on the visual analog scale) before the procedure. However, after the procedure, the hypermenorrhea scores decreased to 1.2 ± 1.3 and 0.9 ± 1.3 at 3 and 6 mo, respectively ($P < 0.001$). The mean follow-up duration was 33.8 ± 16.8 mo. Although 10 women (31.3%) developed amenorrhea during this period, none experienced a recurrence of hypermenorrhea. No surgical complications were observed.

Research conclusions

Reducing the size of uterine myomas by combining MEA and TCR can safely and effectively treat hypermenorrhea in patients with submucous myomas.

Research perspectives

MEA may be ineffective in menorrhagia with uterine myomas. Combining TCR and endometrial ablation can help reduce the tumor volume, and cauterization can ensure the effectiveness of this procedure. This can facilitate the pathological evaluation of the excised specimen. The therapeutic effect of this method is considered to be a reduction in the number of uterine myomas. Furthermore, patient satisfaction with this surgical procedure is high.

FOOTNOTES

Author contributions: Toshiyuki Kakinuma: methodology, software, validation, and formal analysis, writing-original draft preparation, writing-review and editing, visualization, supervision, and project administration; all authors did investigation, resources, data curation, and have read and agreed to the published version.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the International University of Health and Welfare Hospital.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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

Data sharing statement: All the data related to the study have been disclosed in the manuscript. No additional data are available.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Antibody and complement levels in patients with hypersplenism associated with cirrhotic portal hypertension and therapeutic principles

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Abstract

BACKGROUND

Hypersplenism associated with cirrhotic portal hypertension is a common condition often resulting from hepatitis B-related cirrhosis. However, the levels of immunoglobulin (Ig) and complement in patients with hypersplenism associated with cirrhotic portal hypertension remain unclear. This study was undertaken to determine the levels of Ig and complement in these patients, the relationship between these levels and Child-Pugh class and their clinical significance.

AIM

To investigate the antibody (Ig) and complement levels in patients with hypersplenism associated with cirrhotic portal hypertension and their clinical significance.

METHODS

Clinical data of 119 patients with hypersplenism associated with cirrhotic portal hypertension were statistically analyzed and compared with those of 128 control patients.

RESULTS

IgA and IgG levels in patients with hypersplenism were significantly higher than controls ($P < 0.001$). There was no significant difference in IgM between the two

groups (P = 0.109). C3 and C4 levels in patients with hypersplenism were significantly lower than controls (P < 0.001). As liver function decreased, IgA and IgG levels increased (P < 0.001), and C3 and C4 levels decreased (P < 0.001).

CONCLUSION

Patients with hypersplenism associated with cirrhotic portal hypertension have significantly higher antibody (IgA and IgG) levels and significantly lower complement (C3 and C4) levels, which are both related to liver damage. Clinically, the administration of anti-hepatitis virus agents and protection of liver function should be strengthened.

Key Words: Hypersplenism associated with cirrhotic portal hypertension; Complement; Treatment; Hepatitis; B-immunoglobulin

Core Tip: Patients with cirrhotic portal hypertension and hypersplenism are clinically common. The spleen is an important immune organ, but studies on antibody and complement levels in patients are scarce. This study found that IgA and IgG levels increased and complement levels decreased in our patient population compared to the healthy controls. These findings indicate liver damage, supporting the need for anti-viral treatment in these patients.

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INTRODUCTION

Hypersplenism associated with cirrhotic portal hypertension is a common condition often resulting from hepatitis B-related cirrhosis[1]. Hepatitis B is a chronic infectious disease caused by hepatitis B virus (HBV) infection[2]. Under normal circumstances, the immune system protects the body by defending against external invading pathogens, maintaining physiological balance and eliminating diseased cells through cellular and/or humoral immunity. An abnormal immune response, whether hyperactive (*i.e.* allergy) or hypoactive (*i.e.* immunodeficiency), can cause tissue damage and immunopathological reactions[3].

HBV infection is a global public health issue; in particular, China has a high prevalence of HBV[4]. The pathogenesis of HBV infection is not yet fully understood. Numerous studies have shown that the immunopathological response and the interaction between the virus and host cells are the main causes of liver cell damage[5]. The progression and outcome of HBV infection is therefore related to the host's immune response. Immunosuppression or immune system disorder can cause HBV replication, leading to chronic infection, and then develop cirrhosis. Liver cirrhosis caused by any reason may lead to hypersplenism related to portal hypertension[6] and possibly liver cancer.

Antibodies are important effector molecules that mediate humoral immunity by binding to specific antigens. They are immunoglobulins (Ig) produced by plasma cells, which are differentiated from B cells and memory B cells in the immune system under antigen stimulation[7]. They are distributed in the serum, tissue fluid, exocrine fluid and on the surface of some cell membranes. They demonstrate antibody-dependent cell-mediated cytotoxicity and play a role in neutralization, opsonization and complement activation[8,9].

By combining different heavy and light chains, Igs form complete antibody molecules that can be classified into five types: IgG, IgM, IgA, IgD and IgE. IgG is the only antibody that can cross the placental barrier and is the main component of serum Igs[10]. It is the main antibody produced during the immune response and the "main force" to fight against infection; in fact, most antibody activity in the serum is related to IgG. It activates complement through the classical pathway and binds to Fc receptors on the surface of macrophages and natural killer cells to regulate antibody-dependent cell-mediated cytotoxicity[11]. IgM accounts for 5%-10% of the total serum Ig pool. It is the first antibody to be produced during ontogeny[12] and to appear in the primary humoral immune response, serving as the "vanguard" for specific defense against infection. IgA is an exocrine Ig that participates in local mucosal immunity and plays an important role as the "border guard" for local defense against infection. IgE is mainly present in the allergic response[13], and IgD is present only in trace amounts[14,15].

Complement proteins play vital roles in the immune response, affecting both innate and adaptive immunity, regulating the immune response at different stages and influencing the immunological function of antibodies. In particular, the complement protein C3 plays a critical role. The level of serum C3 is proportional to the total amount of complement, and the serum C3 and C4 levels provide a good estimate for the total serum complement level[16,17]. However, the levels of Ig and complement in patients with hypersplenism associated with cirrhotic portal hypertension remain unclear. This study was undertaken to determine the levels of Ig and complement in these patients, the relationship between these levels and Child-Pugh class and their clinical significance.

MATERIALS AND METHODS

Patients and methods

A total of 119 patients with hypersplenism were compared with a control group of 128 patients. All methods were performed in accordance with the relevant guidelines and regulations/Declaration of Helsinki. Informed consent was obtained from all patients.

The hypersplenism group was composed of hypersplenism caused by cirrhosis and portal hypertension. Patients with hypersplenism caused by non-cirrhotic portal hypertension, such as lymphoma, pulmonary tuberculosis, connective tissue and inflammatory diseases, were excluded. The 119 patients included 93 males and 26 females, with a male-to-female ratio of 3.6:1. Their ages ranged from 41 years to 82 years, with a mean of 51 years. Among them, 95 patients (80.0%) had hepatitis B cirrhosis, 13 (10.9%) had hepatitis C cirrhosis, 3 (2.5%) had biliary cirrhosis, and 8 (6.6%) had other types of cirrhosis. Liver cirrhosis and splenomegaly (as assessed by B-Mode ultrasound and computed tomography), mono- or multilineage peripheral cytopenias (as assessed by laboratory tests) and moderate or severe varices in the lower esophagus and gastric fundus (as assessed by computed tomography and endoscopy), were found in all patients.

Furthermore, all patients underwent surgical treatment. Specifically, 45 patients (37.8%) underwent hepatic lobectomy for concomitant liver cancer, 33 (27.7%) underwent devascularization of the lower esophagus and gastric fundus + splenectomy for massive gastrointestinal bleeding (≥ 1000 mL), 12 (10.1%) underwent splenectomy for splenomegaly in which the spleen extends beyond the midline of the abdomen or below the line joining the two anterior superior iliac spines-and reduced quality of life, 15 (12.6%) underwent splenectomy + portal-azygos disconnection for moderate or severe hypersplenism, 11 (9.3%) underwent splenectomy alone, and 3 (2.5%) underwent portacaval shunt alone. Liver tissue was collected during the operation and sent for pathological examination, which revealed cirrhosis.

The control group was composed of surgical patients without hypersplenism associated with cirrhotic portal hypertension. These patients had no history of hepatitis virus infection or cirrhosis caused by other reasons. The liver function was normal, and the spleen volume was not enlarged. The 128 control patients included 65 males and 63 females, with a male-to-female ratio of 1:1. Their ages ranged from 20 years to 93 years, with a mean of 49 years. Specifically, 49 patients with cholecystolithiasis and 9 with gallbladder polyps underwent laparoscopic cholecystectomy, 38 with choledocholithiasis underwent choledocholithotomy, 19 with inguinal hernia and femoral hernia underwent laparoscopic hernia repair, and 13 with nodular goiter underwent subtotal thyroidectomy.

Detection method

Ig, C3 and C4 were detected by turbidimetric inhibition immunoassay. Briefly, 2 mL of peripheral venous blood was drawn from the patient, placed in a dry test tube and sent to the hospital laboratory for routine detection.

Statistical analysis

Statistical analysis was performed using SPSS software v25.0 (IBM Corp., Armonk, NY, United States). Measurement data were expressed as (average of x ± standard deviation) and [mean (P_{25}, P_{75})]. The t/z test and Wilcoxon rank sum test for two independent samples were used for comparison between groups. $P < 0.05$ or $P < 0.001$ were considered statistically significant.

RESULTS

Comparison of sex and age between the two groups

There were significantly more males than females in the hypersplenism group compared to controls ($P < 0.05$). There was no significant difference in age between the two groups ($P > 0.05$).

Comparison of Ig levels before treatment between the two groups

Compared with the control group, IgA and IgG levels were significantly higher in the hypersplenism group (Z = -6.61 and -7.16, respectively; P < 0.001). There was no significant difference in IgM levels between the two groups (Z = -1.60, P = 0.109) (Figure 1).

Comparison of complement levels between the two groups before treatment

Compared with the control group, C3 and C4 levels were significantly lower in the hypersplenism group (t/z = 4.28 and -6.65, respectively; P < 0.001) (Figure 2).

The relationship between Child-Pugh class and Ig and complement levels in patients with hypersplenism associated with cirrhotic portal hypertension

For comparison of IgA, there were significant differences between class A and B (Z = 3.773, P < 0.001) and class A and C (Z = 2.373, P = 0.018) but not between class B and C (Z = 0.190, P = 0.850). For comparison of IgG, there were significant differences between class A and C (t = 3.732, P < 0.001) and class B and C (t = 2.225, P = 0.032) but not between class A and B (t = 1.252, P = 0.213). There were no statistically significant differences between the IgM groups. For comparison of C3, there were significant differences between class A and B (t = 3.149, P = 0.002), and class A and C (t = 3.857, P < 0.001) but not between class B and C (t = 0.486, P = 0.630). For comparison of C4, there were significant differences between class A and B (Z = 3.364, P < 0.001) but not between class A and C (Z = 1.851, P = 0.064) nor class B and C (Z = 0.298, P = 0.765) (Figure 3).

DISCUSSION

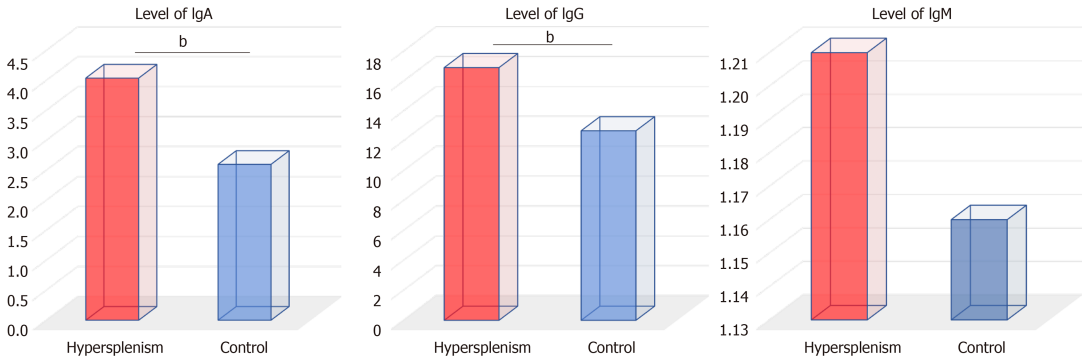
Based on B-Mode ultrasound and computed tomography findings, endoscopy revealed moderate-to-severe varices in the lower esophagus and gastric fundus. Liver tissue was collected during the operation and sent for pathological examination. These findings supported the diagnosis of cirrhotic portal hypertension. Dameshek[18] proposed four criteria for a diagnosis of hypersplenism: (1) Splenomegaly; (2) One or several types of cytopenia; (3) Bone marrow is normal or in hyperplastic state; and (4) Pathological changes of blood cells disappeared after splenectomy. The clinical manifestations of portal hypertension include splenomegaly, and for patients with hypersplenism, peripheral cytopenia should be present and blood counts should become normal after splenectomy[4]. The diagnosis of hypersplenism in cirrhotic portal hypertension is consistent with all patients[19].

Although there was a significant difference in sex composition between the two groups, there was no significant difference in age. Hence, there should be no age-related effect on the Ig and complement measurements between the hypersplenism patients and controls. IgA and IgG levels were significantly higher than controls, indicating that patients with hypersplenism associated with cirrhotic portal hypertension had elevated serum levels of the two dominant Igs. This phenomenon has gained the attention of clinicians[11] and has been repeatedly confirmed[20,21]. Elevated serum Ig levels are of great significance in clinical diagnosis[20] and are suggestive of liver damage.

In this study, hypersplenism patients with Child-Pugh class C had significantly higher IgA and IgG levels than those with class A or B, indicating that the liver function was inversely correlated with serum levels of the two main Igs. There was no significant difference in IgM among the Child-Pugh classes, which may be related to its low total amount in all groups. There are two reasons for the increased Ig levels in the class C patients. Namely, a large number of antibodies are produced to eliminate the virus, and cirrhosis caused by HBV results in liver cell dysfunction and a reduced ability to remove antibodies[22]. Further research is required to determine whether and to what extent enhanced splenic macrophage function is correlated with increased Ig levels in patients with hypersplenism associated with cirrhotic portal hypertension[23].

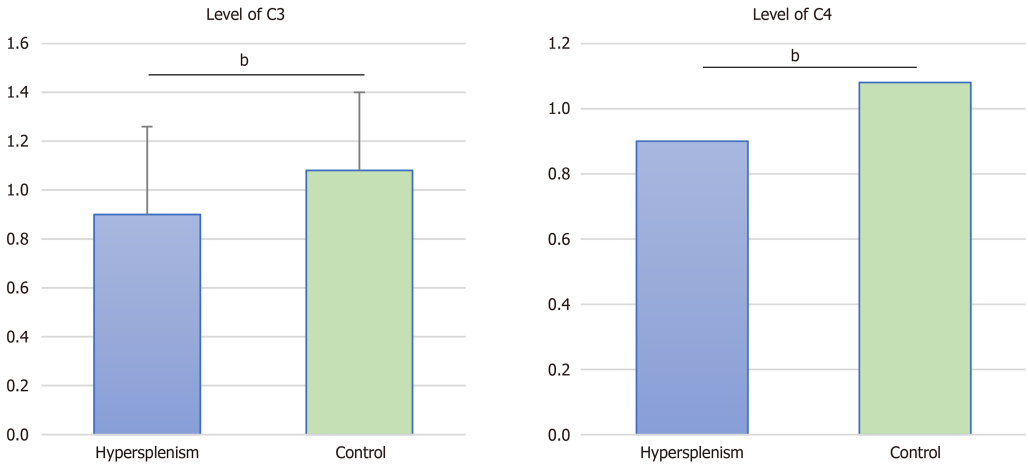
The significantly lower serum levels of complements C3 and C4 in patients with hypersplenism associated with cirrhotic portal hypertension are also related to liver function impairment. One possible explanation is the reduced ability of damaged liver cells to synthesize complements. Another possibility is the development of a portal systemic collateral circulation, allowing a large amount of endotoxin to enter the bloodstream, which simultaneously activates the classical and alternative pathways, resulting in a large amount of complements to be consumed[24] and a substantial reduction in C3 and C4 levels [25].

This study shows that increased liver function impairment corresponds to lower levels of C3 and C4. As a type of globulin with antibody activity in human serum or fluid, Igs are antimicrobial and antiviral and enhance phagocytosis. Moreover, they can kill or dissolve pathogenic microorganisms with the assistance of complements, which is an important defense function in anti-infection immunity. Therefore, understanding serum Ig levels and their relationship to liver function in patients with hypersplenism associated with cirrhotic portal hypertension is of great clinical significance for assessing the disease progression and strengthening liver-protective treatment.



DOI: 10.12998/wjcc.v10.i36.13208

Figure 1 Comparison of immunoglobulin levels (g/L) between the hypersplenism group and the control group. $^{b}P < 0.001$. Ig: Immunoglobulin.



DOI: 10.12998/wjcc.v10.i36.13208

Figure 2 Comparison of complement levels (g/L) between the hypersplenism group and the control group. $^{a}P < 0.05$; $^{b}P < 0.001$.

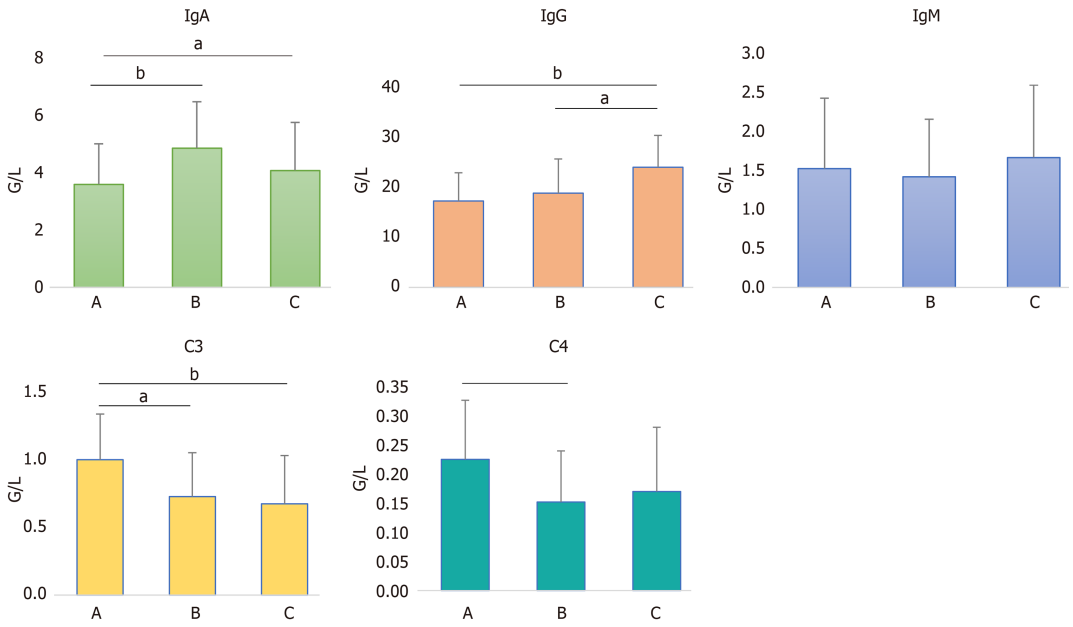


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Figure 3 Relationship between Child-Pugh class and immunoglobulin and complement levels. $^{a}P < 0.05$; $^{b}P < 0.001$. Ig: Immunoglobulin.

CONCLUSION

Patients with hypersplenism associated with cirrhotic portal hypertension have significantly higher antibody (IgA and IgG) levels and significantly lower complement (C3 and C4) levels. The increase of antibodies and the decrease of complement are related to liver function damage. Clinically, the administration of anti-hepatitis virus agents and protection of liver function should be strengthened[26-28].

ARTICLE HIGHLIGHTS

Research background

The antibody and complement levels in patients with cirrhosis and hypersplenism due to portal hypertension are not clear, which affects the diagnosis and treatment to some extent.

Research motivation

There are no studies determining the levels of immunoglobulins (Ig) and complements in patients with hypersplenism due to cirrhosis and portal hypertension, which affects the diagnosis and treatment.

Research objectives

To investigate the antibody (Ig) and complement levels in patients with hypersplenism due to liver cirrhosis and portal hypertension and how to treat them.

Research methods

The levels of IgA, IgG, IgM, C3 and C4 were determined and compared in 119 patients with confirmed hypersplenism and 128 control patients.

Research results

The levels of IgA and IgG in the hypersplenism group were significantly higher than those in the control group ($P < 0.001$). The levels of C3 and C4 in the hypersplenism group were significantly lower than those in the control group ($P < 0.001$). The worse the liver function was, the higher the IgA and IgG levels were ($P < 0.001$) and the lower the C3 and C4 levels were ($P < 0.001$).

Research conclusions

Antibodies in patients with liver cirrhosis and portal hypertension and hypersplenism were significantly increased, while complements (C3 and C4) were significantly decreased. Both the increase of antibody and the decrease of complement are related to the damage of liver function.

Research perspectives

It is important to know the antibody (Ig) and complement levels of patients with hypersplenism due to cirrhosis and portal hypertension. Anti-hepatitis virus and liver function protection should be strengthened in treatment.

FOOTNOTES

Author contributions: Zhang K, Zeng M, Li YJ, Wu JC, Zheng JF and Lv YF contributed equally to this work; Lv YF was responsible for project design and thesis writing; Zhang K and Li YJ were responsible for implementation and statistical information; Wu JC, Zheng JF and Zeng M were responsible for data and statistical information collection; Wu HF and Zhang ZS participated in data collection and registration; all authors have read this article and consent to publication.

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ORIGINAL ARTICLE

Retrospective Study

Case series in Indonesia: B.1.617.2 (delta) variant of SARS-CoV-2 infection after a second dose of vaccine

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Abstract

BACKGROUND

The B.1.617.2 (delta) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first discovered in Maharashtra in late 2020 and has rapidly expanded across India and worldwide. It took only 2 mo for this variant to spread in Indonesia, making the country the new epicenter of the delta variant as of July 2021. Despite efforts made by accelerating massive rollouts of current vaccines to protect against infection, cases of fully-vaccinated people infected with the delta variant have been reported.

AIM

To describe the demographic statistics and clinical presentation of the delta variant infection after the second dose of vaccine in Indonesia.

METHODS
A retrospective, single-centre case series of the general consecutive population that worked or studied at Faculty of Medicine, Universitas Indonesia with confirmed Delta Variant Infection after a second dose of vaccine from 24 June and 25 June 2021. Cases were collected retrospectively based on a combination of author recall, reverse transcription-polymerase chain reaction (RT-PCR), and whole genome sequencing results from the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia.

RESULTS
Between 24 June and 25 June 2021, 15 subjects were confirmed with the B.1.617.2 (delta) variant infection after a second dose of the vaccine. Fourteen subjects were vaccinated with CoronaVac (Sinovac) and one subject with ChAdOx1 nCoV-19 (Oxford-AstraZeneca). All of the subjects remained in home isolation, with fever being the most common symptom at the onset of illness (n = 10, 66.67%). The mean duration of symptoms was 7.73 d (± 5.444). The mean time that elapsed from the first positive swab to a negative RT-PCR test for SARS-CoV-2 was 17.93 d (± 6.3464). The median time that elapsed from the second dose of vaccine to the first positive swab was 87 d (interquartile range: 86-128).

CONCLUSION
Although this case shows that after two doses of vaccine, subjects are still susceptible to the delta variant infection, currently available vaccines remain the most effective protection. They reduce clinical manifestations of COVID-19, decrease recovery time from the first positive swab to negative swab, and lower the probability of hospitalization and mortality rate compared to unvaccinated individuals.

Key Words: COVID-19/SARS-CoV-2 infection; B.1.617.2 (delta) variant; Fully vaccinated; Case series

Core Tip: The emergence of the B.1.617.2 (delta) variant has been attributed to an unexpected increase in coronavirus disease 2019 cases. This variant exhibits a high transmission rate and presents evidence of a more severe disease. Despite efforts made by accelerating massive rollouts of current vaccines and increasing vaccination doses, this delta variant has quickly spread in various countries. Two months after it spread through India, Indonesia has become the new epicenter of the delta variant. Therefore, the effectiveness of currently available vaccines in Indonesia has remained unknown because fully-vaccinated individuals have been infected with the delta variant.

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INTRODUCTION

For nearly 2 years, the coronavirus disease 2019 (COVID-19) pandemic has been a major issue in human global health. In early March 2021, there were 116 million cases of infection worldwide, with 2.6 million global deaths. There was only modest genetic evolution at the start of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, mainly because of the global lack of immunity against this new pathogen[1]. In December 2020, the emergence of new SARS-CoV-2 variants was attributed to an unexpected increase in COVID-19 cases[2]. These new variants are the result of the remarkable capacity of RNA viruses to adapt to new hosts and environments[3]. They are able to develop a high number of mutations, mainly in the S protein, causing potential harm to human health.

The World Health Organization (WHO) has classified SARS-CoV-2 variants into two categories: variants of concern (VOC) and variants of interest[1]. VOC is a term that has been used by the WHO to describe SARS-CoV-2 variants that exhibit a high transmission rate in the context of high population immunity, evidence of a more severe disease, and reduced effectiveness of vaccines[2]. For example, the B.1.617.2 (delta) variant of SARS-CoV-2 was first discovered in Maharashtra in late 2020 and has rapidly expanded across India and worldwide, outcompeting other lineages, such as the B.1.617.1 (kappa) and

B.1.1.7 (alpha) variants. This delta variant is six-fold less sensitive to serum neutralizing antibodies from a recovered individual, and eight-fold less sensitive to vaccine-elicited antibodies *in vitro*[4].

A key issue has surfaced of whether currently available COVID-19 vaccines are able to protect against infection of the new delta variant. A total of 19 current SARS-CoV-2 vaccines worldwide are based on the original strains. With the newly emerging variants, scientists have been challenged to establish response strategies to control the SARS-CoV-2 pandemic[1,5].

Despite efforts made by accelerating massive rollouts of current vaccines and increasing vaccine immunogenicity by increasing vaccination doses, the delta variant of COVID-19 has quickly spread in various countries such as Bangladesh, Iran, Iraq, Malaysia, Myanmar, South Korea, Japan, and Indonesia[5,6]. Two months after spreading through India, Indonesia has become the new epicenter of the delta variant as of July 2021, where only 5.5% of its citizens have been fully vaccinated. As of 15 July 2021, Indonesia had 56.767 new cases, with a test positivity rate of 26%, indicating that large numbers of cases are being missed, and reporting an average of 919 deaths a day over the past week[6]. The effectiveness of currently available vaccines in Indonesia, namely CoronaVac (Sinovac), BNT162b2 (Pfizer-BioNTech), and ChAdOx1 nCoV-19 (Oxford-AstraZeneca), has remained unknown because fully-vaccinated individuals have been infected with the B.1.617.2 (delta) variant[7].

Here, we report a case series describing the demographic statistics and clinical presentation of the first cluster of delta variant infection after a second dose of vaccine.

MATERIALS AND METHODS

Patients

This study included patients who tested positive for the B.1.617.2 (delta) variant between 24 June and 25 June 2021 (based on data http://www.gisaid.org). The SARS-CoV-2 variant was collected retrospectively based on a combination of author recall, reverse transcription-polymerase chain reaction (RT-PCR), and whole genome sequencing (WGS) results from the Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia (Depok, Indonesia). The cases included in this case series were subjects fully vaccinated against COVID-19 with confirmed delta variant infection between 24 and 25 June 2021, who worked or studied at Faculty of Medicine, Universitas Indonesia.

Statistical analysis

Subject data are presented as absolute values, percentages, mean ± SD, or median using SPSS 26 (IBM Corp, Armonk, NY, United States). Continuous and discrete variables are expressed as the mean ± SD or median depending on the results of the normality test. Categorical variables are expressed as *n* (%).

Literature survey paper

Sources: A comprehensive search of PubMed was performed for all studies published prior from March 2020 to April 2022, using the search terms "COVID-19", "Delta Variant OR B.1.617.2 Variant" , "Fully vaccinated OR Full-Dose Vaccine", and "Case Series" which yielded 26 results (Figure 1). A systematic review of these papers were performed, and after the full text of all articles were evaluated to determine whether results were included. There were no language restrictions. Two results were used for our paper (Table 1).

RESULTS

We described the first 15 subjects with the B.1.617.2 (delta) variant SARS-CoV-2 collected from nasopharyngeal swabs between 24 and 25 June 2021 at the Clinical Microbiology Laboratory Universitas Indonesia. Table 2 shows the demographic statistics of the subjects enrolled. The mean age of the subjects was 29 years (± 5.097), and 10 were males. Of the 15 subjects, 2 (13.34%) had one or more coexisting medical conditions: chronic respiratory disease in 1, and obesity with a history of rhinitis allergy in 1. The mean body mass index (BMI) of subjects was 24.768 kg/m^2 (± 3.531), which was statistically in a normal category according to the WHO and overweight at risk according to the Asian-Pacific BMI with a mean height of 167.00 cm (± 8.384) and a mean weight of 69.20 kg (± 11.706)[8]. Subjects were primarily employees working at Universitas Indonesia and included a total of 11 (73.34%) employees, 1 (6.67%) medical student, and 3 (20%) residents. Of the 15 subjects, 14 (93.34%) were vaccinated with CoronaVac (Sinovac), which was widely available in the first phase of vaccination in Indonesia.

Table 3 shows the clinical characteristics of the subjects included in this case series. Of the 15 subjects enrolled, 1 (6.67%) was reinfected. The first infection occurred before the patient had the first vaccination, and reinfection occurred after the second dose of vaccine. Most subjects (7, 46.67%) were thought to be infected by their coworkers, followed by family in 3 (20%), patients in 3 (20%), and unknown sources in 2 (13.34%). Eleven subjects (73.34%) used a surgical mask during work and daily

Table 1 Literature survey papers

Ref.	Publication date	Journal	Sample size	Subjects	Limitations
Park *et al* [22]	January 4, 2022	*Clinical Infection Disease*	108	Delta Variant	Statistic of fully vaccinated sample not included, sample from different ethnic
Hu *et al* [23]	March 1, 2022	*Frontiers in Medicine*	156	Delta Variant Fully Vaccinated	Sample from different ethnic

Table 2 Demographic statistics of the subjects enrolled

Demographic factor	All
Subjects, *n*	15
Age class, *n* (%)	
21-25	3 (20)
26-30	5 (33.34)
31-35	4 (26.67)
35-40	3 (20)
Age in yr, mean ± SD	29.87 ± 5.097
Sex	
Male	10 (66.67)
Female	5 (33.33)
Height in cm, mean ± SD	167.00 ± 8.384
Weight in kg, mean ± SD	69.20 ± 11.706
Body mass index as kg/m^2, mean ± SD	24.768 ± 3.531
Occupation, *n* (%)	
Employee	11 (73.34)
Medical students	1 (6.67)
Residents	3 (20)
Comorbidity, *n* (%)	2 (13.34)
Chronic respiratory disease	1 (6.67)
Obesity	1 (6.67)
Vaccination type, *n* (%)	
CoronaVac (Sinovac)	14 (93.34)
ChAdOx1 nCoV-19 (Oxford-AstraZeneca)	1 (6.67)

activity, three (20%) used an N95 mask, and one (6.67%) used a KN95 mask.

Of the 15 subjects enrolled, 1 (6.67%) was asymptomatic and 14 (93.34%) were symptomatic. Among the symptomatic patients, the most common symptoms at the onset of illness were fever (10, 66.67%), defined as an axillary temperature of 37.5 °C or higher, rhinorrhea (9, 60%), anosmia (8, 53.34%), cough (7, 46.67%), headache (5, 33.34%), ageusia/dysgeusia (4, 26.67%), fatigue (4, 26.67%), myalgia (4, 26.67%), diarrhea (3, 20%), sore throat (2, 13.34%), dyspnea (1, 6.67%), and nausea (1, 6.67%). All of the subjects were in home isolation. The mean time for symptom duration was 7.73 d (± 5.444). The mean time from the first positive swab to a negative RT-PCR test for SARS-CoV-2 was 17.93 d (± 6.3464). The median time that elapsed from the second dose of vaccine to the first positive swab was 87 d [interquartile range (IQR): 86-128 d].

Each of the 15 subjects received pharmacological treatment. Vitamin C was used in 14 subjects (93.34%), vitamin D in 12 (80%), paracetamol in 8 (53.34%), azithromycin in 5 (33.34%), favipiravir in 3 (20%), oseltamivir in 1 (6.67%), and phytopharmaca (*Andrographis paniculata*, known as Sambiloto in Indonesia) in 1 (6.67%).

Table 3 Clinical characteristics of the subjects enrolled

Characteristic		All
Reinfection, *n* (%)		1 (6.67)
Predicted source of infection, *n* (%)		
	Family	3 (20)
	Patient	3 (20)
	Coworker	7 (46.67)
	Unknown	2 (13.34)
Mask usage during outside activity, *n* (%)		
	Surgical mask	11 (73.34)
	N95 mask	3 (20)
	KN95 mask	1 (6.67)
Symptoms, *n* (%)		
	Fever	10 (66.67)
	Cough	7 (46.67)
	Rhinorrhea	9 (60)
	Headache	5 (33.34)
	Sore throat	2 (13.34)
	Anosmia	8 (53.34)
	Ageusia/Dysgeusia	4 (26.67)
	Diarrhea	3 (20)
	Fatigue	4 (26.67)
	Myalgia	4 (26.67)
	Dyspnea	1 (6.67)
	Nausea	1 (6.67)
Time in d of symptom duration, mean ± SD		7.73 ± 5.444
Time in d of PCR conversion, mean ± SD		17.93 ± 6.364
Time in d that elapsed from second dose of vaccine to a positive PCR result, median IQR		87 (86-128.00)
In-home isolation, *n* (%)		15 (100)
Drug treatment, *n* (%)		
	Vitamin C	14 (93.34)
	Vitamin D	12 (80)
	Paracetamol	8 (53.34)
	Azithromycin	5 (33.34)
	Oseltamivir	1 (6.67)
	Favipiravir	3 (20)
	Phytopharmaca	1 (6.67)

IQR: Interquartile range; PCR: Polymerase chain reaction.

DISCUSSION

In this case series, we reported 15 subjects with confirmed infection with the B.1.617.2 (delta) variant of SARS-CoV-2 after a second dose of vaccine. From the statistics acquired, men are more prone to SARS-CoV-2 infection. Angiotensin-converting enzyme 2 (ACE2) is expressed in various human tissues. The expression levels are not significantly different between males and females, between young and old

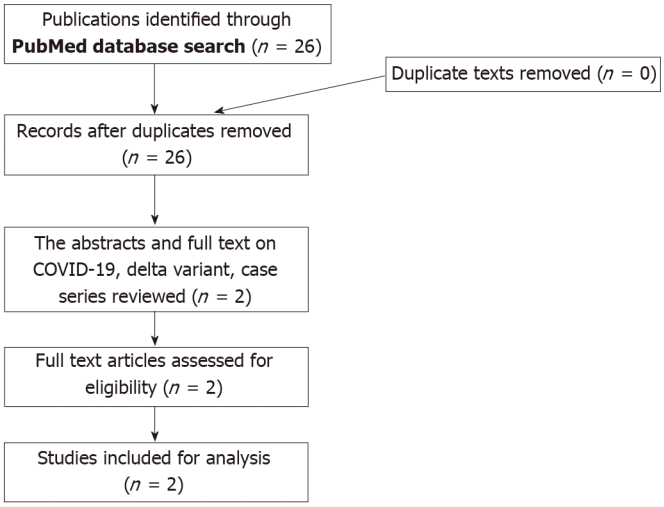

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Figure 1 Flow Chart outlining the selection of articles.

persons, nor among races, indicating that SARS-CoV-2 may equally infect persons of different sexes, ages, and races. The different host immune responses to infection may explain why males *vs* females and young *vs* old person persons infected with SARS-CoV-2 have distinct disease severity. Studies have found that the X chromosome and sex hormones play important roles in innate and adaptive immunity, which makes women less susceptible to viral infection[9]. Age also plays a key factor, as the body's immunity declines with age. Aging has been linked to abnormally high cellular functioning, cellular hyperfunctions that may eventually lead to cellular exhaustion, and function loss in later stages[10]. However, in this case series, the subjects were of productive age (15-64 years), with a mean age of 29 years (± 5.097)[11]. Subjects with underlying diseases such as diabetes, hypertension, cardiovascular disease, chronic respiratory disease, and obesity also have increased risk of SARS-CoV-2 infection. A long-term history of diabetes, hypertension, and cardiovascular disease damages the vascular structure and is more likely to reduce the body's immunity. When a subject has previous respiratory diseases that damaged their lung function such as lung tuberculosis or chronic obstructive pulmonary disease, they have lower resistance to the virus and are prone to developing acute respiratory distress syndrome[9]. Obesity or excess ectopic fat deposition may also be a unifying risk factor for SARS-CoV-2 infection, as it reduces protective cardiorespiratory reserve as well as potentiates the immune dysregulation that appears to mediate the progression to critical illness[12]. In this case series, 1 subject had a history of lung tuberculosis (6.67%) and 1 subject (6.67%) was obese according to the WHO BMI. However, the Asia-Pacific BMI has stated that BMI between 23.0 and 24.9 is considered overweight, which makes the subject in this case series more susceptible to SARS-CoV-2 infection, as the mean BMI was 24.768 kg/m^2 (± 3.531)[9,12].

Of the 15 subjects, 14 individuals (93.34%) were confirmed to have a second dose of CoronaVac (Sinovac) and 1 individual (6.67%) had a second dose of ChAdOx1 nCoV-19 (Oxford-AstraZeneca). Both vaccines are widely available in Indonesia, as other vaccines such as BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) have not arrived. According to a study in China, the vaccine effectiveness (VE) of two doses of CoronaVac was 59.0% (95%CI: 16.0%-81.6%) against the delta variant infection. However, a single dose vaccine of CoronaVac was not sufficiently protective against the delta variant [13]. However, ChAdOx1 nCoV-19 (Oxford-AstraZeneca) and BNT162b2 (Pfizer-BioNTech) vaccines had higher VE rates compared to CoronaVac (Sinovac). It has been reported that the VE after the second dose of Oxford-AstraZeneca vaccine is 67.0% (95%CI: 61.3%-71.8%) and 88.0% (95%CI: 85.3%-90.1%) with Pfizer-BioNTech. A single dose of Oxford-AstraZeneca or Pfizer-BioNTech vaccine was notably lower among people with the delta variant (30.55; 95%CI: 25.2%-35.7%)[14].

WGS data of the samples showed that the most common mutations found in the S protein domains were L452R, T478K, D614G, and P681R, which might affect the sensitivity in neutralizing monoclonal antibodies[15]. Research has shown that the L452R mutation can cause a decrease in the titer of vaccine-induced serum neutralizing antibody against the pseudovirus and recognition by antibodies while maintaining binding to ACE2[16]. P681R and D614G mutations also cause a partial decrease in neutralizing antibodies. A study by Saito *et al*[18] showed that the neutralizing antibodies of immune serum induced by BNT162b2 vaccine against D614G/P681R virus was significantly decreased[18]. The T478K mutation also exhibited a reduction in its neutralization sensitivity towards the post-vaccination sera. This phenomenon might explain the incidence of infection in vaccinated subjects.

From this case series, there was 1 subject (6.67%) who had been diagnosed twice with SARS-CoV-2 infection, before vaccination and after two doses of vaccine. A study by Altawalah[19] showed that the

immune responses induced by COVID-19 vaccination are greater than those induced by natural SARS-CoV-2 infection. Therefore, individuals that have recovered from a confirmed COVID-19 infection are still prone to another reinfection. A study by Ebinger *et al*[20] also showed that the anti-S immunoglobulin G antibody response following a single vaccine dose in people who have recovered from confirmed prior COVID-19 infection is comparable to the antibody reaction following two doses of vaccine in people who have never been infected ($P > 0.58$). Thus, individuals who once had confirmed COVID-19 infection and also had a double dose regimen are expected to have better immunity against COVID-19. Reinfection in this case still remained unclear, but age, sex, and underlying diseases such as obesity, chronic respiratory disease, and cardiovascular disease could be independent risk factors that contribute to susceptibility to viral infection[10].

According to a study by Das *et al*[21], different types of masks have different effectiveness in protecting subjects against SARS-CoV-2. A surgical face mask has the lowest filtration rate of 60%-80% and can filter particles as small as 0.3 μm. The N95 face mask has the highest filtration rate (95%) compared to the other two; it can filter particles of 0.1-0.3 μm in size. The KN95 face mask has an 80%-95% filtration rate and can filter particles down to 0.3 μm. Since SARS-CoV-2 is a 0.1 μm enveloped virus, the N95 mask has a better probability of protecting against COVID-19 infection[21]. The current study showed that 11 (73.34%) of the 15 subjects who tested positive for COVID-19 were using surgical masks for daily usage. The correct use of N95/KN95 masks requires a fit test or seal test, which is sometimes not done properly. It was also noted that masks were used during their daily activities, and no subject had performed an aerosol-generating procedure before infection with COVID-19.

The common clinical manifestations of COVID-19 patients in this case series were fever in 10 (66.67%), rhinorrhea in 9 (60%), anosmia in 8 (53.34%), and cough in 7 (46.67%). A recent study by Park *et al*[22], also strengthen our findings, from a total of 108 delta variant subjects that were enrolled, common symptoms for the delta variant are fever (73.7%), myalgia (51.5%), cough (49.5%), sore throat (43.4%), and cephalgia (34.3%). In comparison, Myalgia was more common in the delta group (51.5%) than in the non-delta group (26.9%). Non-delta variant also showed significant symptoms of loss of taste (26.9%) and loss of smell (15.4%) compare to delta group with loss of taste (2.0%) and loss of smell (7.1%)[22]. Another study by Hu *et al*[23] with 156 full vaccinated delta variant patients that admitted at Yangzhou, China in 2021 also indicate that most common symptoms are cough (48.7%), fever (34.6%), sore throat (25.6%), fatigue (19.2%), and expectoration (8.3%). Another study also showed that between delta variant and alpha variant are quite similar, except patients with delta variant could become rapidly ill and have higher viral loads in the respiratory tract. Delta variant could also cause auditory impairment and gangrene from worse blood clots[24]. Viral infection triggers an inflammatory pathway in the human body. Various inflammatory factors produced by the inflammatory storm can cause systemic immune damage and manifest as high temperatures. It explains why the most common symptom was fever. SARS-CoV-2 also binds to the ACE2 receptor, which is mainly distributed in the respiratory tract, cardiovascular, kidneys, and colon. It causes multiple symptoms, such as dyspnea, cough, anosmia, ageusia, diarrhea, and sore throat[9] (Table 4).

Although subjects with two-dose vaccination can still be infected with SARS-CoV-2, the results from a current trial suggest that there is a 90% reduction in symptomatic COVID-19 with vaccine. However, it remains unknown whether this efficacy is mediated by decreasing SARS-CoV-2 infection susceptibility (VE_{SUSC}) or the development of symptoms after infection (VE_{SYMP})[25]. In our case series, symptoms that developed in COVID-19 patients were mild to moderate according to the Indonesian COVID-19 Guideline. In addition, vaccination decreased the symptom duration of COVID-19 patients (7.73 ± 5.444 d), increased the recovery time from the first positive swab to negative swab (17.93 ± 6.364 d), and prevented the subjects from needing hospitalization. A recent study revealed that VE in terms of protection against deaths was 72%, with a lower reduction of mortality for B.1.1.7 *vs* non-B.1.1.7 variants (70% *vs* 78%, respectively)[26]. A study from a hospital in New Delhi, India showed that among those fully vaccinated, there was 12.5% (23/184) mortality compared to 31.45% (309/984) among the unvaccinated (OR = 0.3, 95%CI: 0.2-0.5; $P < 0.0001$)[27].

The most common drugs used in our case series were vitamin C (14 subjects, 93.34%) and vitamin D (12 subjects, 80%). Low levels of micronutrients have been associated with adverse clinical outcomes during SARS-CoV-2 infection. As a result, daily vitamin intake may be beneficial in maximizing the immune response to viral infection. Recent studies have shown that vitamin D improves the physical barrier against viruses and stimulates the production of antimicrobial peptides. It may also prevent cytokine storm by lowering the production of inflammatory cytokines. Vitamin C is considered an antiviral agent as it increases immunity. It also increases antiviral cytokines and free radical formation, lowering viral yield and attenuating excessive inflammatory responses and hyperactivation of immune cells[28]. However, the effectiveness of vitamin C and vitamin D against the B.1.617.2 (delta) variant remain unknown. In this study, 1 subject had consumed *Andrographis paniculata* as phytopharmaca. According to current studies, *Andrographis paniculate*can act as a potential inhibitor of the main protease of SARS-CoV-2, but further studies should be considered[29].

This study had some limitations. First, due to the mandatory WGS results, there were limitations in the subjects included. Thus, the case series might not be representative of the general population and extrapolation to other settings should be done with caution. Second, the data were collected using a questionnaire filled out by the patients themselves, which may have led to bias. Finally, due to

Table 4 Comparative study with other paper

	Our study (*n* = 15)	Park *et al*[22] (*n* = 108)	Hu *et al*[23] (*n* = 156)
Age	29.87 ± 5.097	34.5 (26.5-46.0)	43.0 (33.0-56.8)
Comorbidity			
Hypertension		12 (11.1)	31 (19.9)
Hyperlipidaemia		4 (3.7)	
Diabetes		7 (6.5)	9 (5.8)
Psychiatric illness		1(0.9)	
Cancer		1 (0.9)	
Obesity (BMI > 30)	1 (6.67)	12 (11.1)	
Cardiovascular disease			5 (3.2)
Respiratory disease	1 (6.67)		
Symptoms			
Fever	10 (66.67)	73 (73.7)	54 (34.6)
Cough	7 (46.67)	49 (49.5)	76 (48.7)
Rhinorrhoea	9 (60)	4 (4.0)	
Headache	5 (33.34)	34 (34.3)	
Sore throat	2 (13.34)	43 (43.4)	40 (25.6)
Anosmia	8 (53.34)	7 (7.1)	
Ageusia/dysgeusia	4 (26.67)	2 (2.0)	
Diarrhoea	3 (20)	3 (3.0)	14 (9.0)
Fatigue	4 (26.67)		30 (19.2)
Myalgia	4 (26.67)		
Dyspnoea	1 (6.67)	1 (1.0)	1 (0.6)
Nausea	1 (6.67)		

BMI: Body mass index.

Table 5 Research gap analysis

Ref.	Reasons(s) for gap	Population	Results	Free text of gap
Park *et al* [22]	D	Delta variant	A total of 141 patients [Delta group, *n* = 108 (77%); non-Delta group, *n* = 33 (23%)]; Delta group: Median age 34.5 (26.5-46.0); Hypertension 12 (11.1); Hyperlidemia 2 (6.1); Diabetes 5 (15.2); Psychiatric Illness 1(3.0); Asthma/Rhinitis 1 (3.0); Cancer 1 (3.0); Obesity BMI > 30.4 (12.1)	Results may not be applicable for reference as full vaccinated criteria not included and our subject only had chronic respiratory disease 1 (6.67) and obesity 1 (6.67)
Hu *et al*[23]	D	Delta variant fully vaccinated	A total of 677 patients (Wild type = 341; Delta unvaccinated = 120; Delta Partially vaccinated = 60; Delta fully vaccinated = 156); Delta fully vaccinated: Median age 43.0 (33.0-56.8); Hypertension 31 (19.9); Diabetes 9 (5.8); Cardiovascular disease 5 (3.2)	Results may not be applicable for reference as median age in our subject 29.87 ± 5.097 with comorbidity chronic respiratory disease 1 (6.67) and obesity 1 (6.67)

D: Not the right information (results not applicable/optimal outcomes not assessed/studies too short). BMI: Body mass index.

regulations, the RT-PCR test was not performed daily. Duration of conversion was considered the time from the first positive swab until the first negative result. It is possible that a patient had a negative result before RT-PCR was conducted (Table 5).

CONCLUSION

This case series highlights that the currently available treatment for the B.1.617.2 (delta) variant of SARS-CoV-2 infection is still unknown. Further studies and research should be conducted. Although this case shows that after two doses of vaccine, subjects are still susceptible to the B.1.617.2 (delta) variant, currently available vaccines remain the most effective protection. They reduce the clinical manifestations of COVID-19, decrease the recovery time from first positive swab to negative swab, and lower the probability of hospitalization and mortality rate compared to unvaccinated individuals. We should also support efforts to maximize vaccine uptake with two doses among vulnerable populations to protect them against the B.1.617.2 (delta) variant.

ARTICLE HIGHLIGHTS

Research background

The delta variant of coronavirus disease 2019 (COVID-19) has quickly spread around the globe and infected not only unvaccinated population but fully vaccinated citizens. The demographic statistics and clinical presentation of the first cluster of delta variant infection in this population remained unknown and neglected.

Research motivation

The authors aimed to provide an insight into the demographic statistics and clinical presentation of the first cluster of delta variant infection after a second dose of vaccine. This could help others with lack of laboratory facility to diagnose delta variant infection.

Research objectives

The objective of this case series was to describe the demographic statistics and clinical presentation of the first cluster of delta variant infection after a second dose of vaccine.

Research methods

This is a retrospective, single-center case series of the general consecutive population that worked or studied in Our University with confirmed Delta Variant Infection after a second dose of vaccine from 24 June and 25 June 2021. We decided to collect data based on a combination of author recall, reverse transcription-polymerase chain reaction (RT-PCR), and whole genome sequencing results. Epidemiological, demographic, clinical, and laboratory data were analyzed.

Research results

Among 15 subjects recruited, Fourteen subjects were vaccinated with CoronaVac (Sinovac) and one subject with ChAdOx1 nCoV-19 (Oxford-AstraZeneca). All of the subjects remained in home isolation, with fever being the most common symptom at the onset of illness (n = 10, 66.67%). The mean duration of symptoms was 7.73 d (± 5.444). The mean time that elapsed from the first positive swab to a negative RT-PCR test for SARS-CoV-2 was 17.93 d (± 6.3464). The median time that elapsed from the second dose of vaccine to the first positive swab was 87 d (interquartile range: 86-128).

Research conclusions

After two doses of vaccine, subjects are still susceptible to the delta variant infection. Currently available vaccines remain the most effective protection.

Research perspectives

The case series might not be representative of the general population. It is necessary to collect more subjects infected with delta variant after second dose of vaccination to improve the quality of this study.

FOOTNOTES

Author contributions: Syam AF and Achmadsyah A contributed equally to this work and wrote a draft of the paper; Achmadsyah A, Fadilah F, and Ibrahim F collected the patient's clinical data; All authors analyzed the data and wrote the paper; Karuniawati A, Syam AF, Ibrahim F, Saharman YR, Sudarmono P, Fadilah F, and Rasmin M made important intellectual contributions and revised the paper; Syam AF and Achmadsyah A edited all drafts of the paper; and All authors approved the final version of the manuscript.

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

Data sharing statement: The datasets used and/or analyzed during the current study are available from the

corresponding author on reasonable request.

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ORIGINAL ARTICLE

Retrospective Study

Endobronchial ultrasound-guided transbronchial needle aspiration in intrathoracic lymphadenopathy with extrathoracic malignancy

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Abstract

BACKGROUND

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for the diagnosis of mediastinal and hilar lymph is poorly studied in patients with extrathoracic malignancies.

AIM

To evaluate the value of EBUS-TBNA for the diagnosis of enlarged intrathoracic lymph nodes in patients with extrathoracic malignancies.

METHODS

This was a retrospective study of patients with extrathoracic malignancies who were referred to Peking University Cancer Hospital from January 2013 to December 2018 for EBUS-TBNA due to intrathoracic lymphadenopathy. The specimens were defined as positive for malignancy, negative for non-malignancy (tuberculosis, sarcoidosis, *etc.*), and without a definitive diagnosis. Sensitivity, negative predictive value (NPV) for malignancy, and overall accuracy were calculated. Complications were recorded.

RESULTS

A total of 80 patients underwent EBUS-TBNA and had a final diagnosis, among which 50 (62.5%) were diagnosed with extrathoracic malignancy with intrathoracic lymph nodes metastasis, 14 (17.5%) were diagnosed with primary lung cancer with nodal involvement, and 16 (20.0%) exhibited benign behavior including tuberculosis, sarcoidosis and reactive lymphadenitis or who had benign follow-up. The diagnostic sensitivity, NPV, and accuracy of EBUS-TBNA for intrathoracic lymphadenopathy in patients with extrathoracic malignancy were 93.8% (n = 60/64), 80.0% (n = 16/20), and 95.0% (n = 76/80), respectively. In the

multivariate analysis, longer short axis of the lymph node (OR: 1.200, 95%CI: 1.024-1.407; P = 0.024) and synchronous lung lesion (OR: 19.449, 95%CI: 1.875-201.753; P = 0.013) were independently associated with malignant intrathoracic lymphadenopathy. No characteristics of the lymph nodes and EBUS-TBNA were associated with the location of malignant intrathoracic lymphadenopathy, and no major complication was observed.

CONCLUSION
EBUS-TBNA is a simple and accurate procedure for the diagnosis of intrathoracic lymphadenopathy with extrathoracic malignancy.

Key Words: Endobronchial ultrasound; Intrathoracic lymphadenopathy; Extrathoracic malignancy; Transbronchial needle aspiration; Diagnosis

Core Tip: This was a retrospective study of patients referred to Peking University Cancer Hospital from January 2013 to December 2018 for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) due to intrathoracic lymphadenopathy. The specimens were defined as positive for malignancy, negative for non-malignancy (tuberculosis, sarcoidosis, *etc.*), and without definite diagnosis. Sensitivity, negative predictive value for malignancy, and overall accuracy were calculated. EBUS-TBNA was found to be a simple and accurate procedure for the diagnosis of intrathoracic lymphadenopathy with extrathoracic malignancy.

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INTRODUCTION

Intrathoracic lymphadenopathy is a common incidental finding by computed tomography (CT) or positron emission tomography (PET)-CT in cases with synchronous or metachronous extrathoracic malignancies[1-3]. In such conditions, the causes of mediastinal or hilar nodal enlargement may be distal metastasis of the extrathoracic lesion, metastasis from a primary lung cancer synchronous with the extrathoracic malignancy, or even benign lesions including tuberculosis, granulomatous inflammation, and reactive changes[3-5]. In all of these situations, pathologic confirmation of the enlarged lymph node is crucial for the proper staging and management of patients[1].

Mediastinoscopy is considered the "gold standard" in nodal evaluation for intrathoracic lymphadenopathy, but it is invasive and requires general anesthesia[6]. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is currently the preferred modality to sample both mediastinal and hilar lymph nodes in primary lung cancer because it is not only minimally invasive but also can be performed under moderate conscious sedation or even under intratracheal surface anesthesia only[7,8]. Tournoy *et al*[9] showed that EBUS-TBNA is a diagnostic test for lung lesions after failed diagnostic bronchoscopy. A number of studies have shown that EBUS-TBNA is of value for the staging of lung cancer, as reviewed by Sehgal *et al*[10]. EBUS-TBNA is also of value for the diagnosis of mediastinal lymphoma[11]. In clinical practice, EBUS-TBNA could be considered the first-line examination for suspicious mediastinal lymph nodes in patients with extrathoracic cancer, preventing surgery in 50% of them[12]; in contrast, the use of EBUS-TBNA in intrathoracic lymphadenopathy in patients with extrathoracic solid organ malignancy is a relatively less investigated topic[13,14].

Therefore, the aim of this study was to evaluate the value of EBUS-TBNA for the diagnosis of enlarged intrathoracic lymph nodes in patients with extrathoracic malignancies.

MATERIALS AND METHODS

Patients

This study was designed as a single-center retrospective case series study. Data from patients who were referred to Peking University Cancer Hospital (Beijing, China) from January 2013 to December 2018 for EBUS-TBNA due to intrathoracic lymphadenopathy were retrieved from the hospital database. The

study was conducted according to good clinical practice and the Declaration of Helsinki. The protocol was approved by the ethics committee of Peking University Cancer Hospital (No. 2018YJZ72), which waived the need for individual consent.

The inclusion criteria for patients were synchronous or metachronous extrathoracic solid organ malignancy, and available radiological data including from CT or PET-CT scan. The exclusion criteria were synchronous or metachronous lymphoma or leukemia, or follow-up of < 12 mo when no definite diagnosis could be obtained by EBUS-TBNA with/without other interventional procedures including mediastinoscopy or thoracoscopy.

EBUS-TBNA procedures

Before EBUS-TBNA, the target lymph nodes for sampling were selected according to enlarged mediastinal or hilar lymph node with a short axis > 10 mm in thorax CT or maximum standardized uptake (SUV_{max}) value > 2.5 in PET-CT. The lymph node map was determined according to the classification proposed by the International Association for the Study of Lung Cancer[15].

EBUS-TBNA was performed in an outpatient setting using a flexible bronchoscope (BF-UC260F-OL8; Olympus, Tokyo, Japan) by 1 of 2 experienced endoscopists (QW or SJL). First, local anesthesia was applied *via* aerosol inhalation and intratracheal spray of 2% lidocaine. Then, the EBUS scope was introduced, and all reachable lymph node stations were examined. Sampling was performed from mediastinal and hilar lymph nodes that had been previously identified as suspicious by imaging and were able to be accessed by EBUS-TBNA. For each target lesion, real-time punctures were made using a standard 22-gauge needle (ECHO-HD-22-EBUS-O; Cook Medical, Bloomington, IN, United States). Attempts were made to acquire both cytological and histological specimens during sampling, if possible (Figure 1). Major complications (*e.g.*, serious hemorrhage > 100 mL, pneumothorax, and post-procedure infection) that occurred during and/or after surgery were recorded.

Pathological examinations

The cytological samples were prepared as air-dried smears on glass slides and in liquid fixative for thinprep cytological test. They histological specimens were fixed in formalin solution, and immunohistochemistry was performed when necessary (Figure 1).

The specimens obtained from EBUS-TBNA were defined as positive for malignancy, negative for non-malignancy (tuberculosis, sarcoidosis, *etc.*), and without definite diagnosis. In cases of no definite diagnosis, mediastinoscopy, video-assisted thoracic surgery (commonly known as VATS), or repeated EBUS-TBNA was recommended; patients who refused were subject to at least 12 mo of radiological and clinical follow-up every 3 mo. Follow-up was censored on December 31, 2018.

Statistical analyses

SPSS 20.0 software (IBM Corp., Armonk, NY, United States) was used for the statistical analyses. Continuous variables are presented as either means ± SD (normal distribution, Kolmogorov-Smirnov test) or median (minimum-maximum) (non-normal distribution). Categorical variables are presented as numbers and percentages and were analyzed using either the χ^2 test or the Fisher's exact test, as appropriate. Sensitivity for malignancy, negative predictive value (NPV) for non-malignancy, and overall accuracy were calculated. Predictors of malignant lymphadenopathy were modeled using logistic regression (enter method); variables with $P < 0.05$ in univariate analyses were included in multivariate analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 1204 patients who underwent EBUS-TBNA were reviewed. After exclusion of 1124 cases [without known extrathoracic malignancy (n = 1112), with previously or concurrent lymphoma or leukemia (n = 7), with sites of puncture not at the intrathoracic lymph node (n = 3), and with follow-up of less than 12 mo (n = 2)], 80 fulfilled the eligibility criteria (Figure 2). Among the cases included in the study (Table 1), the most common extrathoracic malignancies (65%) were breast, colorectal, and gastric cancers.

Details of the EBUS-TBNA procedures

The 80 included patients had a total of 123 enlarged lymph nodes sampled by EBUS-TBNA (median of one lymph node every patient; range: 1-4). Cytological specimens were successfully acquired from all 80 patients, and histological specimens were available for 74 (92.5%). The paratracheal region was the most common site (42.2%) for puncture (Table 2). The median number of puncture times was two for each lymph node (range: 1-6).

Table 1 Patient characteristics, *n* = 80

Characteristics	*n* (%) or mean ± SD
Age (yr)	58.5 ± 8.8
Male sex	36 (45.0)
Site of the primary extrathoracic malignancy	
Breast	18 (22.5)
Colon	12 (15.0)
Rectal	11 (13.8)
Gastric	11 (13.8)
Renal cell	7 (8.8)
Thyroid	6 (7.5)
Head and neck[1]	5 (6.3)
Endometrial	3 (3.8)
Hepatic cell	2 (2.5)
Other[2]	5 (6.3)
Site of intrathoracic lymphadenopathy	
Mediastinal only	43 (53.8)
Mediastinal and hilar	21 (26.2)
Hilar only	16 (20.0)
Status of the extrathoracic malignancy	
Metachronous	66 (82.5)
Synchronous	14 (17.5)
CT findings	
Intrathoracic nodal enlargement with pulmonary lesion	39 (48.8)
Short axis of the target lymph node in mm	18.1 ± 6.7
PET-CT findings	
Patients with PET-CT examination	49 (61.3)
SUV_{max} of the target lymph nodes	9.2 ± 5.0

[1]Oropharyngeal (*n* = 2), nasopharyngeal (*n* = 1), laryngeal (*n* = 1), and parotid (*n* = 1).
[2]Cervical (*n* = 1), ovarian (*n* = 1), melanoma (*n* = 1), pancreatic (*n* = 1), and prostate (*n* = 1).
CT: Computed tomography; PET: Positron emission tomography; SUV_{max}: Maximum standardized uptake.

Pathology of lymph nodes

EBUS-TBNA diagnosed intrathoracic nodal metastasis from extrathoracic malignancy in 47 (58.8%) patients, and intrathoracic lymphadenopathy due to primary lung cancer in 13 (16.3%) patients (including 8 Lung adenocarcinomas, 3 Lung squamous carcinomas, and 2 small cell lung cancers). Regarding the 9 patients with benign diagnosis, sarcoidosis was diagnosed in 3, caseous granulomatosis with suspected tuberculosis in 3, and non-caseating granulomatous inflammation in 3. For the last 3, the inflammation was clinically inconsistent with sarcoidosis because of negative fungal and mycobacterial cultures. All 3 refused further interventional procedures, and after a median follow-up of 15 (14-19) mo, clinical and radiological results suggested benign behavior (all enlarged lymph nodes remained stable).

EBUS-TBNA found normal lymph node tissue or non-specific tissue for pathologic diagnosis in 11 (13.8%) patients. Six of them received surgical intervention (four mediastinoscopy procedures and two VATS procedures) to obtain pathologic results. Reactive change was found in 2 patients, tuberculosis was found in 1, squamous carcinoma of lung with hilar lymph node metastasis in 1, rectal cancer lung metastasis with nodal involvement in 1, and renal cell cancer with mediastinal nodal involvement in 1. The remaining 5 patients who refused surgical intervention received periodical clinical and radiologic follow-up. One patient had progressive lymphadenopathy that was clinically considered metastasis from extrathoracic malignancy (colon cancer) and accepted the recommendation of systemic

Table 2 Primary extrathoracic malignancy site and the final pathologic result of the intrathoracic lymphadenopathy

Extrathoracic malignancy	*n* (%)	Location			EBUS			Surgery			Follow-up	
		Paratracheal	Subcarinal	Hilar and lobar	ETM LNM	PLC LNM	Benign	ETM LNM	PLC LNM	Benign	FO	ETM LNM
Breast cancer	18 (22.5)	12	8	8	11	3	2	-	-	1	1	-
Colon cancer	12 (15.0)	8	4	4	7	3	-	-	-	-	1	1
Rectal cancer	11 (13.8)	4	2	8	7	3	-	1	-	-	-	-
Gastric cancer	11 (13.8)	7	5	6	6	2		-	-	1	1	-
Renal cell cancer	7 (8.8)	6	4	2	6	-	-	1	-	-	-	-
Thyroid cancer	6 (7.5)	6	2	2	1	2	3	-	-	-	-	-
Head and neck cancer[1]	5 (6.3)	3	3	2	3	-	-	-	1	1	-	-
Endometrial cancer	3 (3.8)	1	2	2	2	-	1	-	-	-	-	-
Hepatic cell cancer	2 (2.5)	1	1	0	2	-	-	-	-	-	-	-
Other[2]	5 (6.3)	4	2	4	2	-	2	-	-	-	1	-
Total	80 (100.0)	52	33	38	47	13	9	2	1	3	5	

[1]Oropharyngeal cancer (*n* = 2), nasopharyngeal cancer (*n* = 1), laryngeal cancer (*n* = 1), and parotid cancer (*n* = 1).
[2]Cervical cancer (*n* = 1), ovarian cancer (*n* = 1), melanoma (*n* = 1), pancreatic cancer (*n* = 1), and prostate cancer (*n* = 1).
EBUS: Endobronchial ultrasound-guided transbronchial needle aspiration; ETM: Extrathoracic malignancy; FO: Favorable outcome; LNM: Lymph node metastasis; PLC: Primary lung cancer.

chemotherapy by multidisciplinary team. The remaining 4 patients showed a favorable outcome (1 was stable and 3 showed regressive lymphadenopathy) during a median follow-up of 16 (13-18) mo.

Diagnostic accuracy

Ultimately, 50 (62.5%) patients were diagnosed with extrathoracic malignancy with intrathoracic lymph nodes metastasis and 14 (17.5%) with primary lung cancer with nodal involvement; the remaining 16 (20.0%) patients exhibited benign behavior including tuberculosis, sarcoidosis and reactive lymphadenitis, or who had benign follow-up. The diagnostic sensitivity, NPV, and accuracy of EBUS-TBNA for intrathoracic lymphadenopathy in patients with extrathoracic malignancy were 93.8% (*n* = 60/64), 80.0% (*n* = 16/20), and 95.0% (*n* = 76/80), respectively.

Predictors of malignant lymphadenopathy

Univariate analyses revealed that longer short axis of the lymph node and synchronous lung lesion were associated with the presence of metastatic lymphadenopathy (*P* = 0.003 and *P* = 0.001, respectively). In the logistic regression multivariate model, longer short axis of the lymph node (OR: 1.200, 95%CI: 1.024-1.407) and synchronous lung lesion (OR: 19.449, 95%CI: 1.875-201.753) were independently associated with malignant intrathoracic lymphadenopathy (*P* = 0.024 and *P* = 0.013, respectively; Table 3).

Univariate analyses demonstrated that no characteristics of the lymph nodes themselves and EBUS-TBNA were associated with the yield of malignant intrathoracic lymphadenopathy (Table 4).

Safety of the EBUS-TBNA procedure

No major complications occurred during the EBUS-TBNA procedures. Twelve (15.0%) patients experienced transient hypoxemia and all recovered after immediate increase of oxygen flow.

DISCUSSION

EBUS-TBNA for the diagnosis of mediastinal and hilar lymph is poorly studied in patients with extrathoracic malignancies. This study's evaluation of the value of EBUS-TBNA for the diagnosis of enlarged intrathoracic lymph nodes in patients with extrathoracic malignancies suggested that the procedure is simple and accurate for diagnosis of intrathoracic lymphadenopathy with extrathoracic malignancy. Moreover, there were no complications.

Table 3 Risk factors of being malignant for intrathoracic lymphadenopathy

Covariates	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Sex				
Female	1			
Male	1.720 (0.727-4.071)	0.217		
Age (yr)				
≤ 60	1			
> 60	1.647 (0.696-3.900)	0.257		
Size of sampled lymph node	1.113 (1.036-1.196)	0.003	1.200 (1.024-1.407)	0.024
Site of lymphadenopathy				
Mediastinal and hilar	1			
Mediastinal only	1.244 (0.528-2.932)	0.617		
Hilar only	6.788 (0.819-56.257)	0.076		
Status of synchronous lung lesion				
Without	1		1	
With	8.082 (2.292-28.501)	0.001	19.449 (1.875-201.753)	0.013
Status of synchronous ETM				
Synchronous	1			
Metachronous	1.057 (0.629-1.776)	0.834		
SUV_{max} of sampled lymph node	0.987 (0.887-1.098)	0.806		

ETM: Extrathoracic malignancy; SUV_{max}: Maximum standardized uptake.

With the rapid development of cancer therapies, overall survival of patients has improved significantly[16]. Regular follow-up and surveillance are essential and, unfortunately, the detection of intrathoracic lymphadenopathy is not uncommon, due in part to improvements in imaging technologies. Up to 30% of extrathoracic malignancies may lead to intrathoracic lymph node metastasis[17]. The most common solid malignancies responsible include breast, colorectal, head and neck, melanoma, kidney, and stomach cancers[14,18,19]. This study showed that breast, colorectal, gastric, and renal cell cancers accounted for 73.4% (59/80) of the extrathoracic malignancies in our patients; of note, however, differences in other cancer types might simply be due to the differences in cancer types treated at our hospital.

Primary lung cancer with nodal involvement accounts for the majority of mediastinal and hilar lymphadenopathy cases[20], but Mehta *et al*[13] showed a high frequency of benign diagnoses. EBUS-TBNA is considered safe and feasible for tissue sampling with access to both mediastinal and hilar lymph nodes, which is recommended by both the American College of Chest Physicians and European Society of Thoracic Surgeons in primary lung cancer[7,8]. In a meta-analysis that included nine studies and 1066 patients, EBUS-TBNA had pooled sensitivity of 90%, accuracy of 96%, and NPV of 93% for mediastinal staging[21]. EBUS-TBNA also showed an acceptable diagnostic ability in determining intrathoracic lymphadenopathy with extrathoracic malignancy. In a meta-analysis of six studies (553 patients) by Yang *et al*[17], EBUS-TBNA provided pooled sensitivity of 85%, accuracy of 85%, and negative likelihood ratio of 16%. The present study revealed sensitivity, accuracy, and NPV of 93.8%, 95.0%, and 80.0%, respectively, by EBUS-TBNA for intrathoracic lymphadenopathy in patients with extrathoracic malignancy, in accordance with a previous study[17]. As intrathoracic metastasis always indicates an advanced stage of the primary extrathoracic malignancy, early and accurate identification of the nature of the lymph node is important for staging, treatment strategy, and prognosis. Considering the promising diagnostic value of EBUS-TNBA, the procedure could be recommended as the first diagnostic procedure for mediastinal and hilar lymphadenopathies seen in extrathoracic malignancies.

Regarding granulomatous lymphadenitis, the diagnostic yield of EBUS-TBNA seems efficacious. A meta-analysis of 15 studies with 553 patients found that the pooled diagnostic accuracy for sarcoidosis was 79% by EBUS-TBNA[22]. Concerning tuberculous lymphadenitis diagnosis, in a meta-analysis of 14 studies with 684 patients, EBUS-TBNA showed a pooled diagnostic yield of 80%[23]. In regard to EBUS-TBNA for non-caseating granulomatous, more attention should be paid. Sanz-Santos *et al*[14] reported a

Table 4 Factors influencing endobronchial ultrasound-guided transbronchial needle aspiration accuracy in intrathoracic malignant lymphadenopathy, *n* = 94

Covariates	Accurate number, *n* (%)	Univariate analysis OR (95%CI)	*P* value
Sex			
Female	46 (92.0)	1	
Male	41 (93.2)	1.783 (0.310-10.246)	0.571
Age (yr)			
≤ 60	47 (92.2)	1	
> 60	40 (93.0)	1.702 (0.296-9.785)	0.551
Location of sampled lymph node			
Hilar	27 (93.1)	1	
Paratracheal	36 (92.3)	2.000 (0.312-12.815)	0.465
Subcarinal	24 (92.3)	2.667 (0.260-27.381)	0.409
Determination of target lymph node			
PET-CT and CT	52 (90.0)	1	
CT only	35 (97.2)	3.365 (0.377-30.052)	0.277
Size of short axis in sampled lymph node in mm	18.9 ± 7.0	1.093 (0.975-1.248)	0.191
SUV_{max} of sampled lymph node	8.8 ± 5.1	0.877 (0.753-1.015)	0.077
Number of passes per lymph node, times, median (range)	2 (1-5)	2.097 (0.691-6.253)	0.193
Histological specimen acquired			
No	7 (87.5)	1	
Yes	80 (93.0)	2.286 (0.233-22.387)	0.478
Operator of EBUS-TBNA			
Dr. LSJ	70 (92.1)	1	
Dr. WQ	17 (94.4)	1.124 (0.133-11.085)	0.863

Data are presented as *n* (%) or mean ± SD, unless otherwise indicated. CT: Computed tomography; EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; PET-CT: Positron emission tomography-computed tomography; SUV_{max}: Maximum standardized uptake.

case of non-caseating granulomatous detected by EBUS-TBNA that was diagnosed with lymphoma after 6 mo of follow-up. Kitamura *et al*[24] reported that 6% of patients with thoracic malignancy may have sarcoid-like reactions in non-metastatic lymph nodes. The present study found 3 patients with tuberculosis and 3 with sarcoidosis, but we could not obtain specimens for the 3 granulomatous cases and their benign behavior was merely determined through follow-up. These results suggest that in the case of the possibility of undiscovered malignancy, all granulomatous lymphadenitis cases diagnosed by EBUS-TBNA without obvious infection or sign of sarcoidosis should be followed with more attention or surgical interventions should be advised. Evison *et al*[25] suggested that for suspicious mediastinal and/or hilar lymph nodes but negative EBUS-TBNA, follow-up rather than resampling could be an appropriate approach.

The radiologic diagnosis of nodal involvement is mostly based on morphologic changes such as increase in size, coexistence of pulmonary lesions on CT scans, and lymph nodes > 2 cm in short axis [26]. In this study, both univariate and multivariate regression suggested that the diameter of the lymph node and synchronous lung lesion can be malignancy indicators. As intrathoracic lymph node metastasis is relatively common in primary lung cancer[4], patients with a history of extrathoracic malignancy, exhibiting intrathoracic lymphadenopathy combined with lung lesion, should be distinguished between distal metastasis and extrathoracic lesion and between intrathoracic metastasis and lung cancer. In such conditions, EBUS-TBNA may provide help in pathologic evidence acquisition.

PET-CT is widely used in cancer staging and distant metastasis detection. Generally, a SUV_{max} value > 2.5 could be clinically correlated with the risk of malignancy, and a SUV_{max} value > 6.3 is considered malignant with sensitivity and specificity of 70.6% and 83.3%, respectively[27]. In the present study, no

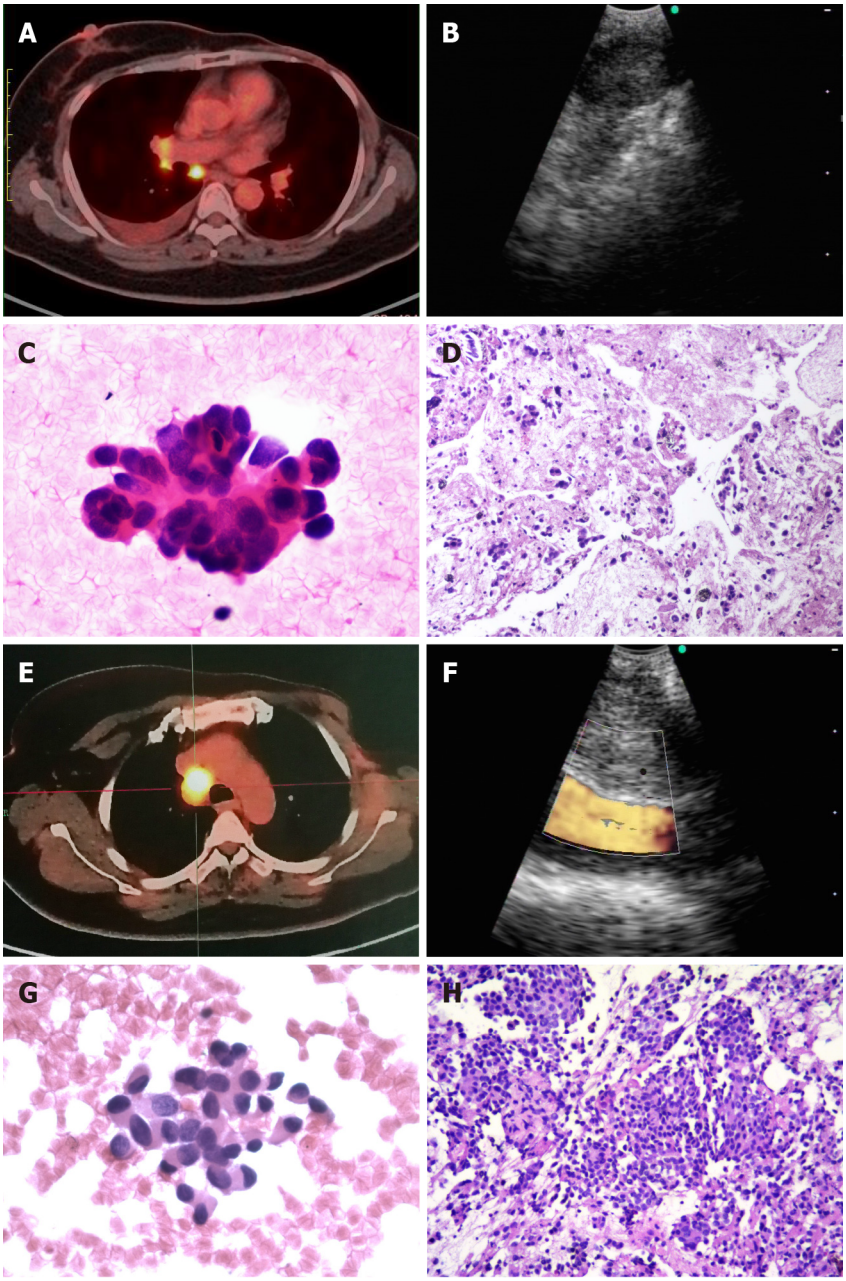

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Figure 1 Endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal lymphadenopathy in patients with history of resected breast cancer. A-D: Female (F)/age: 49 yr, left breast cancer resected 6 yr prior; A: Positron emission tomography-computed tomography (PET-CT) showed subcarinal region lymph node enlarged with maximum standardized uptake (SUV_{max}) value of 8.1 and right pleura effusion; B: Endobronchial ultrasound (EBUS) scanning for the subcarinal region lymph node; C: Cytology showed adenocarcinoma cells. Hematoxylin and eosin (H&E) staining 40 × 10; D: Histology showed pulmonary adenocarcinoma, H&E staining 40 × 10; E -F: F/age: 45 yr, left breast cancer resected 3 yr prior; E: PET-CT showed right lower paratracheal region lymph node enlarged with SUV_{max} value of 8.8; F: EBUS scanning for the right lower paratracheal region lymph node; G: Cytology showed adenocarcinoma cells; H: Histology showed breast cancer metastasis, H&E staining 40 × 10).

significant relationship was found between the SUV_{max} value and the presence of malignancy. This may be due to the possibility that increased SUV_{max} values can also be seen in benign pathologies involving inflammation such as sarcoidosis and infectious disease[5]. Moreover, not all patients in our study underwent PET-CT, which may have also caused data bias.

As with other interventional procedures, the high diagnostic yield of EBUS-TBNA is associated not only with lesion-related factors such as size, location, and metabolic activity but also with procedure-related factors such as the operator's experience, number of passes, and number of lymph nodes sampled[28]. In this study, none of the above factors showed a significant relationship with accurate diagnosis in malignancy. That may be caused by mixture of multiple lesion categories.

This study had a couple of limitations. First, it was a retrospective study, which intrinsically has a certain selection bias. Second, several cases without definite diagnosis by EBUS-TBNA did not have histological confirmation. In the future, a well-designed prospective study should overcome the

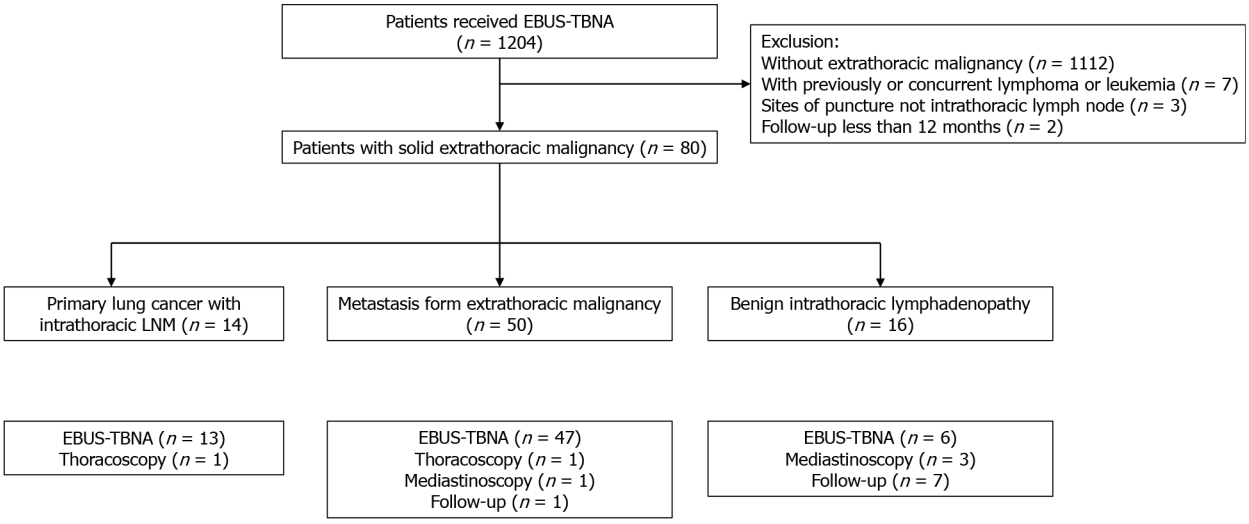

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Figure 2 Patient flowchart by endobronchial ultrasound-guided transbronchial needle aspiration findings, follow-up, and final diagnosis.
EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; LNM: Lymph node metastasis.

limitations above.

CONCLUSION

In conclusion, EBUS-TBNA is a simple and accurate procedure for the diagnosis of intrathoracic lymphadenopathy with extrathoracic malignancy. Its application resulted in no major complications.

ARTICLE HIGHLIGHTS

Research background

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is an established technique for the diagnosis of mediastinal and hilar lymphadenectasis in primary lung cancer, but is poorly studied in patients with extrathoracic malignancies.

Research motivation

Regular follow-up and surveillance are essential in cancer patients, and the detection of intrathoracic lymphadenopathy in those with extrathoracic malignancies is not uncommon. EBUS-TBNA is recommended for tissue sampling both in mediastinal and hilar lymph nodes in lung cancer. Data on the usefulness of this technique in patients with extrathoracic malignancies remain limited.

Research objectives

In this study, we describe our experience with the use of EBUS-TBNA in patients with extrathoracic malignancies due to intrathoracic lymphadenopathy.

Research methods

The results of the sample acquired by EBUS-TBNA were defined as positive for malignancy, negative for non-malignancy (tuberculosis, sarcoidosis, *etc.*), and without definite diagnosis. Sensitivity, negative predictive value (NPV) for malignancy, and overall accuracy were ca-lculated. Complications were recorded.

Research results

The diagnostic sensitivity, NPV, and accuracy of EBUS-TBNA for intrathoracic lymphadenopathy in patients with extrathoracic malignancy were 93.8% (n = 60/64), 80.0% (n = 16/20), and 95.0% (n = 76/80), respectively. Longer short axis of the lymph node (P = 0.024) and synchronous lung lesion (P = 0.013) were independently associated with malignant intrathoracic lymphadenopathy. No major complication was observed.

Research conclusions

EBUS-TBNA is a simple and accurate procedure for the diagnosis of intrathoracic lymphadenopathy with extrathoracic malignancy. Its application resulted in no major complications.

Research perspectives

This retrospective study demonstrates that EBUS-TBNA is effective and safe for diagnosis of intrathoracic lymphadenopathy in patients with extrathoracic malignancy. Additional prospective studies are warranted to establish standards for higher diagnostic yield.

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FOOTNOTES

Author contributions: Li SJ and Wu Q carried out the studies; Li SJ performed the analyses and collected the data; Li SJ drafted the manuscript; Wu Q conceived and designed the study; All authors approved the final draft submitted.

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

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Data sharing statement: Contact lishijie@bjmu.edu.cn to obtain the anonymized dataset.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of the clinical efficacy of two-stage revision surgery in the treatment of periprosthetic joint infection in the knee: A retrospective study

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Abstract

BACKGROUND

Periprosthetic joint infection (PJI) is a catastrophic complication that can occur following total knee arthroplasty (TKA). Currently, the treatment for PJI mainly includes the use of antibiotics alone, prosthetic debridement lavage, primary revision, secondary revision, joint fusion, amputation, *etc.*

AIM

To explore the clinical effect of two-stage revision surgery for the treatment of PJI after TKA.

METHODS

The clinical data of 27 patients (3 males and 24 females; age range, 47–80 years; mean age, 66.7 ± 8.0 years; 27 knees) with PJI treated with two-stage revision surgery in our hospital between January 1, 2010 and December 31, 2020 were analyzed retrospectively. The following outcomes were compared for changes between preoperative and last follow-up results: Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), visual analogue scale (VAS) scores, Hospital for Special Surgery (HSS) scores, knee range of motion (ROM), and infection cure rates.

RESULTS

All 27 patients were followed up (range, 13–112 mo). The ESR (14.5 ± 6.3 mm/h) and CRP (0.6 ± 0.4 mg/dL) of the patients at the last follow-up were significantly lower than those at admission; the difference was statistically significant ($P < 0.001$). The postoperative VAS score (1.1 ± 0.7), HSS score (82.3 ± 7.1), and knee ROM (108.0° ± 19.7°) were significantly improved compared with those before the surgery; the difference was statistically significant ($P < 0.001$). Of the 27 patients, 26 were cured of the infection, whereas 1 case had an infection recurrence; the infection control rate was 96.3%.

CONCLUSION

Two-stage revision surgery can effectively relieve pain, control infection, and retain good joint function in the treatment of PJI after TKA.

Key Words: Total knee arthroplasty; Periprosthetic joint infection; Two-stage; Revision; Antibiotic therapy

Core Tip: The two-stage revision surgery approach, which includes the first stage of thorough debridement, removal of prosthesis, antibiotic bone cement placeholder exclusion for 3–6 mo, three normal consecutive routine blood examination results for erythrocyte sedimentation rate and C-reactive protein, selection of a suitable prosthesis for the second-stage revision, and the use of a sufficient amount of a full course of sensitive antibiotics, is a reliable method for the treatment of periprosthetic joint infection after total knee arthroplasty A. This approach can effectively relieve pain, control infection, and preserve good joint function.

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INTRODUCTION

Periprosthetic joint infection (PJI) is a catastrophic complication after total knee arthroplasty (TKA), with an incidence of approximately 2% after primary TKA[1]. PJI can be classified as early (occurring within 3 mo after surgery), delayed (3–24 mo after surgery), and late (2 years after surgery)[2]. Currently, the treatment for PJI primarily includes the use of antibiotics alone, prosthetic debridement lavage, primary revision, secondary revision, joint fusion, amputation, *etc.*[3,4]. Tsukayam *et al*[5] grouped PJIs into four types and proposed corresponding treatment strategies: Type I, no symptoms of infection but with positive intraoperative culture, mostly observed in preoperative diagnosis of aseptic loosening of the knee prosthesis and positive culture of the tissue specimen during revision surgery, which can be treated with intravenous antibiotics; type II, an early infection that occurs within 1 mo after surgery and can be treated by debridement to preserve the prosthesis; type III, an acute hematogenous infection that occurs suddenly in a well-functioning joint, which can also be treated, and the prosthesis is preserved; type IV, an advanced chronic infection that requires removal and revision of the prosthesis. PJI staging is the most widely used staging method and provides guidance on when to retain the prosthesis. One-stage revision leads to short hospitalization time, requires minimal cost, and has low impact on joint function[6]. However, its use is controversial because of the associated high recurrence rate of postoperative infection, and its effectiveness needs to be further explored[7]. Second-stage revision requires multiple surgeries and has the disadvantages of long hospital stay, increased costs, and impaired joint function, but it is effective and remains the gold standard of PJI treatment[8-10]. This study aimed to retrospectively analyze 27 patients with PJI who were treated with one-stage debridement, implant removal, antibiotic bone cement spacer exclusion, and two-stage revision and compare their preoperative and follow-up results.

MATERIALS AND METHODS

Inclusion and exclusion criteria

The inclusion criteria were as follows: Patients with PJI treated for the first time after TKA between January 1, 2010, and December 31, 2020; a diagnosis of PJI that conforms to the diagnosis standard set by of the International Consensus Group on Periprosthetic Joint Infection in 2014[11]; patients able to tolerate surgery; provision of informed consent for one-stage debridement, implant removal, antibiotic bone cement spacer exclusion, and two-stage revision; with complete follow-up data.

Patients with previous revision surgery due to infectious or non-infectious causes, those with termination of treatment using antibiotic bone cement spacer, those who were under anti-infection treatment for another infection site, and those lost to follow-up were excluded.

General information

We retrospectively analyzed the clinical data of 27 patients (3 males and 24 females; age range, 47–80 years; mean age, 66.7 ± 8.0 years; 27 knees) with PJI who were treated with phase I absences and phase II revisions from January 1, 2010, to December 31, 2020, at our hospital. There were 15 and 12 PJI cases in the right and left knees, respectively. There were 16 initial TKA cases recorded in our hospital and 11 cases from an outside hospital. The primary disease was osteoarthritis of the knee in 20 cases and rheumatoid arthritis in 7 cases. In all the cases, postoperative pathology was suggestive of acute/chronic septic inflammation. The surgery for all the cases was performed by the same team of surgeons.

Surgical methods

Surgery was performed under general anesthesia or combined lumbar epidural anesthesia, and the skin around the knee was cleaned thoroughly with a soft brush dipped in soap and water placed under the table. The surgical incision site was disinfected according to the infected area, the incision was made layer by layer along the original incision, the necrotic tissue and pus were cleared from outside to inside the infection site, any encountered sinus was completely removed, the joint capsule was opened to reveal the prosthesis, and the joint capsule, membranous tissue on the surface of the prosthesis, prosthesis, and bone cement were removed. At least three points of the interface granulation tissue and any other abnormal or septic tissue were sampled for bacterial culture and rapid frozen pathological and postoperative pathological examinations. The joint capsule, synovium, and diseased bone tissue were debrided thoroughly, and the surrounding tissue was completely excised. The bone cement was thoroughly cleaned after the prosthesis and pad were removed, and the remaining diseased tissue of the posterior joint capsule was completely excised again. The joint cavity was rinsed at least three times with hydrogen peroxide, dilute iodophor, and saline, with a liquid volume of more than 5000 mL, and the joint cavity was soaked with concentrated iodophor for at least 15 min and finally rinsed thoroughly with a large amount of saline using a pulse gun. The surgical gown, sterile gloves, and surgical instruments were changed for the next phase of the surgery. Depending on the size of the joint space after the prosthesis had been removed, an antibiotic cemented spacer of appropriate size was handmade (40 g of bone cement + 4 g of vancomycin, vancomycin-resistant, or specific pathogenic bacteria; antibiotics were added according to drug sensitivity results). Two groups of flushing and drainage tubes were left in place, and 4000 mL of saline/24 h of continuous drainage was administered after the surgery. Drainage fluid was collected and sent for culturing three times after 5–7 postoperative days, and the drainage tubes were removed after negative results were obtained.

For the reexamination of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and routine blood culture to monitor infection control regularly, exclusion for 3–6 mo is generally recommended, and three normal consecutive reexamination results are required for the second revision surgery to be performed. The bone and soft tissue are carefully explored, and three different parts of the soft tissue are sampled for rapid frozen pathological examination to assess the infection control. If the high magnification field was still greater than 10 neutrophils, thorough debridement and reinsertion of a new antibiotic bone cement placeholder is repeated. If the infection was completely controlled, the appropriate knee revision prosthesis was selected according to the degree of bone defect, bone quality, and stability of the collateral ligament, metal pad, and extension rod.

Postoperative management

For pain management, advanced, individualized, and multi-mode analgesia was used. For thrombosis prevention, 5000 IU of low molecular weight heparin calcium was injected subcutaneously once a day. For functional exercise, isometric and isotonic exercises of the quadriceps muscle, ankle pump exercises, and other functional exercise were performed as soon as possible after the administration of postoperative analgesia, and the exercise routine was gradually transitioned to active and passive functional exercises of the affected joints. For drainage, continuous knee cavity lavage was performed for 7–10 d after the first-stage spacer exclusion using 4000 mL of normal saline solution every day. Drainage fluid was tested by routine bacterial culture for 3 consecutive days from the 7th postoperative day, and the flushing and drainage tubes were removed after all the results were negative. Based on the

drainage condition, the drainage tube should be removed within 48 h after the two-stage revision.

Antibiotic application

The preoperative puncture fluid, intraoperative pus, necrotic tissue, and postoperative drainage fluid were all subjected to bacterial culture and drug sensitivity tests, and corresponding antibiotics were selected according to the drug sensitivity results. During the results waiting period or when the culture results are negative, empirical antibiotics should be administered for treatment, and broad-spectrum antibiotics should also be selected administered to treat most gram-negative and gram-positive bacterial infections. After first-stage exclusion, an adequate amount of sensitive antibiotics was administered intravenously for 2 wk (if the culture result was negative, intravenous vancomycin combined with third-generation cephalosporins or quinolones and other antibiotics was administered); oral sensitive antibiotics was also administered for 4 wk after the 2 wk (if the culture result was negative, oral rifampicin + ciprofloxacin were administered), and the decision to stop or extend the antibiotics (intravenous + oral sensitive antibiotics) < 6 wk of the drug course was based on a patient's condition. The initial intravenous antibiotic regimen was continued after second-stage revision until the intraoperative culture results were clear or stopped if the results were negative; treatment was continued according to new PJI if there were 2 or more positive results.

Evaluation indicators

ESR, CRP, visual analogue scale (VAS) score, Hospital for Special Surgery (HSS) score, range of motion (ROM), and infection control rate were recorded before the surgery and at the last follow-up. Infection control was defined as the absence of infection recurrence and prosthesis loosening after revision and follow-up. ESR and CRP were used to evaluate infection control, and pain VAS score, HSS score, and ROM were used to evaluate symptom improvement and recovery of knee function. Two years after the surgery, radiographic images were reviewed to determine whether the prosthesis was loose.

Statistical analysis

SPSS version 23.0 (IBM, Chicago, IL, United States) was used to analyze the data. ESR, CRP, VAS score, HSS score, and ROM were all expressed as mean ± SD. Paired sample t test was used to compare the results obtained before surgery and at last follow-up, and $P < 0.05$ was considered to be statistically significant.

RESULTS

Analysis of evaluation indicators

All 27 patients were followed up for 13–112 mo (average, 59 ± 26 mo). Twenty-six patients were cured of the infection, and 1 patient had recurrence after 6 years of follow-up, with an infection control rate of 96.3%. The time between the initial joint replacement and the diagnosis of PJI ranged from 7 to 195 mo (mean, 41 ± 35 mo), with 9 cases (33.3%) of delayed PJI and 18 cases (66.7%) of advanced PJI. The duration of spacer exclusion was 2.8–6.3 mo (mean, 3.8 ± 0.8 mo). Positive bacterial culture results were obtained in 17 of the 27 patients (Table 1), with a positive rate of 63.0%, including 13 g-positive bacterial infection [8 cases of *Staphylococcus aureus*, 2 cases of methicillin-resistant *S. aureus* (MRSA), 2 cases of *Staphylococcus epidermidis*, and 1 case of *Streptococcus griseus*], 3 g-negative bacterial infection (2 cases of *Enterobacter cloacae*, 1 case of *Pseudomonas aeruginosa*), and 1 case of fungal infection (*Candida*). An articulating spacer was used in all 27 patients. All 27 patients with the following types of prosthesis underwent revision surgery: Surface knee prosthesis (3 cases), Legacy® (Zimmer Biomet, Warsaw, IN, United States) constrained condylar knee (LCCK) prosthesis (20 cases), and rotating hinge (RH) knee prosthesis (4 cases). The ESR (14.5 ± 6.3 mm/h) and CRP (0.6 ± 0.4 mg/dL) levels at the last follow-up were significantly ($P < 0.001$) lower than those obtained preoperatively (ESR, 57.1 ± 21.8 mm/h; CRP, 2.9 ± 2.1 mg/dL), and this difference was statistically significant (Table 2). The patients' VAS score (1.1 ± 0.7), HSS score (82.3 ± 7.1), and knee ROM (108.0° ± 19.7°) at the last follow-up improved significantly ($P < 0.001$) compared with the preoperative scores (VAS, 4.0 ± 0.8; HSS score, 57.9 ± 9.4; knee ROM, 91.9° ± 26.9°) (Table 3).

Typical case 1

The patient was a 78-year-old woman whose primary disease was left knee osteoarthritis (Kellgren-Lawrence stage VI). More than 4 years after the left TKA was performed in another hospital, her left knee joint became swollen and painful with limited movement for more than 6 mo, and there was sinus tract formation and secretion discharge for 2 mo (Figure 1). After admission, the bacterial culture of the knee joint puncture showed MRSA. Drug sensitivity test showed sensitivity to vancomycin and rifampin. After ensuring no contraindications to surgery, lumbar anesthesia was administered for one-stage debridement, implant removal, and antibiotic bone cement spacer exclusion (Figure 2). Postoperative intravenous vancomycin (1 g, twice a day) was administered for 2 wk. After discharge,

Table 1 Pathogenetic results of periprosthetic joint infection after total knee arthroplasty in 27 cases

	Pathogenic bacteria	Number of cases	Proportion (%)
Gram-positive bacteria	*S. aureus*	8	48.1
	Methicillin-resistant *S. aureus*	2	
	S. epidermidis	2	
	Ste. griseus	1	
Gram-negative bacteria	*E. cloacae*	2	11.1
	P. aeruginosa	1	
Fungi	*Candida*	1	3.7
Negative bacterial culture	Not assessed	10	37.0

Table 2 Comparison of preoperative and final follow-up erythrocyte sedimentation rate and C-reactive protein results

Indicators	Preoperative exclusion	Final follow-up	T value	*P* values
ESR (mm/h)	57.1 ± 21.8	14.5 ± 6.3	9.043	< 0.001
CRP (mg/dL)	2.9 ± 2.1	0.6 ± 0.4	5.804	< 0.001

Data are presented as mean ± SD. $P < 0.05$ indicates statistical significance. ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 3 Comparison of preoperative and final follow-up knee pain visual analogue scale scores, hospital for special surgery scores, and range of motion results

Indicators	Preoperative exclusion	Final follow-up	T value	*P* values
VAS (score)	4.0 ± 0.8	1.1 ± 0.7	18.028	< 0.001
HSS (score)	57.9 ± 9.4	82.3 ± 7.1	-21.813	< 0.001
ROM (°)	91.9 ± 26.9	108.0 ± 19.7	-7.148	< 0.001

Data are presented as mean ± SD. $P < 0.05$ indicates statistical significance. VAS: Visual analogue scale; HSS: hospital for special surgery; ROM: Range of motion.

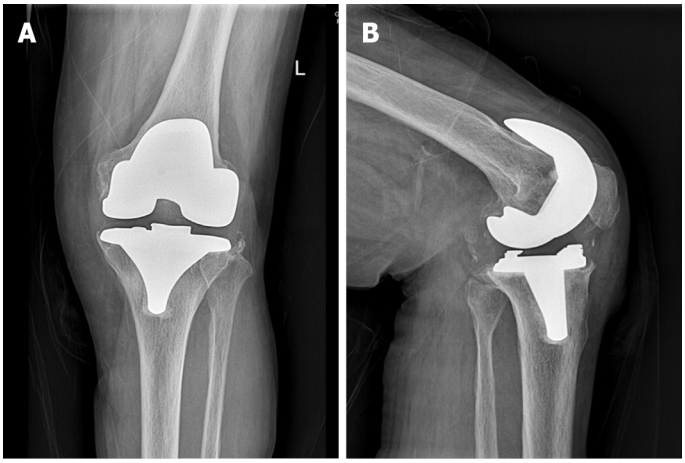
rifampicin capsule (0.45 g, once a day) and ciprofloxacin hydrochloride capsule (0.5 g, twice a day) were taken orally for 6 wk; the exclusion time was 4 mo. After three consecutive routine blood examinations, ESR and CRP were normal, and knee arthroplasty was performed in the second stage of the treatment (Figure 3).

Typical case 2

Case 2 was a 51-year-old woman with rheumatoid arthritis of the right knee, which occurred more than 6 years after right TKA (Figure 4). The patient's chief complaints were right knee swelling and pain with limited movement for 6 mo. Negative bacterial culture results were obtained throughout the treatment, and pathological examination showed chronic purulent inflammation. After ensuring no contraindications to surgery, lumbar anesthesia was administered for stage debridement, implant removal, and antibiotic bone cement spacer exclusion. Postoperative intravenous vancomycin (1 g, twice a day) combined with cefoperazone sulbactam sodium (3 g, twice a day) was administered for 2 wk. After discharge from the hospital, the patient had to take oral rifampin (0.45 g, once a day) and ciprofloxacin (0.5 g, twice a day) for 6 wk, with an exclusion time of 4.8 mo. Three consecutive routine blood examinations revealed that the ESR and CRP were normal on all three instances. Knee arthroplasty was then performed in the second stage of the treatment.

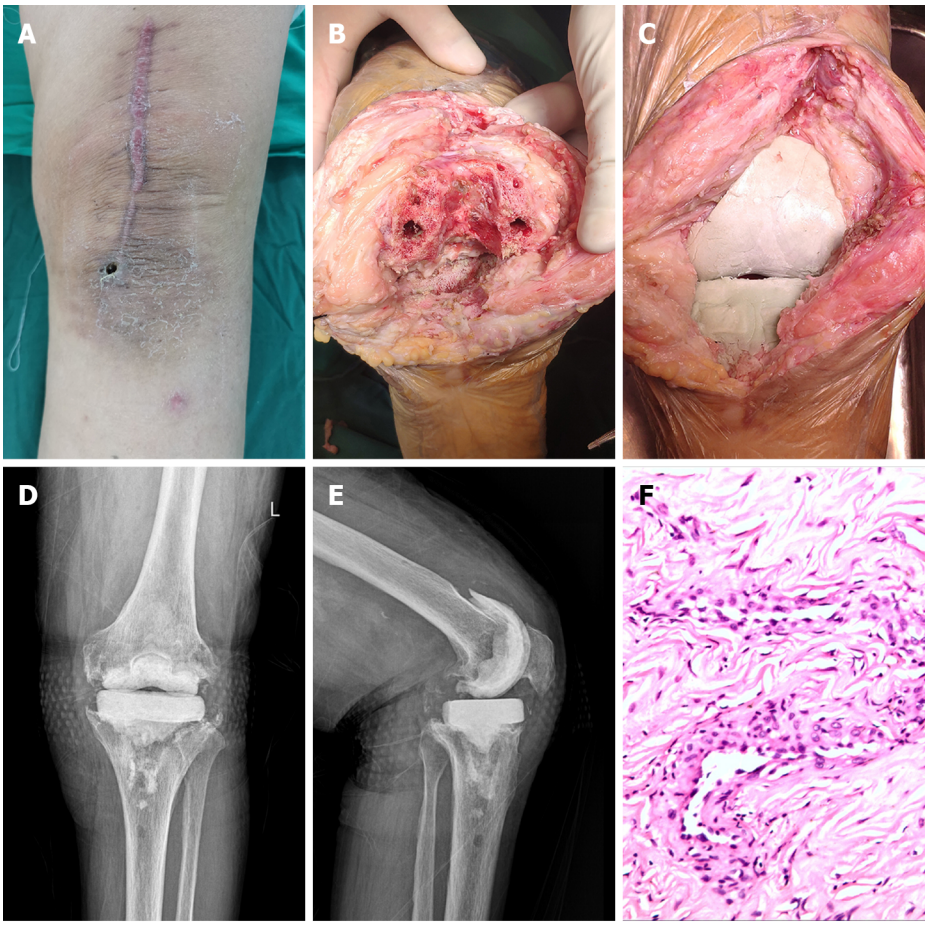
DISCUSSION

As one of the most serious complications of TKA, PJI is characterized by difficult treatment, long treatment period, high recurrence rate, and high disability rate. Different treatments have been reported



DOI: 10.12998/wjcc.v10.i36.13239

Figure 1 A 78-year-old female patient with periprosthetic joint infection after left knee arthroplasty. Radiographic image of the left knee joint showing good position of the prosthesis without significant loosening. A: Anteroposterior; B: Lateral.



DOI: 10.12998/wjcc.v10.i36.13239

Figure 2 A 78-year-old female patient after one-stage debridement, implant removal, and antibiotic bone cement spacer exclusion. A: Appearance of the infected skin around the prosthesis after left knee arthroplasty with sinus canal formation; B: Complete debridement after prosthesis removal; C: After the placement of antibiotic bone cement placeholders, the space is moderate; D and E: Radiographic images of the left knee after exclusion: Anteroposterior (D) and lateral (E); F: Pathology showing chronic suppurative inflammation.

in recent years. Prosthetic knee revision, including primary and secondary revision, is one of the basic treatment options for PJI. Currently, second-stage revision is the gold standard for PJI treatment[12], and the cure rate varies greatly among different joint centers. In the present study, we retrospectively analyzed 27 patients with PJI that was diagnosed and treated in our hospital. The infection control rate of the second-stage revision was 96.3%, and the success rate of treatment was significantly higher than

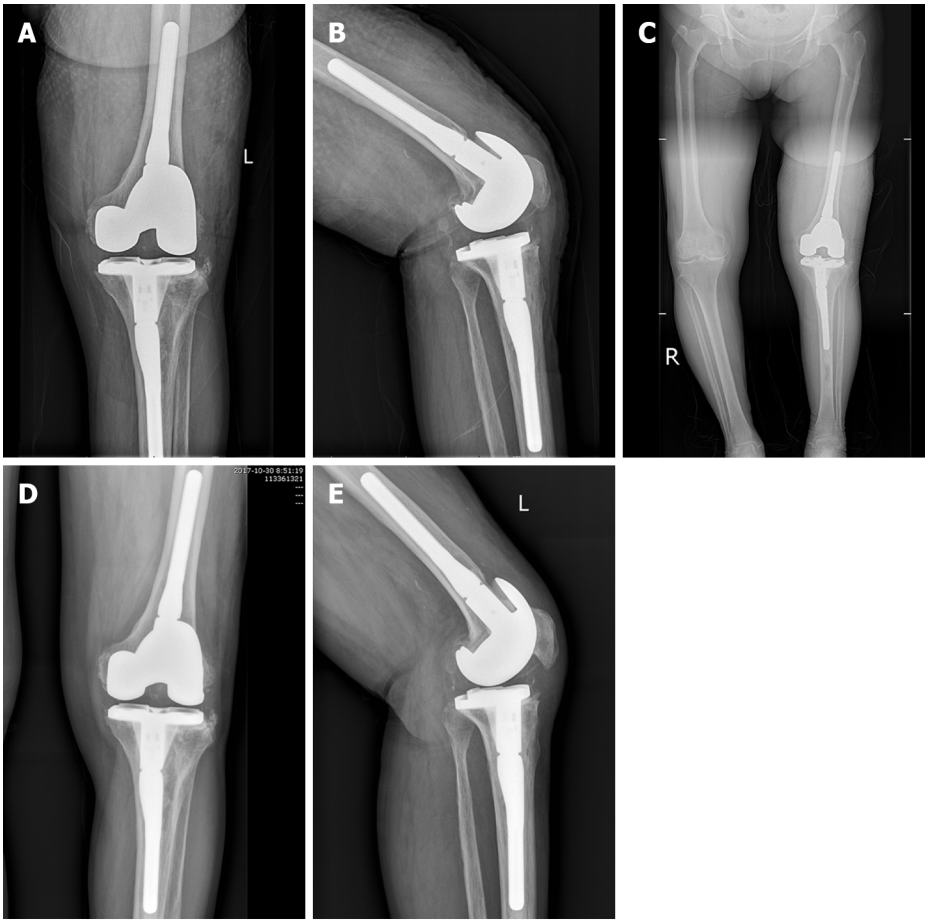


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Figure 3 Radiographic image of the left knee of a 78-year-old female patient after phase II revision. A and B: Radiographic images of the left knee after revision: Anteroposterior (A) and latera (B); C: Full-length orthotopic position of the lower limbs after revision; D and E: Radiographic images of the left knee 2 yr after revision: Anteroposterior (D) and lateral (E).

that reported in previous studies[13,14].

According to the bacterial biofilm formation theory proposed by Costerton[15], bacteria adhere to the surface of prosthesis and secrete polysaccharide, fibrin, lipoprotein, and other substances to form a multi-membrane structure called biofilm. The bacterial biofilm forms irreversible changes in approximately 3 wk, and it can resist human immunity and the effects of antibiotics. Therefore, the application of antibiotics alone cannot completely eradicate the infection around the joint. The formation of biofilm is the main reason for the difficulty in the late treatment of PJI. Radical treatment of PJI requires removal of the entire prosthesis and intensive debridement to the point of complete exposure. Mechanical operation should be performed to remove the biofilm, which is very important for infection control and is the primary factor for successful surgical outcome[3,16,17]. Debridement should not be forceful, and soft tissue injury and bone defect around the joint should be minimized as much as possible. Soft tissue injury of the skin has a significant influence on wound healing in the first stage, and collateral ligament injury and bone defect increase the difficulty of second-stage revision. Correct application of antibiotics plays a crucial role in the prognosis of PJI. After identifying the pathogenic bacteria and determining drug sensitivity through bacterial culture, selecting a sufficient amount and appropriate course of sensitive antibiotics can improve outcomes. A previous study reported that the main pathogenic bacteria of PJI are gram-positive bacteria such as *S. epidermidis* and *S. aureus*, which are basically sensitive to vancomycin[18]. PJI with negative bacterial culture is called refractory PJI and is common in the clinic. In this study, the failure rate of bacterial culture was 37% (10/27), which is approximately equivalent to the rate (20%–50%) reported in the literature[19]. Negative bacterial cultures make the diagnosis of and antibiotic selection for PJI difficult. The main reason for the low pathogen detection rate may be that the patient has been empirically treated with antibiotics before the specimens were obtained[20]. Therefore, it is important to seek effective methods to improve the positive rate of bacterial culture. Emergence of metal-artifact-free magnetic resonance imaging technology, polymerase chain reaction technology, ultrasonic pyrolysis, mass spectrometry analysis, second-generation sequencing, and other technologies[4,21-23] has made identification of pathogens relatively easy. However, with the widespread application and even abuse of antibiotics, the incidence of drug-resistant bacteria, such as MRSA, is increasing, and the treatment is difficult and requires a prolonged cycle. Fungi detected in PJI

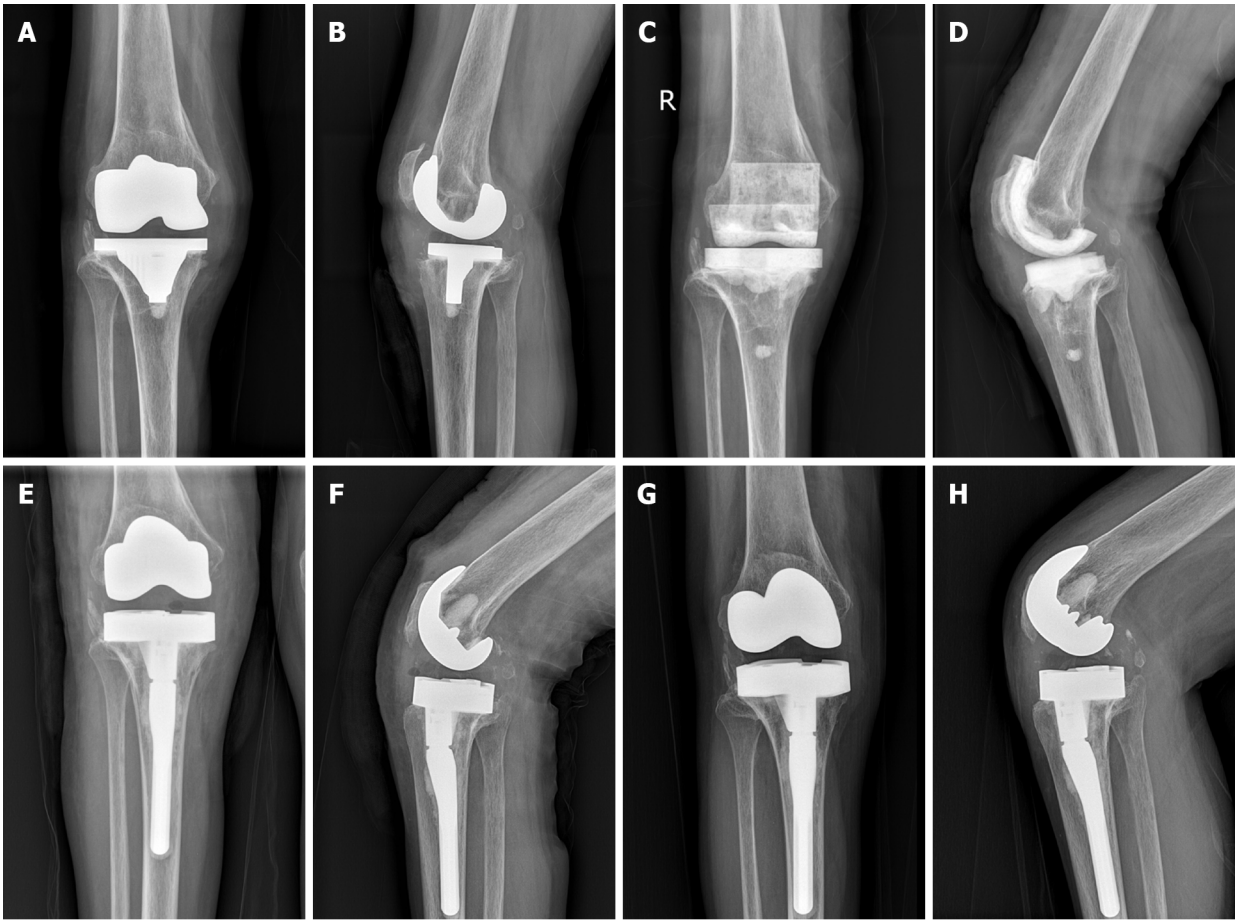

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Figure 4 A 51-year-old female patient with periprosthetic joint infection after right knee arthroplasty. A and B: Radiographic images of the right knee arthroplasty: Anteroposterior (A) and lateral (B); C and D: Radiographic images of the right knee after exclusion: Anteroposterior (C) and lateral (D); E and F: Radiographic images of the right knee after revision surgery: Anteroposterior (E) and lateral (F); G and H: Radiographic images of the right knee 2 yr after revision: Anteroposterior (G) and lateral (H).

are extremely rare, accounting for approximately 1%–2%. The diagnosis of fungal PJI is very difficult, and negative bacterial cultures do not rule out fungi as the cause of PJI; therefore, treatment is also extremely challenging[24].

The application of antibiotic bone cement spacer is an important step in second-stage revision. Spacers are classified as non-jointed (stationary) and jointed (mobile). Spacer, made with a ratio of 40 g bone cement to 4 g vancomycin, sustainably releases high concentrations of antibiotics locally to control infection. Individually made articular spacers can appropriately maintain the knee space and lateral collateral ligament tension, effectively prevent soft tissue contracture around the prosthesis, and maximally preserve knee function, which is convenient for the second-stage revision exposure of the surgical field and the recovery of postoperative joint function[25-27]. Studies have shown that 3D-printed articular spacers can provide satisfactory ROM during the spacer exclusion period, prevent bone loss, and reduce the rate of infection and complications[28]. At present, there is no unified standard for the duration of the exclusion period. If the exclusion period is too long, the overall treatment time is prolonged and treatment cost is increased, which is not conducive to knee joint function. Spacer poses the risk of wear, dislocation, and fracture; the infection might not clear within an extremely short exclusion period, and there is a risk of infection recurrence. Our hospital recommends an interval of 3–6 mo between the first and second surgeries, and the knee joint should be normal during the open period. If the patient's general condition is stable, the incision is adequately healed, without symptoms of infection (such as swelling, heat, and pain), and three consecutive routine blood examination results of CRP and ESR are normal, the second revision can be performed. If signs of infection are identified during the surgery, the revision should be abandoned, and debridement and exclusion should be performed again.

Correct selection of revision prosthesis is the key to the success of the second phase of knee revision [29]. Ensuring prosthesis stability and maintaining joint stability are the basic principles for the selection of revision prosthesis. Because of bone defects, injury or loss of collateral ligaments, and other reasons, a special prosthesis system is often required for the second phase of knee revision. The ultimate goal of second-stage revision is to eradicate infection and rebuild a painless, functional, and stable knee. On the

premise of achieving soft tissue balance and optimal joint stability, knee prosthesis with less limitation should be selected as much as possible. In the case of good bone structure and mild bone defect, the use of a prosthesis with less limitation can lead to effective load sharing in surrounding soft tissues, reduce prosthesis wear and loosening, and improve the success rate of revision[30]. When the bone structure is poor, the bone defect is obvious, and the stability of the prosthesis is poor. The stress on the contact surface of the prosthesis can be dispersed maximally to the pulp cavity using the extender rod and spacer to increase the stability of the prosthesis. In the case of collateral ligament insufficiency, the LCCK prosthesis not only provides anterior-posterior stability but also controls the balance between varus and varus, partially compensating for the collateral ligament function. RH prosthesis should be used in cases of severe lateral collateral ligament dysfunction combined with severe bone defects or complete loss of stability of the knee joint. RH prosthesis has good internal stability and does not require balancing of soft tissues. A large prosthesis module can replace bone defects, and a long handle can disperse the interface stress of the prosthesis.

This study has some limitations. This is a retrospective study with a relatively small sample size. It is not a multicenter study with a large sample or a randomized controlled trial. Some patients had negative bacterial cultures, and antibiotic use was mainly empirical. The reliability and accuracy of the study should be further confirmed in future studies with large samples.

CONCLUSION

The two-stage revision surgery approach, which includes the first stage of thorough debridement, removal of prosthesis, antibiotic bone cement placeholder exclusion for 3–6 mo, three normal consecutive routine blood examination results for ESR and CRP, selection of a suitable prosthesis for the second-stage revision, and the use of a sufficient amount of a full course of sensitive antibiotics, is a reliable method for the treatment of PJI after TKA. This approach can effectively relieve pain, control infection, and preserve good joint function.

ARTICLE HIGHLIGHTS

Research background

Periprosthetic joint infection (PJI) is a catastrophic complication after total knee arthroplasty (TKA).

Research motivation

This study aimed to retrospectively analyze 27 patients with PJI who were treated with one-stage debridement, implant removal, antibiotic bone cement spacer exclusion, and two-stage revision and compare their preoperative and follow-up results.

Research objectives

This study aimed to explore the clinical effect of one-stage debridement, implant removal, antibiotic bone cement spacer exclusion, and two-stage revision in the treatment of PJI after TKA.

Research methods

Of 27 patients with PJI treated with two-stage revision surgery were analyzed retrospectively. The following outcomes were compared for changes between preoperative and last follow-up results: Erythrocyte sedimentation rate, C-reactive protein, visual analogue scale scores, Hospital for Special Surgery scores, knee range of motion, and infection cure rates.

Research results

Of the 27 patients, 26 were cured of the infection, whereas 1 case had an infection recurrence; the infection control rate was 96.3%.

Research conclusions

Two-stage revision surgery can effectively relieve pain, control infection, and retain good joint function in the treatment of PJI after TKA.

Research perspectives

Whether the PJI can be cured using the one-stage debridement, implant removal, antibiotic bone cement spacer exclusion, and two-stage revision.

FOOTNOTES

Author contributions: Qiao YJ, Li F and Zhang LD contributed equally to this work; Qiao YJ, Li F and Zhang LD designed the study, collected data, performed the statistical analysis, and wrote the manuscript; Zhang HQ and Yu XY assisted with data collection; Yang WB drafted the manuscript; Zhang HQ and Song XY helped with data interpretation and critically reviewed the manuscript; Zhou SH conceived of the study, helped with data interpretation, and critically reviewed the manuscript; All the authors read and approved the final manuscript.

Institutional review board statement: Formal institutional approval was not deemed necessary since anonymised data routinely collected in our centre for clinical practice purposes were used.

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

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

Data sharing statement: Participants gave informed consent for data sharing.

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ORIGINAL ARTICLE

Retrospective Study

Prognostic factors for disease-free survival in postoperative patients with hepatocellular carcinoma and construction of a nomogram model

Pan-Quan Luo, Zheng-Hui Ye, Li-Xiang Zhang, En-Dong Song, Zhi-Jian Wei, A-Man Xu, Zhen Lu

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and has a high risk of invasion and metastasis along with a poor prognosis.

AIM

To investigate the independent predictive markers for disease-free survival (DFS) in patients with HCC and establish a trustworthy nomogram.

METHODS

In this study, 445 patients who were hospitalized in The First Affiliated Hospital of Anhui Medical College between December 2009 and December 2014 were retrospectively examined. The survival curve was plotted using the Kaplan–Meier method and survival was determined using the log-rank test. To identify the prognostic variables, multivariate Cox regression analyses were carried out. To predict the DFS in patients with HCC, a nomogram was created. C-indices and receiver operator characteristic curves were used to evaluate the nomogram's performance. Decision curve analysis (DCA) was used to evaluate the clinical application value of the nomogram.

RESULTS

Longer DFS was observed in patients with the following characteristics: elderly, I–II stage, and no history of hepatitis B. The calibration curve showed that this

nomogram was reliable and had a higher area under the curve value than the tumor node metastasis (TNM) stage. Moreover, the DCA curve revealed that the nomogram had good clinical applicability in predicting 3- and 5-year DFS in HCC patients after surgery.

CONCLUSION

Age, TNM stage, and history of hepatitis B infection were independent factors for DFS in HCC patients, and a novel nomogram for DFS of HCC patients was created and validated.

Key Words: Hepatocellular carcinoma; Disease-free survival; Prognosis; Nomogram

Core Tip: In this study, age, tumor node metastasis (TNM) stage, and hepatitis B history were shown to be independent predictors of disease-free survival (DFS) in individuals with hepatocellular carcinoma (HCC). Additionally, we developed and validated a new nomogram for estimating 3- and 5-year DFS in HCC patients. The calibration curves of the nomogram were reliable, and the new nomogram had a higher area under the curve value than the TNM stage. We believe that our findings will be of interest to the readers of the *World Journal of Clinical Cases*.

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INTRODUCTION

Many individuals with hepatocellular carcinoma (HCC) pass away each year worldwide, making it the fourth most prevalent cancer-related cause of death[1,2]. Considerable improvements in examination and treatment methods have increased the 5-year survival rate of patients with early stage liver cancer to 70% after radical resection[3]. However, the majority of HCC patients reach the middle or late stages when they are treated, and their 5-year survival rate is around 15%[4].

The pathogenesis of HCC is controversial and complicated[5], and viral hepatitis has been linked to liver cancer incidence[6]. Radical hepatectomy is the first route for HCC patients, and chemotherapy is administered as required according to the postoperative pathological results[7]. Clinical investigations have indicated that age, differentiation degree, hepatitis B surface antigen (HBsAg) level, tumor size, alpha-fetoprotein (AFP) level, tumor node metastasis (TNM) stage, tumor number, gamma-glutamyl transpeptidase (GGT) level, and other factors are important prognostic factors for HCC[8-11]. According to Zheng *et al*[12], who noted that the neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio represent new prognostic markers for HCC outcomes. Microvascular invasion, number of cancer nodules, margin positive and Child-Pugh status were discovered by Goh *et al*[13] to be independent predictors of overall survival (OS). Furthermore, research has demonstrated that GGT and aspartate aminotransferase/alanine aminotransferase levels are prognostic factors for OS of HCC patients[14]. However, there has been little research on disease-free survival (DFS) indicators in HCC patients. Therefore, this study aimed to identify clinical indicators that determine DFS in HCC patients.

MATERIALS AND METHODS

Patients

The First Affiliated Hospital of Anhui Medical University treated 445 HCC patients with curative hepatectomy as part of this study's retrospective evaluation. The inclusion criteria were as follows: (1) Histopathological confirmation of HCC; (2) R0 resection of liver cancer; (3) Availability of comprehensive clinical information; (4) Follow-up data were available; and (5) Absence of any further therapies, such as chemoradiotherapy and interventional therapy, ahead of surgery. The exclusion criteria were as follows: (1) Postoperative pathology revealed cholangiocarcinoma or metastatic liver cancer; (2) Inadequate data were provided; (3) Child–Pugh grade C; and (4) An inability to keep up with follow-up appointments. Based on the threshold for each indicator in the blood, patients were divided into high and low groups. The median negative likelihood ratio (NLR) and positive likelihood ratio

(PLR) were used as cut-off values. All patients submitted written informed permission for this study, which was authorized by the First Affiliated Hospital of Anhui Medical University's ethics committee.

Follow-up and treatment

Calls and outpatient visits were used to gather patient follow-up data. Subsequent examinations were carried out at fixed intervals (follow-up began one week after discharge and occurred every 4 mo after the first year). According to the inclusion criteria, we included a total of 445 postoperative HCC patients and excluded 14 patients who were lost to follow-up and 73 who were excluded. Finally, a cohort of 358 patients was analyzed.

Statistical analysis

SPSS software (version 19.0) was used to statistically evaluate all patient data. Categorical variables were investigated using Fisher's exact test or the chi-squared test. DFS was analyzed using the Kaplan-Meier method, and verified by the log-rank test. An elevated risk of mortality was indicated by a hazard ratio (HR) >1.0. The R Project (3.5.5) was used to create the nomogram.

RESULTS

Clinical characteristics of the patients

344 HCC patients were enrolled in this study (Table 1). The patients were divided into two groups: Elderly (aged ≥ 70 years) and young (aged < 70 years). Patients with a history of hepatitis B accounted for 25% of the total. 256 individuals had cirrhosis, while the majority of the 88 patients who did not have cirrhosis had abnormal liver function, such fatty liver disease. The median NLR and PLR were 2.19 and 97.67, respectively. The average follow-up period was 52 mo. HCC patients had 1-, 3-, and 5-year DFS rates of 73.26%, 59.30%, and 44.48%, respectively.

Prognostic factors for DFS

Tables 2 and 3 show the results of univariate and multivariate regression analyses, respectively. Age, past hepatitis B infection history, and TNM stage were independent predictors of DFS in HCC patients. The HR was 0.543 for patients < 70 years and 0.654 among those who did not have a history of hepatitis B.

DFS results according to different age groups, TNM stage, and hepatitis B history

Young patients had a higher recurrence risk or mortality risk within 6 mo after surgery as a significant downhill trend was seen in these patients in the first 6 mo (Figure 1A). The DFS outcomes in patients who had different TNM stages and a history of hepatitis B are shown in Figures 1B and C, respectively. The median DFS for stages III–IV was 12 mo, and was 68 mo for stages I–II.

To determine the relationship between TNM stage and age, the DFS results are shown in Figure 2A and B. Figure 2A shows that, in stages I-II, patients ≥ 70 years had a longer DFS than those who were < 70 years. However, no discernible differences between stages III-IV were seen. In addition, we revealed an association between age and various TNM stages (Figure 3A and B). According to our results, individuals at stages I and II who were < 70 years had a better prognosis. The relationship between TNM stage and a history of hepatitis B was also examined (Figure 4A and B), but the difference was not statistically significant.

Development and validation of the prediction model

Age, TNM stage, and previous hepatitis B infection were utilized to create a nomogram (Figure 5). The C-index was calculated to be 0.713 (95%CI: 0.660–0.767) using 1000 bootstrap resampling methods, which indicated that the nomogram had a strong level of predictability. The actual survival curve of the nomogram matched closely, based on calibration curves for the 3- and 5-year DFS (Figure 6A and B). We compared the nomogram's receiver operator characteristic against that of the TNM stage to further assess the performance of the model and discovered that the nomogram's area under the curve was greater than that of the TNM stage (Figure 7). The nomogram enhanced the capacity to predict DFS in patients with HCC throughout a large range of risk threshold probabilities, according to the 3- and 5-year decision curve analysis curves (Figure 8A and B).

DISCUSSION

HCC has a high incidence and fatality rate, and increasing attention has been focused on HCC prognostic factors[15,16].

Table 1 Clinicopathological characteristics of the 344 patients, *n* (%)

Characteristics	Median (25^{th}–75^{th} percentile)
Gender	
Male	279 (81.10)
Female	65 (18.90)
Age (yr)	
≥ 70	46 (13.37)
< 70	298 (86.63)
Smoking history	
Yes	151 (43.90)
No	193 (56.10)
Alcohol consumption history	
Yes	133 (38.66)
No	211 (61.34)
History of hepatitis B	
Yes	86 (25.00)
No	258 (75.00)
Hypertension	
Yes	80 (23.26)
No	264 (76.74)
Diabetes	
Yes	41 (11.92)
No	303 (88.08)
BMI	
< 18.5	26 (7.56)
≥ 18.5, < 23	160 (46.51)
≥ 23	158 (45.93)
Liver cirrhosis	
Yes	256 (74.42)
No	88 (25.58)
Ascites	
Yes	44 (12.79)
No	300 (87.21)
Cancer nodules	
Single	299 (86.92)
Multiple	45 (13.08)
Capsule	
Yes	290 (84.30)
No	54 (15.70)
Tumor diameter	
≥ 5 cm	163 (47.38)
< 5 cm	181 (52.62)
Differentiation grade	

Low	85 (24.71)
Moderate and High	259 (75.29)
TNM stage	
I	262 (76.16)
II	38 (11.05)
III	40 (11.63)
IV	4 (1.16)
Portal vein thrombus	
Yes	13 (3.78)
No	331 (96.22)
HBsAg	
Positive	268 (77.91)
Negative	76 (22.09)
Surgical method	
Proximal stomach	86 (25.00)
Full stomach	258 (75.00)
5-year survival	
Yes	162 (47.09)
No	182 (52.91)
Prothrombin time (s)	13.80 (13.30-14.50)
Fibrinogen (g/L)	2.91 (2.41-3.54)
ALB (g/L)	40.45 (37.23-43.78)
TBIL (μmol/L)	10.00 (8.00-15.00)
TC (mmol/L)	4.35 (3.62-4.86)
ALT (U/L)	34.50 (24.00-49.00)
AST (U/L)	36.00 (27.00-52.00)
GGT (U/L)	55.50 (34.00-122.75)
NLR	2.19 (1.64-3.31)
PLR	97.67 (72.10-138.17)

BMI: Body mass index; TNM: Tumor node metastasis; HBsAg: Hepatitis B surface antigen; AFP: Alpha-fetoprotein; ALB: Albumin-bilirubin; TBIL: Total bilirubin; TC: Total cholesterol; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

Recently, nomograms have been widely used as diagnostic and prognostic tools for various cancers [17]. We attempted to develop a prognostic nomogram that combines most of the important serum markers and clinicopathological characteristics. Many studies have shown that carbohydrate antigen 199 and AFP are related to the OS of patients with HCC[18,19], and the NLR and PLR levels found in the current investigation were similar to earlier results[20,21]. However, we discovered that hematological markers such as NLR, and AFP were not predictive of DFS.

Based on earlier published studies, the elderly group of HCC patients in our study was classified as those ≥ 70 years[22,23]. We examined the DFS of patients aged ≥ 70 and < 70 at TNM stages I-II and III-IV to further understand how age affects DFS in patients with various TNM stages. Sakakibara *et al*[24] used 40 years as the cutoff between young and elderly patients, and found that the 3-year OS of stage IIB patients in the young group was considerably lower than that of the elderly group, which is comparable to our results. Similar findings were obtained by Zhao *et al*[25], who retrospectively selected 995 colorectal cancer patients aged 35 years and discovered that they had a poorer prognosis. Faber *et al*[26], on the other hand, retrospectively examined 141 individuals and reported that those under the age of 35 often had a considerably better prognosis. Regardless of age, we discovered that stages I and II had a more favorable survival than stages III and IV, which is in line with the results of Lu Wu *et al*[27].

Table 2 Univariate analysis of different factors associated with disease-free survival in hepatocellular carcinoma patients

Characteristics	HR value (95%CI)	*P* value
Gender		
Male	1.00 (reference)	
Female	0.840 (0.574, 1.230)	0.371
Age (yr)		
< 70	1.00 (reference)	
≥ 70	0.577 (0.350, 0.951)	0.031[a]
Smoking history		
No	1.00 (reference)	
Yes	1.031 (0.770, 1.381)	0.839
Alcohol use history		
No	1.00 (reference)	
Yes	0.813 (0.601, 1.101)	0.182
History of hepatitis B		
No	1.00 (reference)	
Yes	1.392 (1.008, 1.921)	0.044[a]
Hypertension		
Yes	1.00 (reference)	
No	0.684 (0.471, 0.993)	0.046[a]
Diabetes		
No	1.00 (reference)	
Yes	0.816 (0.513, 1.298)	0.390
BMI		
≥ 23	1.00 (reference)	
< 23	0.912 (0.682, 1.221)	0.537
Liver cirrhosis		
No	1.00 (reference)	
Yes	1.321 (0.930, 1.876)	0.120
Ascites		
No	1.00 (reference)	
Yes	1.172 (0.774, 1.776)	0.453
Cancer nodules		
Single	1.00 (reference)	
Multiple	1.668 (1.140, 2.497)	0.013[a]
Capsule		
No	1.00 (reference)	
Yes	1.349 (0.925, 1.966)	0.120
Tumor diameter (cm)		
< 5	1.00 (reference)	
≥ 5	1.350 (1.010, 1.804)	0.043[a]
Differentiation grade		0.124
Moderate and High	1.00 (reference)	

Low	1.291 (0.932, 1.787)	0.124
TNM stage		
I-II	1.00 (reference)	
III-IV	1.692 (1.224, 2.340)	0.001[a]
Portal vein thrombus		
No	1.00 (reference)	
Yes	2.862 (1.508, 5.432)	0.001[a]
HBsAg		
Negative	1.00 (reference)	
Positive	1.107 (0.774, 1.582)	0.579
AFP (ng/mL)		
≥ 400	1.00 (reference)	
< 400	0.958 (0.683, 1.345)	0.805
Fibrinogen (g/L)		
≤ 4	1.00 (reference)	
> 4	1.494 (1.037, 2.152)	0.031[a]
Prothrombin time		
Abnormal	1.00 (reference)	
Normal	0.836 (0.565, 1.236)	0.369
ALB (g/L)		
< 40	1.00 (reference)	
≥ 40	0.988 (0.746, 1.335)	0.457
TBIL (μmol/L)		
≤ 20.5	1.00 (reference)	
> 20.5	1.180 (0.762, 1.827)	0.457
TC (mmol/L)		
≤ 5.2	1.00 (reference)	
> 5.2	1.401 (0.980, 2.003)	0.065
ALT (U/L)		
≤ 50	1.00 (reference)	
> 50	1.049 (0.743, 1.481)	0.786
AST (U/L)		
≤ 40	1.00 (reference)	
> 40	1.055 (0.785, 1.416)	0.724
GTT (U/L)		
≤ 60	1.00 (reference)	
> 60	1.279 (0.957, 1.709)	0.097
NLR		0.938
< 2.19	1.00 (reference)	
≥ 2.19	0.988 (0.740, 1.321)	0.938
PLR		
< 97.67	1.00 (reference)	
≥ 97.67	0.956 (0.715, 1.277)	0.759

[a]*P* < 0.05.

BMI: Body mass index; TNM: Tumor node metastasis; HBsAg: Hepatitis B surface antigen; AFP: Alpha-fetoprotein; ALB: Albumin-bilirubin; TBIL: Total bilirubin; TC: Total cholesterol; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

Table 3 Multivariate analysis of different factors associated with disease-free survival in hepatocellular carcinoma patients

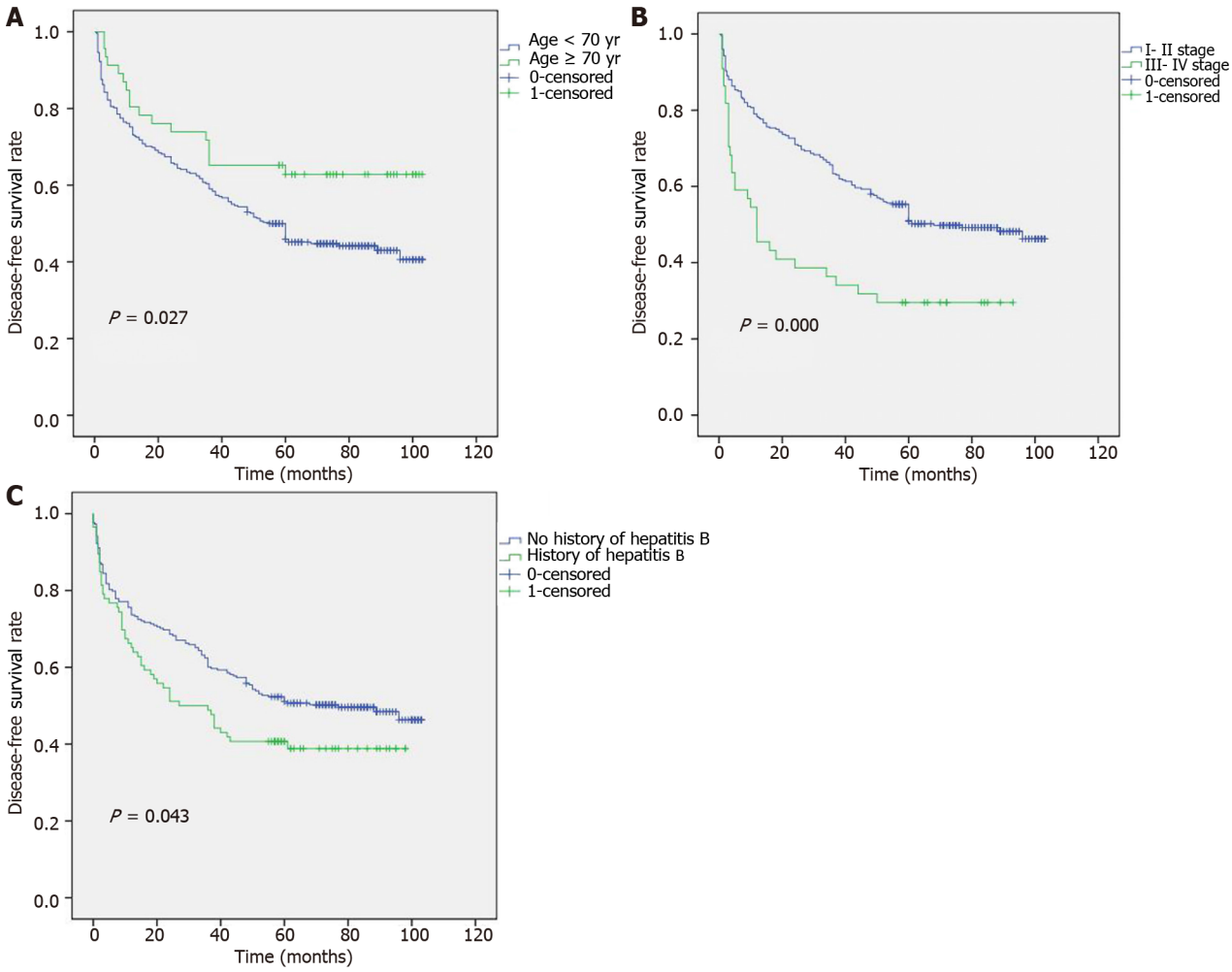
Characteristics	HR value (95%CI)	*P* value
Age (yr)		
< 70	1.00 (reference)	
≥ 70	0.543 (0.328, 0.898)	0.017[a]
History of hepatitis B		
Yes	1.00 (reference)	
No	0.654 (0.472, 0.907)	0.011[a]
Hypertension		
Yes	1.00 (reference)	
No	0.754 (0.510, 1.114)	0.156
Cancer nodules (Single/ Multiple)		
Single	1.00 (reference)	
Multiple	1.009 (0.579, 1.757)	0.975
Tumor diameter (cm)		
< 5	1.00 (reference)	
≥ 5	1.125 (0.817, 1.548)	0.471
TNM stage		
III-IV	1.00 (reference)	
I-II	0.585 (0.423, 0.810)	0.001[a]
Portal vein thrombus		
No	1.00 (reference)	
Yes	1.784 (0.885, 3.597)	0.106
Fibrinogen (> 4 g/L/≤ 4 g/L)		
≤ 4 g/L	1.00 (reference)	
> 4 g/L	1.304 (0.872, 1.951)	0.196

[a]*P* < 0.05.

TNM: Tumor node metastasis.

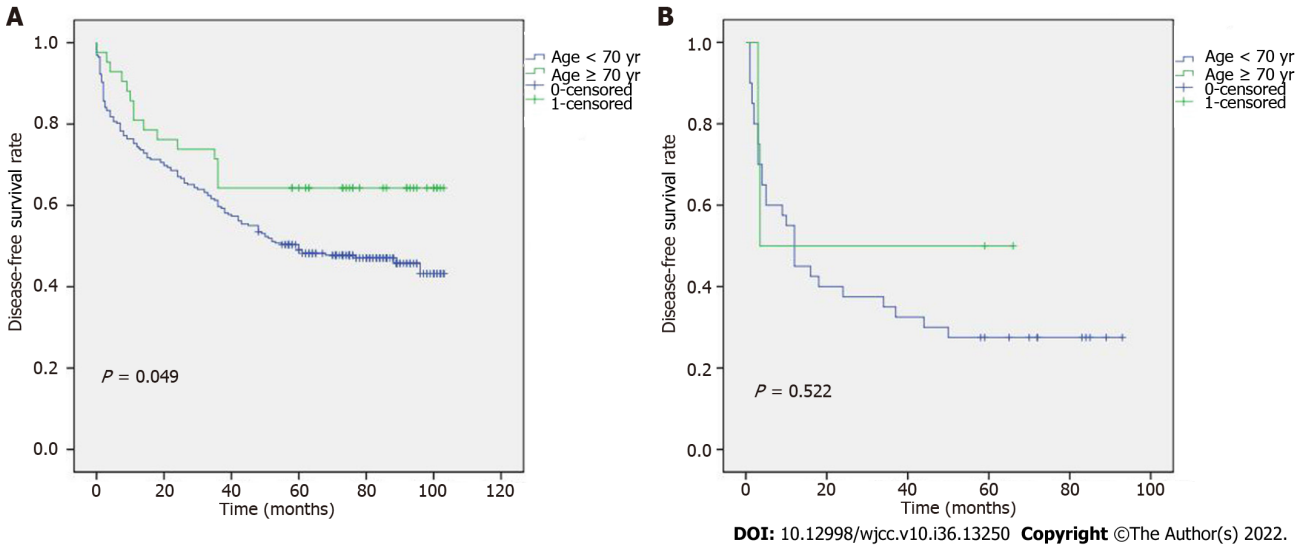
Hepatitis B virus (HBV), which affects 30% of people globally and is particularly widespread in China [28], is the main culprit in HCC. According to Li *et al*[29], preoperative HBV DNA levels over 2000 IU/mL were associated with a poorer prognosis and were strongly correlated with OS and DFS. In terms of the pathogenesis of HCC brought on by HBV, the integration of HBV DNA into the host genome triggered changes in gene protrusions, leading to the occurrence of liver cancer. In contrast, HBV-associated proteins, such as HBsAg, hepatitis B core antigen, and HBx, can mediate oxidative stress in cells[30]. Hence, for patients with HCC, more attention should be paid to a history of HBV in clinical practice.

This study had certain limitations, including an insufficient number of elderly patients and was a single center study. A limited relationship was observed between hepatitis B and HCC in Western countries; therefore, this study failed to collect clinical information from more patients (including foreign patients) through the Surveillance, Epidemiology and End Results and other databases to develop a more comprehensive and convincing nomogram model.



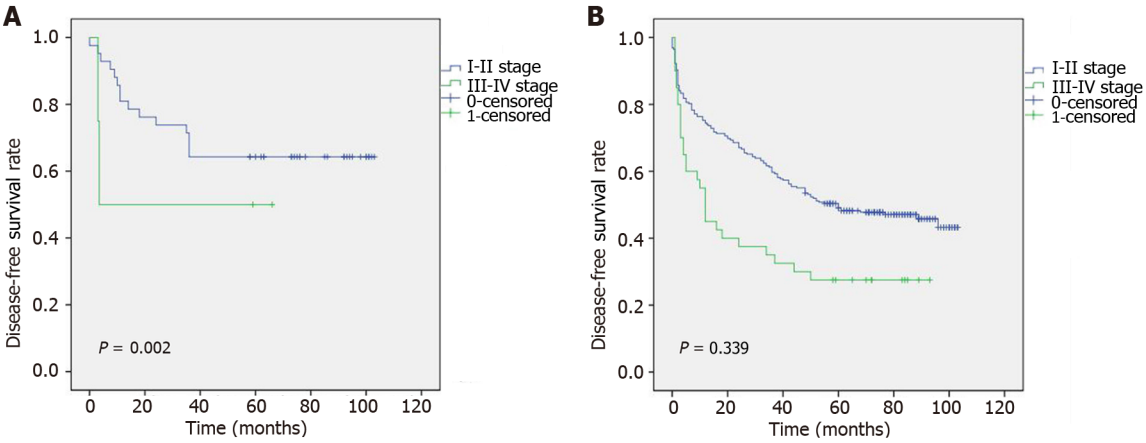
DOI: 10.12998/wjcc.v10.i36.13250

Figure 1 Kaplan-Meier curve of disease-free survival according to different subgroups. A: Age groups; B: Stage groups; C: History of hepatitis B groups.



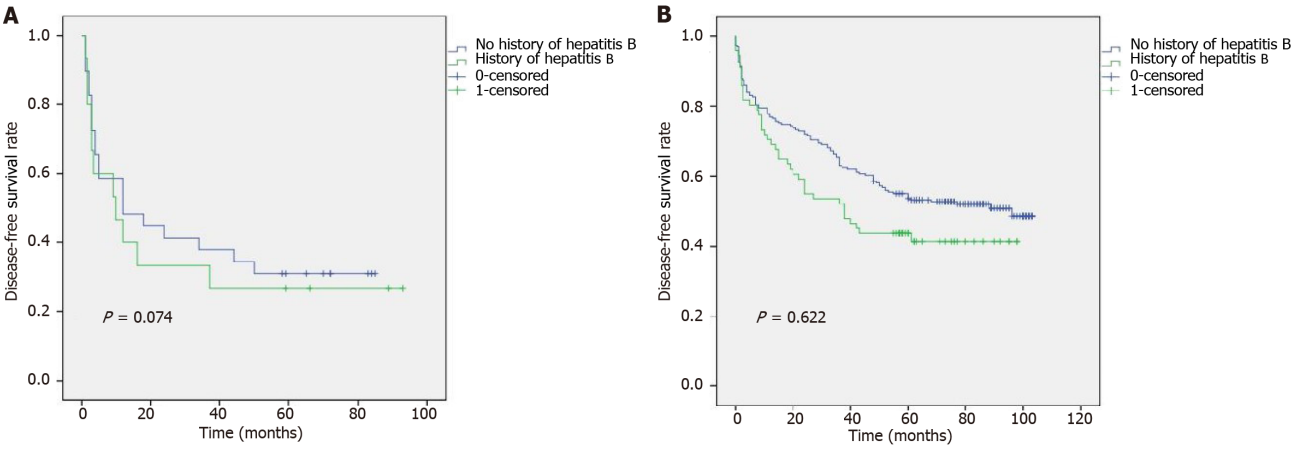
DOI: 10.12998/wjcc.v10.i36.13250

Figure 2 Kaplan-Meier curves of disease-free survival in different age groups based on tumor node metastasis stage. A: Kaplan-Meier curves of disease-free survival (DFS) in different age groups based on I-II stage; B: Kaplan-Meier curves of DFS in different age groups based on III-IV stage.



DOI: 10.12998/wjcc.v10.i36.13250

Figure 3 Kaplan-Meier curves of disease-free survival in different stage groups based on age. A: Kaplan-Meier curves of disease-free survival (DFS) in different stage groups based on age ≥ 70 years; B: Kaplan-Meier curves of DFS in different stage groups based on age < 70 years.



DOI: 10.12998/wjcc.v10.i36.13250

Figure 4 Kaplan-Meier curves of disease-free survival in patients with a different history of hepatitis B based on tumor node metastasis stage. A: Kaplan-Meier curves of disease-free survival (DFS) in groups with a different history of hepatitis B based on I-II stage; B: Kaplan-Meier curves of DFS in groups with a different history of hepatitis B based on III-IV stage.

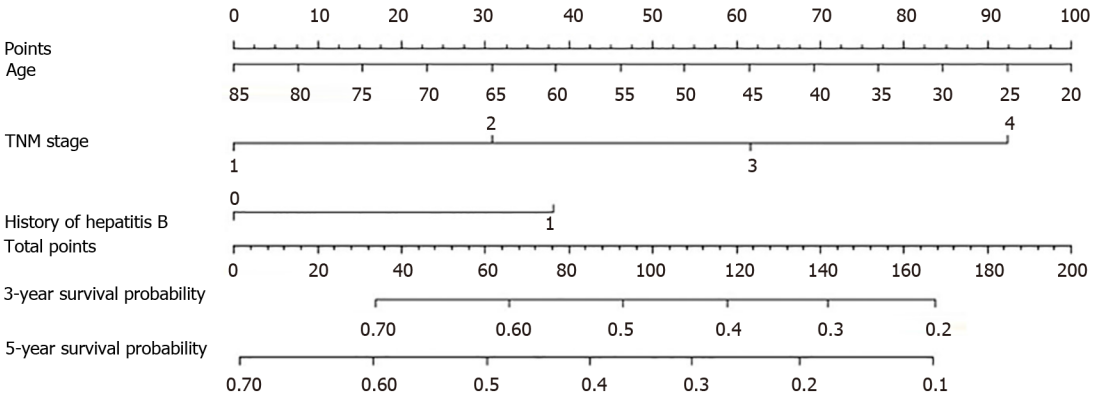


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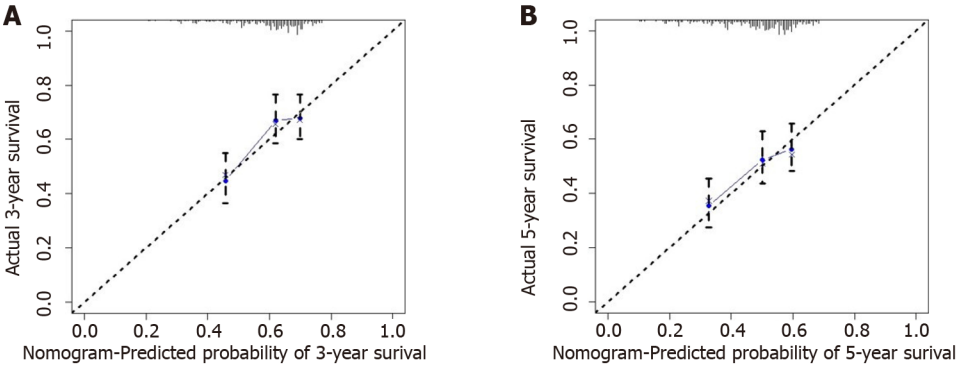
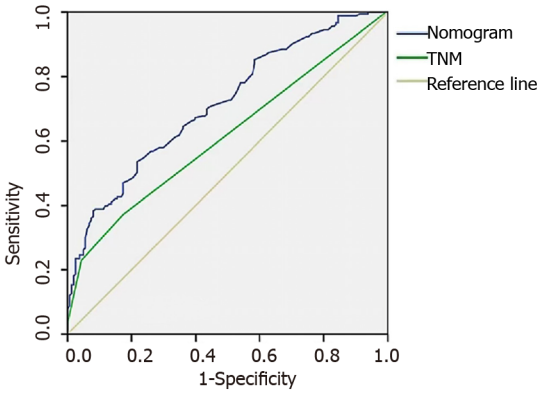
Figure 5 Nomogram for predicting disease-free survival of hepatocellular carcinoma patients after curative resection. TNM: Tumor node metastasis.



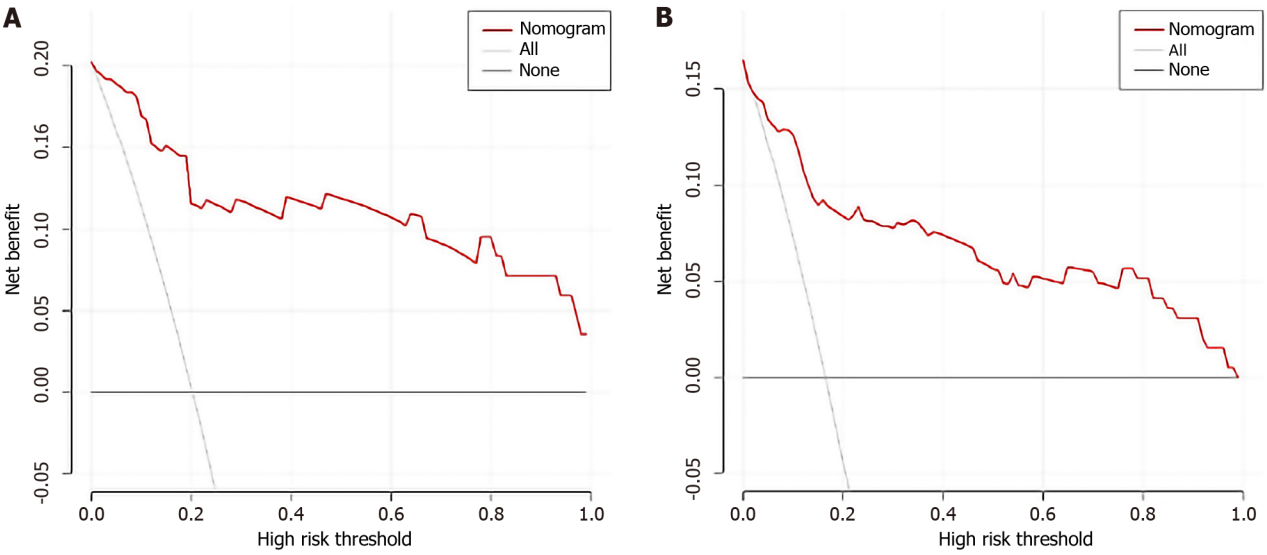
DOI: 10.12998/wjcc.v10.i36.13250

Figure 6 Calibration curves of the prognostic nomogram for disease-free survival in hepatocellular carcinoma patients. A: 3-year calibration curves of the prognostic nomogram for disease-free survival (DFS) in hepatocellular carcinoma (HCC) patients; B: 5-year calibration curves of the prognostic nomogram for DFS in HCC patients.



DOI: 10.12998/wjcc.v10.i36.13250

Figure 7 The receiver operator characteristic curves of the prognostic nomogram and tumor node metastasis stage. TNM: Tumor node metastasis.



DOI: 10.12998/wjcc.v10.i36.13250

Figure 8 The decision curve analysis curve of the prognostic nomogram for disease-free survival in hepatocellular carcinoma patients. A: 3-year decision curve analysis (DCA) curves of the prognostic nomogram for disease-free survival (DFS) in hepatocellular carcinoma (HCC) patients; B: 5-year DCA curves of the prognostic nomogram for DFS in HCC patients.

CONCLUSION

Age, TNM stage, and a history of hepatitis B infection were independent predictive factors of DFS in HCC patients. We constructed and validated an accurate and reliable nomogram that has great reference value for evaluating the prognosis of patients and guiding treatment.

ARTICLE HIGHLIGHTS

Research background

The most prevalent form of liver cancer is hepatocellular carcinoma (HCC), which also has a poor prognosis and a serious risk of invasion and metastasis.

Research motivation

The First Affiliated Hospital of Anhui Medical University treated 445 HCC patients with curative hepatectomy.

Research objectives

The objective of this study was to develop a valid nomogram and explore the independent prognostic markers for disease-free survival (DFS) in HCC patients.

Research methods

A survival curve was plotted using the Kaplan–Meier method and tested using the log-rank method. To identify the prognostic variables, multivariate Cox regression analysis was carried out. To predict DFS in patients with HCC, a nomogram was created. C-indices and receiver operator characteristic curves were used to evaluate the nomogram's performance. Decision curve analysis (DCA) was used to evaluate the clinical application value of the nomogram.

Research results

A longer DFS was observed in patients with the following characteristics: Elderly, I-II stage, and no history of hepatitis B. The calibration curve showed that this nomogram was reliable and had a higher area under the curve value than the tumor node metastasis stage. Moreover, the DCA curve revealed that the nomogram had good clinical applicability in predicting 3- and 5-year DFS in HCC patients after surgery.

Research conclusions

We created and tested a new nomogram to predict DFS in HCC patients, which was accurate and reliable.

Research perspectives

We constructed and validated an accurate and reliable nomogram that has great reference value for evaluating the prognosis of patients and guiding treatment.

FOOTNOTES

Author contributions: Luo PQ, Ye ZH and Zhang LX contribute equally to this manuscript. Luo PQ collected the patients' clinical information, performed the statistical analysis, and completed writing of the manuscript; Ye ZH and Zhang LX assisted in collecting the patients' clinical information and writing the manuscript; Song ED helped them.; Lu Z, Xu AM and Wei ZJ designed the main study and critically revised the manuscript; All authors read and approved the final manuscript.

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Institutional review board statement: The present study was reviewed and approved by Ethics Committee of The First Hospital of Anhui Medical University (Approval No. PJ 2022-12-11).

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

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

Data sharing statement: The data used and/or analyzed during the current study were obtained from the Department of Gastrointestinal Surgery, the First Hospital of Anhui University. The data are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Retrospective Study

Oral higher dose prednisolone to prevent stenosis after endoscopic submucosal dissection for early esophageal cancer

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Abstract

BACKGROUND

Esophageal stenosis is one of the main complications of endoscopic submucosal dissection (ESD) for the treatment of large-area superficial esophageal squamous cell carcinoma and precancerous lesions (≥ 3/4 of the lumen). Oral prednisone is useful to prevent esophageal stenosis, but the curative effect remains controversial.

AIM

To share our experience of the precautions against esophageal stenosis after ESD to remove large superficial esophageal lesions.

METHODS

Between June 2019 and March 2022, we enrolled patients with large superficial esophageal squamous cell carcinoma and high-grade intraepithelial neoplasia experienced who underwent ESD. Prednisone (50 mg/d) was administered orally on the second morning after ESD for 1 mo, and tapered gradually (5 mg/wk) for 13 wk.

RESULTS

In total, 14 patients met the inclusion criteria. All patients received ESD without operation-related bleeding or perforation. There were 11 patients with ≥ 3/4 and < 7/8 of lumen mucosal defects and 1 patient with ≥ 7/8 of lumen mucosal defect and 2 patients with the entire circumferential mucosal defects due to ESD. The longitudinal extension of the esophageal mucosal defect was < 50 mm in 3 patients and ≥ 50 mm in 11 patients. The esophageal stenosis rate after ESD was 0% (0/14). One patient developed esophageal candida infection on the 30th d after

ESD, and completely recovered after 7 d of administration of oral fluconazole 100 mg/d. No other adverse events of oral steroids were found.

CONCLUSION

Oral prednisone (50 mg/d) and prolonged prednisone usage time may effectively prevent esophageal stricture after ESD without increasing the incidence of glucocorticoid-related adverse events. However, further investigation of larger samples is required to warrant feasibility and safety.

Key Words: Early esophageal cancer; Stenosis; Prednisone; Endoscopic submucosal dissection

Core Tip: Esophageal stenosis is one of the main complications of endoscopic submucosal dissection (ESD) for the remedy of large-area superficial esophageal squamous cell carcinoma and precancerous lesions (≥ 3/4 of the lumen). Oral prednisone (30 mg/d) is one of the most commonly used treatment measures to prevent postoperative stenosis after esophageal ESD; however, several studies have drawn inconsistent conclusions. For the first time, we took a higher dose of prednisone (50 mg/d) orally to prevent esophageal stenosis after esophageal ESD and no stenosis occurred in 14 patients, meanwhile, no significant glucocorticoid-related adverse events occurred.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is one of main treatment measures for early esophageal cancer and esophageal high-grade intraepithelial neoplasia[1]. It is minimally invasive and permits *en* bloc resection of large esophageal lesions without esophagectomy. However, esophageal stenosis generally occurs after ESD resection of esophageal lesions, especially for lesions ≥ 3/4 of the lumen. Multivariate analysis has shown that esophageal mucosal membrane defects over 3/4 of the lumen is an important predictor of stenosis formation. Without prophylactic treatment, the occurrence rate of esophageal strictures can reach 83.3%-94.1%; especially when the lesion affects the whole circumference of the esophagus, the rate of esophageal strictures is even higher[2,3]. This often requires repeated endoscopic balloon dilatation (EBD) to alleviate symptoms; however, the benefit is limited[4].

Recently, it has been reported that hormones, as a preventive treatment, can reduce the occurrence of stricture after esophageal ESD[5,6]. Yamaguchi *et al*[5] first reported that oral prednisone 30 mg/d can effectively prevent esophageal stenosis after ESD, and the postoperative stenosis rate can be reduced to 5.3% (1/19). A study also showed that oral prednisone 30 mg /d is not effective in preventing esophageal stenosis in patients with an entire circumference or ≥ 7/8 circumferential mucosal defects [7]. Meanwhile, one case reported that a patient with superficial esophageal squamous cell carcinoma received high-dose dexamethasone therapy (40 mg for 4 d) for multiple myeloma on the 9th d after ESD. After three courses of treatment, no esophageal stenosis was found in the follow-up gastroscopy, the histopathological evaluation showed that the submucosa became thinner, and the fibrosis degree of wound scar after ESD was the lowest[8]. In a prospective study by Nakamura, 11 patients with superficial esophageal squamous cell carcinoma with lesions ≥ 3/4 of the circumference were treated with steroid pulse therapy from the next day after ESD (intravenous infusion of sodium methylprednisolone succinate 500 mg/d for 3 consecutive days from the next day after ESD)[9]. It was found that although steroid pulse therapy was safe, steroid pulse therapy had no preventive effect on esophageal stenosis after ESD. Therefore, oral hormone is an effective method to prevent esophageal stenosis after esophageal ESD, but the dose, use time, effectiveness, and safety of the hormone need to be further studied.

MATERIALS AND METHODS

Patients

Between June 2019 and March 2022, 74 patients with superficial esophageal squamous cell carcinoma or precancerous lesions of esophagus were *en bloc* resected with ESD at the Digestive Endoscopy Center of Shenzhen People's Hospital (Guangdong province, China). Of these, 18 patients accepted mucosal resection *via* ESD, and the mucosal defects involved a 3/4 or larger circumference of the esophageal lumen. However, 1 patient who had received additional chemoradiotherapy (CRT) and 3 patients who had undergone additional surgery were removed from our study. Ultimately, 14 patients were included in this study. The indication criteria were as follows: (1) Before esophageal ESD, the intrapapillary capillary of the lesion mucosa observed by narrow band imaging magnifying endoscopy was type B1; (2) The preoperative lesions of ESD were histologically confirmed as superficial esophageal squamous cell carcinoma or esophageal high-grade intraepithelial neoplasia; (3) Thoracoabdominal enhanced computed tomography (CT) showed no lymph node or distant metastasis; (4) Provision of written informed consent was given; (5) There was no achalasia; and (6) There was no corrosive injury of esophagus. The exclusion criteria were as follows: (1) Patients who could not be followed up for 6 mo or longer; (2) patients whose stenosis formed before esophageal ESD; (3) patients who had prior esophageal cancer with CRT; and (4) patients with additional CRT or additional esophagectomy after non-curative ESD.

ESD procedure

The ESD was operated in an operating room. The patients were endotracheal intubated and kept in the left lying position. An endoscope (GIF-Q260J; Olympus Co., Tokyo, Japan) was attached with forward water delivery function and was used with carbon dioxide insufflation. The head end of the endoscope was connected with a pellucid cap (diameter 12.4 mm, length 4 mm, D-201-11804; Olympus Co.). Iodine 0.75% staining was used for identifying the range of the lesion, and a dual knife (KD-650Q; Olympus Co.) marking dots 3 mm away from the edge of the lesion. An electronic surgical workstation (VIO 200D; ERBE, Tübingen, Germany) was used with an operating mode (Forced Coagulation model, effect 2, maximum power 20 W). The 0.9% saline solution containing 0.3% indigo carmine was used for adequate submucosal injection along the marked dots. After circumferential mucosal incision, submucosal dissection was operated by the dual knife (KD-650Q) from the oral side to the anal side of the lesion under an operating mode (Endocut I mode, Forced Coagulation model, effect 2, maximum power 50 W, VIO 200D; ERBE). Bleeding during the operation and visible blood vessels were handled with hemostatic forceps (FD-410LR; Olympus Co.) under a soft coagulating mode (Soft Coagulation mode, effect 4, maximum power 80 W, VIO 200D; ERBE).

Postoperative-related bleeding was defined as bleeding requiring blood transfusion or surgical intervention, or bleeding that resulted in a 2 g/dL decline in hemoglobin levels. Postoperative-related perforation was diagnosed by endoscopy or chest CT[7]. All patients treated with proton pump inhibitor, esomeprazole, with a dose of 20 mg, twice a day after ESD for 28 d[5,9]. After ESD, each patient received two pieces of calcium carbonate and vitamin D3 chewable tablets (each tablet contains 300 mg calcium and 60 IU vitamin D3) per day until the prednisone was stopped to prevent glucocorticoid-induced osteoporosis[10].

Management for esophageal stenosis prevention

Prednisolone was taken orally at a dose of 50 mg/d from the next morning after ESD for 1 mo, and then decreased gradually (45, 40, 35, 30, 25, 20, 15, 10, and 5 mg for 7 d each) until 13 wk later.

Follow-up

Regular endoscopy was examined at 1, 3, and 6 mo after ESD operation, and then annually thereafter. In addition, endoscopic examination was performed whenever the patient had dysphagia to determine whether there was esophageal stenosis. EBD was performed subsequently if esophageal stricture was identified. Any abnormal mucosa required biopsy for pathological evaluation of whether there was local tumor recurrence. Meanwhile, regular physical and blood examinations were carried out to evaluate the side effects of the steroid. Bone mineral density testing was performed before ESD treatment and 6 mo after ESD treatment.

Outcomes

The main outcome measure was incidence of esophageal stenosis. Esophageal stenosis was defined as the inability of 9.9 mm diameter gastroscope (GIF-Q260J; Olympus) to pass through the esophageal stenosis. Secondary observation indicators of glucocorticoid-related adverse events were observed at 1, 3, and 6 mo after ESD such as newly diagnosed diabetes or aggravation of diabetes, pepticulcer, adrenocortical insufficiency, aggravation of osteoporosis or fracture, and corticosteroid-related mental disorders.

Table 1 Background characteristics of patients, *n* (%)

Characteristics	
Sex	
Male	9 (64)
Female	5 (36)
Age in yr, mean (range)	62.1 (45-75)
Tumor location	
Cervical esophagus	0 (0)
Upper thoracic esophagus	1 (7)
Middle thoracic esophagus	7 (50)
Lower thoracic esophagus	6 (43)
Macroscopic type	
0-IIa	13 (93)
0-IIc	1 (7)
Tumor size in mm, mean (range)	51.7 (43.8-60.7)
Resection size in mm, mean (range)	55.5 (47.5-65.0)
Transverse extension of mucosal defect	
≥ 3/4 and < 7/8 circumference	11 (79)
≥ 7/8 circumference	1 (7)
The entire circumference	2 (14)
Longitudinal extension of the mucosal defect	
< 50 mm	3 (21)
≥ 50 mm	11 (79)
Depth of tumor invasion	
M1 or M2	12 (86)
M3	2 (14)

M1: Tumor limited to the epithelium; M2: Tumor invading the lamina propria; M3: Tumor invading the muscularis mucosa.

End point: The follow-up was terminated if tumor recurrence and serious adverse events of glucocorticoid and procedure-related complications (procedure-related bleeding and procedure-related perforation) occurred.

Statistical analyses

Continuous variables are presented as the mean ± standard deviation or median (interquartile range, 25%-75%). Categorical variables are expressed by proportion. Date analyses were conducted using SPSS 23.0 software (version 23.0 for Mac).

RESULTS

Background characteristics of patients

After ESD surgery, there were 18 patients with mucosal defects more than 3/4 of the esophageal circumference. One patient received additional CRT treatment, and 3 patients received additional surgery and were removed from this study. Eventually, a total of 14 patients met the criteria. Patients and characteristics of lesions are shown in Table 1 and Table 2. Male patients accounted for 64%, with a mean age of 62.1 years (ranging from 45 to 75 years). According to the Paris endoscopic classification,13 cases of endoscopic tumor morphology were classified as type 0-IIa and 1 case was type 0-IIc. The lesions were mainly located in the middle and lower esophagus, and 1 case was located in the upper esophagus. Each patient successfully received esophageal ESD treatment, and postoperative pathology confirmed

Table 2 The feasibility and safety of prophylactic treatment, *n* (%)

Outcome	
Stricture rate	0 (0)
Main complication	1 (7)
Procedure-related bleeding	0 (0)
Procedure-related perforation	0 (0)
Newly diagnosed diabetes or aggravation of diabetes	0 (0)
Pepticulcer	0 (0)
Adrenocortical insufficiency	0 (0)
Aggravation of osteoporosis or fracture	0 (0)
Infection	1 (7)
Corticosteroid related mental disorders	0 (0)
Follow-up period (mo), median (range)	13 (6-28)
Residual	0 (0)
Recurrence	0 (0)

that the lesion was completely removed. All patients had no procedure-related bleeding and procedure-related perforation after esophageal ESD. The mean resection size was 55.5 mm in diameter (ranging from 47.5 mm to 65.0 mm). According to the range of esophageal mucosal defect, 11 cases involved ≥ 3/4 and < 7/8 circumference, 1 case involved ≥ 7/8 circumference, and 2 cases involved the entire circumference. The longitudinal extension of mucosal defect was < 50 mm in 3 patients and ≥ 50 mm in 11 patients. In 12 cases, the depth of invasion of pathological tissues was limited within the epithelium and lamina propria mucosa, whereas 2 lesions were limited within muscularis mucosa without lymphovascular infiltration.

The shortest follow-up time of all cases was 6 mo, the longest follow-up time was 28 mo, and the median follow-up time was 13 mo. During this period, all patients were followed up by endoscopy regularly without dysphagia. The incidence of esophageal stenosis was 0% (0/14) (Table 3). Representative cases are shown in Figures 1 and 2.

Only 1 patient developed esophageal Candida infection on the 30th d after ESD and recovered completely after 7d of treatment with oral fluconazole 100 mg/d. Glucocorticoid-related adverse events were observed such as newly diagnosed diabetes or aggravation of diabetes, pepticulcer, adrenocortical insufficiency, aggravation of osteoporosis or fracture, and corticosteroid-related mental disorders.

DISCUSSION

In the current study, increasing the dose of oral hormone (prednisone acetate 50 mg/d) and prolonging the treatment time (13 wk) were effective to prevent esophageal stenosis in patients with mucosal defects ≥ 3/4 circumference after ESD. Studies have shown that the occurrence of esophageal stricture after ESD is related to the infiltration of postoperative inflammatory cells and vascular proliferation[11,12]. At the same time, epithelial cells proliferate and migrate from the edge of the wound after ESD, fibroblasts proliferate continuously, and finally fibrous scar is formed. This process is divided into three stages: acute inflammation, proliferation, and remodeling; however, the duration of this process is unknown. Through the dog model study, Honda found that within about 1 mo after esophageal EMR, the mucosal defect healed and was covered by squamous cells. Although the proper muscle layer was not damaged, muscle fiber atrophy still occurred in the 1st wk after operation, and finally fibrosis was formed[13]. Some clinical studies have also shown that esophageal stenosis mostly occurs within 2 to 4 wk after surgery[3,14], but this was confined to endoscopic observation. Glucocorticoid has a strong anti-inflammatory effect, which not only inhibits the synthesis of collagen but also promotes the decomposition of collagen to inhibit the formation of stenosis. In our study, all cases did not have esophageal stenosis after ESD. We believe that increasing the dose of prednisolone can enhance the anti-inflammatory effect in the acute inflammatory period, especially in the critical period of the 1st mo after ESD. Meanwhile, we speculate that the process of esophageal stenosis may last longer than expected, and prolonging the usage of prednisolone may inhibit the proliferation of fibroblasts steadily to prevent esophageal remodeling and the formation of esophageal stenosis.

Table 3 Clinical outcomes for 14 patients with early esophageal cancer after circumferential endoscopic submucosal dissection

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14
Sex	Male	Male	Male	Female	Female	Male	Male	Male	Female	Male	Female	Male	Male	Female
Age in yr	66	45	50	75	67	61	63	45	70	72	67	55	66	67
Tumor location	Lt	Ut	Lt	Mt	Mt	Mt	Lt	Lt	Mt	Mt	Mt	Lt	Lt	Mt
Macroscopic type	0-IIa	0-IIa	0-IIa	0-IIa	0-IIc	0-IIa	0-IIa	0-IIa	0-IIa	0-IIa	0-IIa	0-IIa	0-IIa	0-IIa
Tumor size in mm	50.7	49.5	48.4	43.8	47.2	53.3	60.7	49.2	59.8	46.5	59.5	45.2	51.8	58.6
Resection size in mm	56.1	52.6	52.7	47.5	50.8	57.6	65.0	53.2	64.7	50.1	63.5	47.1	54.6	61.2
Transverse extension of mucosal defect	≥ 3/4 and < 7/8	≥ 3/4 and < 7/8	≥ 3/4 and < 7/8	≥ 3/4 and < 7/8	≥ 3/4 and < 7/8	≥ 3/4 and < 7/8	Entire	≥ 3/4 and < 7/8	Entire	≥ 3/4 and < 7/8	≥ 7/8	≥ 3/4 and < 7/8	≥ 3/4 and < 7/8	≥ 3/4 and < 7/8
Longitudinal extension of the mucosal defect in mm	≥ 50	≥ 50	< 50	≥ 50	≥ 50	≥ 50	≥ 50	< 50	≥ 50	≥ 50	≥ 50	< 50	≥ 50	≥ 50
Depth of tumor invasion	M3	M2	M1	M1	M2	M3	M2	M1	M2	M1	M2	M1	M1	M2
Stricture	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Follow up time in mo	9	12	12	12	12	12	15	18	28	28	6	6	7	8
Residual	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Recurrence	No	No	No	No	No	No	No	No	No	No	No	No	No	No

Lt: Lower thoracic esophagus; M1: Tumor limited to the epithelium; M2: Tumor invading the lamina propria; M3: Tumor invading the muscularis mucosa; Mt: Middle thoracic esophagus; Ut: Upper thoracic esophagus.

There are several reports on the application of steroids to prevent stenosis after ESD operation for large-area superficial esophageal squamous cell carcinoma and precancerous lesions. Yamaguchi *et al*[5] reported the therapeutic effect of oral prednisolone after esophageal ESD for the first time. In their report, prednisone was taken on the 3rd d after ESD, with an initial dose of 30 mg/d, and then decreased gradually (30, 30, 25, 25, 20, 15, 10, and 5 mg for 1 wk each). The incidence of stenosis after semi-circumferential ESD resection and entire circumferential ESD resection were 6.3% (1/16) and 0% (0/3), respectively[5]. However, for the cases of circumferential esophageal mucosal defect after ESD, Sato *et al* [15] found that oral prednisone 30 mg/d could not reduce the incidence of postoperative esophageal stenosis, but could decrease the total number of EBD expansions required. In Kadota's[7] study, the stenosis rate of patients with less than entire circumferential ESD resection and with oral prednisone 30 mg/d administration was similar to the results by Yamaguchi *et al*[5], whereas patients with entire circumferential ESD resection showed higher stenosis rate (10/14) even with additional local submucosal steroid injections[7]. Meanwhile, two studies of submucosal injection of triamcinolone acetonide within the mucosal defects combined with oral prednisone in the prevention of esophageal stenosis post-ESD for lesions more than 3/4 circumference have obtained completely opposite results. Chu *et al*[16] reported that after treated with submucosal injection of triamcinolone acetonide within the mucosal defects combined with oral prednisone 30 mg/d, the incidence of esophageal stenosis was only 18.2% (2/11), including lesions with total circumferential resection. Surprisingly, in the Hanaoka *et al* [17] study of 12 cases with whole circumferential defect, the same steroid submucosal injection combined with oral prednisone 5 mg/d were used for post-ESD treatment; nevertheless, 11 patients failed to avoid postoperative stenosis. This discrepancy may be caused by different doses of orally-taken prednisolone in these studies. A study about short-term usage of oral prednisolone (30, 20, and 10 mg/d for 1 wk each) for mucosal defects ≥ 3/4 circumference, including 3 patients with total circumferential resection that showed a stenosis rate of 18% (3/17), and 1 of 3 patients with total circumferential resection withstood stenosis[18]. Accordingly, we speculate that the prevention of esophageal stenosis after esophageal ESD by oral prednisone was correlated with the dose and the use time. In our study, we increased the dose of prednisone to 50 mg/d and prolonged the treatment time to 13 wk. During our follow-up, 14 patients had no feedback of dysphagia symptoms, and no esophageal stenosis observed by endoscopic examination. Especially the 2 patients with entire circumference mucosal defects, although the esophageal wounds were fibrotic, the 9.9 mm diameter gastroscope (GIF-Q260J; Olympus)

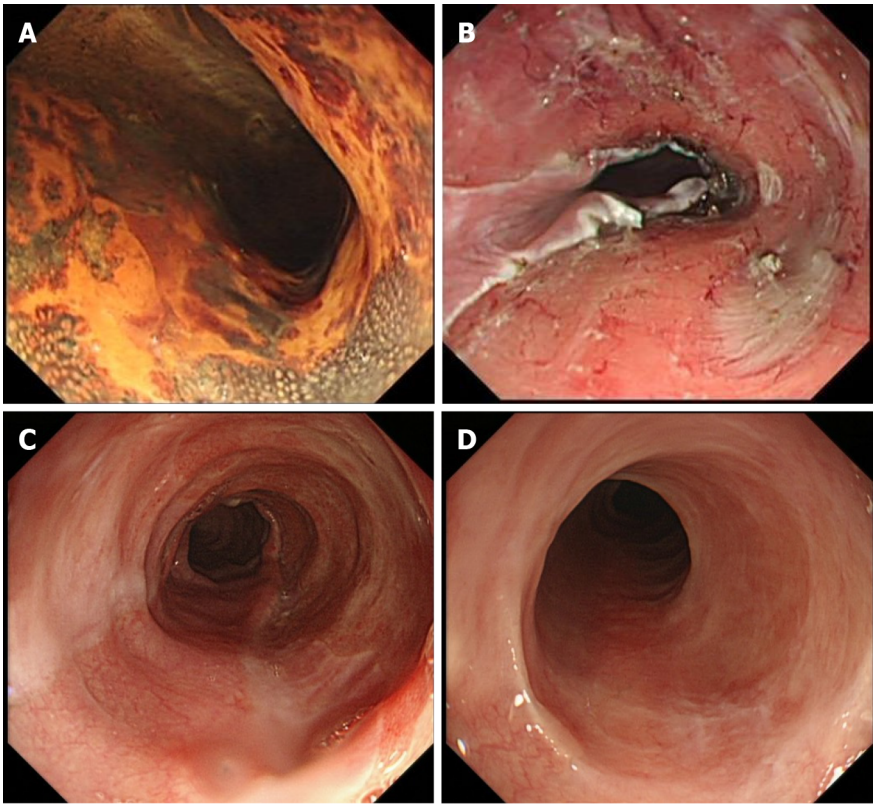

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Figure 1 Representative case (case 1). A 67-yr-old female who underwent endoscopic resection for large superficial esophageal squamous cell carcinoma. A: Endoscopic view of the tumor after Lugol's staining. The tumor spread to more than 3/4 of the circumference of the esophageal lumen; B: Endoscopic view of the ulcer bed immediately after endoscopic submucosal dissection. The width of the mucosal defect was ≥ 3/4 and less than the entire circumference. Then oral steroid was administered as a prophylactic treatment; C: Endoscopic view on the 30th d. The mucosal defect was still undergoing re-epithelialization, and a 9.9 mm diameter gastroscope (Olympus GIF-Q260J) could pass. D: Endoscopic view on the 180th d; Complete epithelialization is shown and a 9.9 mm diameter gastroscope (Olympus GIF-Q260J) could pass without dysphagia.

could pass, and we did not add EBD treatment. In addition, studies have shown that the injury of the intrinsic muscle layer was one of the risk factors for esophageal stenosis after ESD for early esophageal cancer and precancerous lesions[19,20]. Therefore, we paid more attention to avoid the injury of the intrinsic muscle layer as much as possible during ESD operation, which we think is also helpful for the prevention of postoperative esophageal stenosis.

Furthermore, systemic steroids are associated with adverse events, including newly diagnosed diabetes or aggravation of diabetes, pepticulcer, adrenocortical insufficiency, aggravation of osteoporosis or fracture, and corticosteroid-related mental disorders. Stuck *et al*[21] showed that when the cumulative dose of oral prednisone exceeded 700 mg, the risk of infectious complications in patients taking prednisone increased with the increase of prednisone dosage. One study also found that even short-term steroid use is related to increased risks of adverse events[22]. However, in our protocol, the accumulated dose of oral steroids was 3075 mg, which was higher than that of other studies, and proton pump inhibitor, oral calcium, and vitamin D3 were taken simultaneously. One patient was found to have esophageal Candida infection on the 30th d after operation, and completely recovered after 7 d of oral fluconazole 100 mg/d therapy, and no patients experienced other adverse incidents related to orally-taken prednisolone. Therefore, we believe that the treatment scheme of increasing the dose of prednisone (50 mg/d) is safe, but still needs long-term follow-up and observation.

This study had several limitations. First, this study was a retrospective analysis in single-centered, and possible bias could not be avoided. Second, the follow-up time was insufficient and could not comprehensively evaluate the feasibility and safety of the hormone. Third, the number of subjects was relatively small, and the control group was lacking, so statistical difference analysis could not be conducted. Due to these limitations, prospective randomized controlled studies should be established to validate the efficacy and safety of prophylactic steroid therapy.

CONCLUSION

In conclusion, increasing the dose of oral prednisone (50 mg/d) and prolonging the usage time (total 13

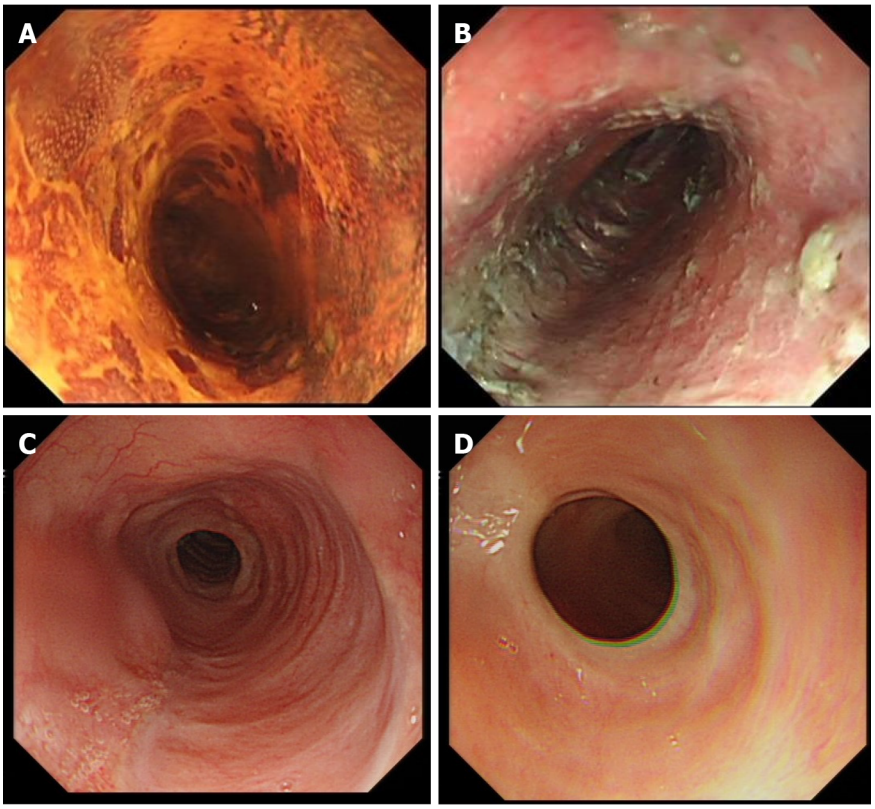

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Figure 2 Representative case (case 3). A 70-yr-old female who underwent endoscopic resection for large superficial esophageal squamous cell carcinoma. A: Endoscopic view of the tumor after Lugol's staining. The tumor spread to about the entire circumference of the esophageal lumen; B: Endoscopic view of the ulcer bed immediately after endoscopic submucosal dissection. The width of the mucosal defect was the entire lumen circumference. Then oral steroid was administered as a prophylactic treatment; C: Endoscopic view 6 mo later. The mucosal defect underwent complete epithelialization, and an 9.9 mm diameter gastroscope (Olympus GIF-Q260J) could pass; D: Endoscopic view after 1 yr. The endoscope could pass without dysphagia.

wk) may effectively prevent esophageal stenosis after ESD to remove large-area superficial esophageal squamous cell carcinoma or precancerous lesions of esophagus, and does not increase the incidence of glucocorticoid-related adverse events.

ARTICLE HIGHLIGHTS

Research background

Esophageal stenosis is one of the main complications of endoscopic submucosal dissection (ESD) for the treatment of large-area superficial esophageal squamous cell carcinoma and precancerous lesions (≥ 3/4 of the lumen). Oral prednisone is useful to prevent esophageal stenosis, but the curative effect remains controversial.

Research motivation

Explore more effective methods to prevent esophageal stenosis after ESD for early esophageal cancer and precancerous lesions.

Research objectives

We shared our experience of the precautions against esophageal stenosis after ESD to remove large superficial esophageal lesions.

Research methods

Patients with large superficial esophageal squamous cell carcinoma and high-grade intraepithelial neoplasia experienced ESD were enrolled. Prednisone (50 mg/d) was administered orally on the 2nd d after ESD for 1 mo, and tapered gradually (5 mg/wk) for 13 wk.

Research results

According to the range of esophageal mucosal defect, 11 cases involved ≥ 3/4 and < 7/8 circumference, 1 case involved ≥ 7/8 circumference, and 2 cases involved the entire circumference. The incidence of esophageal stenosis was 0% (0/14), and only 1 patient developed esophageal Candida infection on the 30th d after ESD and recovered completely after 7d of treatment with oral fluconazole 100 mg/d.

Research conclusions

Further investigation of larger samples is required to warrant feasibility and safety.

Research perspectives

In conclusion, increasing the dose of oral prednisone (50 mg/d) and prolonging the usage time (total 13 wk) may effectively prevent esophageal stenosis after ESD removing large-area superficial esophageal squamous cell carcinoma or precancerous lesions of esophagus, and does not increase the incidence of glucocorticoid-related adverse events.

FOOTNOTES

Author contributions: Zhan SG and Wang LS were responsible for the design of the study and reviewed the manuscript; Zhan SG, Wu BH, Li DF, and Yao J extracted the data; Zhan SG, Xu ZL, Zhang DG, Shi RY, and Tian YH performed the data analysis; Zhan GS and Wang LS were responsible for revising the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of Second Clinical Medical College of Jinan University, Shenzhen People's Hospital (Approval No. LL-KY-2022150-02).

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

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

Data sharing statement: No additional data are available.

Country/Territory of origin: China

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ORIGINAL ARTICLE

Retrospective Study

Predictive value of the unplanned extubation risk assessment scale in hospitalized patients with tubes

Kun Liu, Zheng Liu, Lin-Qian Li, Meng Zhang, Xue-Xue Deng, Hong Zhu

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Abstract

BACKGROUND

Critical patients often had various types of tubes, unplanned extubation of any kind of tube may cause serious injury to the patient, but previous reports mainly focused on endotracheal intubation. The limitations or incorrect use of the unplanned extubation risk assessment tool may lead to improper identification of patients at a high risk of unplanned extubation and cause delay or non-implementation of unplanned extubation prevention interventions. To effectively identify and manage the risk of unplanned extubation, a comprehensive and universal unplanned extubation risk assessment tool is needed.

AIM

To assess the predictive value of the Huaxi Unplanned Extubation Risk Assessment Scale in inpatients.

METHODS

This was a retrospective validation study. In this study, medical records were extracted between October 2020 and September 2021 from a tertiary comprehensive hospital in southwest China. For patients with tubes during hospitalization, the following information was extracted from the hospital information system: age, sex, admission mode, education, marital status, number of tubes, discharge mode, unplanned extubation occurrence, and the Huaxi Unplanned Extubation Risk Assessment Scale (HUERAS) score. Only inpatients were included, and those with indwelling needles were excluded. The best cut-off value and the area under the curve (AUC) of the Huaxi Unplanned Extubation Risk Assessment Scale were been identified.

RESULTS

A total of 76033 inpatients with indwelling tubes were included in this study, and 26 unplanned extubations occurred. The patients' HUERAS scores were between 11 and 30, with an average score of 17.25 ± 3.73. The scores of patients with or without unplanned extubation were 22.85 ± 3.28 and 17.25 ± 3.73, respectively ($P < 0.001$). The results of the correlation analysis showed that the correlation coefficients between each characteristic and the total score ranged from 0.183 to 0.843. The best cut-off value was 21, and there were 14135 patients with a high risk of unplanned extubation, accounting for 18.59%. The Cronbach's α, sensitivity, specificity, positive predictive value, and negative predictive value of the Huaxi Unplanned Extubation Risk Assessment Scale were 0.815, 84.62%, 81.43%, 0.16%, and 99.99%, respectively. The AUC of HUERAS was 0.851 (95%CI: 0.783-0.919, $P < 0.001$).

CONCLUSION

The HUERAS has good reliability and predictive validity. It can effectively identify inpatients at a high risk of unplanned extubation and help clinical nurses carry out risk screening and management.

Key Words: Inpatient; Unplanned extubation; Risk assessment; Prediction; Tube management

Core Tip: This was a retrospective validation study, in which 76033 inpatients with indwelling tubes were included. This study has validated the good predictive value of the Huaxi Unplanned Extubation Risk Assessment Scale. The scale is applicable to the unplanned extubation risk assessment of all types of tubes. The best cut-off value of the scale is 21, and the area under the curve is 0.851.

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INTRODUCTION

Unplanned extubation is defined as the tube falling off by itself, premature removal of the tube by action of the patient, or premature removal due to improper operation by medical staff[1]. In recent years, the literature reported that the number of patients with unplanned extubations accounted for 3.6%-32.1% of hospitalized patients with tubes[2-5]. The occurrence density of unplanned extubation was 0.61-6.6 events/100 intubation days[3,4,6,7]. The occurrence of unplanned extubation could interrupt patients' treatment plans, prolong hospital stays, increase mortality, increase patient pain, increase medical expenses, increase the workload of medical staff, and decrease the bed turnover rate[3,5,8,9]. For patients with unplanned extubation events, 53.5% had adverse consequences[3], the reintubation rate was 28.3%-39.9%[5,9], and the in-hospital mortality rate was 26.4%-39.5%[5,9], significantly higher than those patients without unplanned extubation events. Therefore, the medical industry attaches great importance to the prevention of unplanned extubation. The incidence of unplanned extubation (endotracheal tubes, nasogastric tubes, intravascular catheters, *etc.*) has become an important indicator for evaluating the quality of nursing[10,11]. So, an effective tool for risk assessment and management of unplanned extubation has become particularly important.

In recent years, a few researchers have developed several scales for the risk assessment of unplanned extubation[12-15]. Wang *et al*[12] used Delphi method and developed an unplanned extubation risk assessment tool for various types of tubes and patients over 14 years old. However, the details of unplanned extubation were not reported, and the reliability and validity of the scale lacked the support of clinical data. Vats *et al*[13] developed a scoring tool for unplanned extubation risk, and tried in pediatric patients with endotracheal tubes. While the study did not report the reliability and validity of the scoring tool. Two researches[14,15] designed an assessment tool respectively for unplanned endotracheal extubaiton of artificial airway patients and hospitalized patients with various types of tubes based on literature review and Delphi method. Although the Delphi panel gave good comments, the significance in finding high-risk patients with unplanned extubation lacked clinical application. Although several scales[12-15] for the risk assessment of unplanned extubation have been developed, the reliability and validity of the scales lack the support of clinical data, and their practicability and

popularization need to be confirmed. In addition, the applicable population, age, and tubes of different scales are also inconsistent. Critical patients often have various types of tubes, such as endotracheal intubation, central venous catheter, gastric tube, and various drainage tubes, which require a comprehensive and universal risk assessment tool. Therefore, there is still a lack of a unified, efficient, and recognized evaluation tool. The limitations or incorrect use of the unplanned extubation risk assessment tool may lead to improper identification of patients at a high risk of unplanned extubation and cause delay or non-implementation of unplanned extubation prevention interventions. To effectively identify and manage the risk of unplanned extubation, combined with the literature of previous scale development and the literature reports on the risk factors for unplanned extubation, medical experts in our hospital developed a universal risk assessment tool for unplanned extubation.

Therefore, this retrospective review aimed to validate the predictive value of the Huaxi Unplanned Extubation Risk Assessment Scale (HUERAS) for unplanned extubation.

MATERIALS AND METHODS

This was a retrospective study of hospitalized patient records between October 2020 and September 2021 in a comprehensive tertiary hospital in Sichuan Province, Southwest China. The departments included 41 internal medicine wards, 24 surgery wards, and 8 intensive care units. Inclusion criteria were as follows: (1) Inpatients; and (2) patients with at least one invasive tube (excluding an indwelling needle) during hospitalization. Exclusion criteria were as follows: (1) Patients with refusal to participate in the study; and (2) only temporary tubes during operation.

The medical records extracted from the hospital information system consisted of two parts: the general patient characteristics and the unplanned extubation risk assessment score. The patient characteristics included age, sex, admission mode, length of hospital stay, education level, marital status, and whether unplanned extubation occurred during hospitalization. An unplanned extubation event was defined as the tube falling off by itself, premature removal of the tube by patient or medical staff's improper operation[1]. The risk assessment of unplanned extubation was completed by nurses and recorded in the electronic medical record. Each nurse received training on the use of the unplanned extubation risk assessment scale. The risk assessment has been taken as the routine assessment in our hospital, and it is required to assess when inpatients have tubes or newly placed tubes during hospitalization.

The unplanned extubation risk scores were assessed by the HUERAS. The scale was formulated by the medical experts of the authors' institution based on the analysis of a large number of unplanned extubation events in the previous years of the medical institution, relevant literature reports on the development of unplanned extubation risk assessment tools, combined with the research results of unplanned extubation risk factor assessment. The scale was developed after two rounds of Delphi expert consultation. The method of expert scoring was adapted for the assignment of each item, according to the importance and risk degree of the item. The results of relevant studies[16-19] on the risk factors related to unplanned extubation showed that the fixation mode of the tube and the activity state of patients were high-risk factors for unplanned extubation. Therefore, based on previous studies, this study focused on tube fixation and the evaluation of patients' activity ability. The scale is suitable for hospitalized patients with various types of tubes. The scale consists of 10 characteristics: Age, state of consciousness, degree of understanding, emotional state, degree of cooperation, degree of tolerance, number of tubes, types of tubes, fixation mode of tubes, and activities. The total score of the scale is the sum of the scores of each characteristic. The total score is between 10-30. The higher the score, the higher the risk of unplanned extubation. The scoring method is shown in Table 1.

Statistical analyses were conducted using SPSS Statistics version 21.0. The counting data were described by the frequency and composition ratio, and the measurement data were described by the mean ± standard deviation. A *t*-test was used to compare the unplanned extubation risk scores. Pearson's correlation analysis was used to analyze the correlation between each characteristic of the scale and the total score. Taking the occurrence of unplanned extubation events during hospitalization as the gold standard, the area under the curve (AUC) was used as the predictive value for the risk of unplanned extubation. The sensitivity, specificity, positive predictive value, negative predictive value, Youden index, and AUC were used to test the predictive validity of the scale.

RESULTS

Characteristics of participants

A total of 76033 inpatients with indwelling tubes were included in this study. The participants were mainly males (52.03%), aged from 1 to 106 years (average 51.12 ± 18.46). The length of hospital-stay ranged from 1 to 357 d (average 10.43 ± 11.55). The chief admission mode was outpatient admission (89.47%), the predominant marital status was married (82.73%), and in the majority of the patients, the

Table 1 Scoring method of the Huaxi Unplanned Extubation Risk Assessment Scale

Characteristics	Options	Scoring
Age	14-65 years old/< 14 or ≥ 65 years old	1/2
State of consciousness	Medium or deep coma/Awake/Lethargy, light coma, or drowsiness/Blurred consciousness, irritability, or delirium	1/2/3/4
Degree of understanding	Understanding, newborn or deep sedation/Partial understanding/Incomprehension	1/2/3
Emotional state	Stable or deep sedation/Sometimes stable/Unstable	1/2/3
Degree of cooperation	Cooperative/Sometimes cooperative/Uncooperative	1/2/3
Tolerance degree of tubes	Tolerable/Pain or discomfort, but basically tolerable/Pain or discomfort leads to intolerance of the tube	1/2/3
Number of tubes	1/2-3/3 or more	1/2/3
Type of tubes	PICC; CVC, Jejunostomy, Splittable catheter, Pericardial drainage tube, Abdominal wound drainage tube, Bladder and kidney fistulas, Perirenal drainage tube; Tracheotomy tube, Closed thoracic drainage tube, Urinary catheter, Gastric tube, Nasointestinal canal, Double capsule three lumen tube, Radial artery puncture tube, Internal jugular vein puncture tube, Lumbar cistern drainage tube, Ventricular drainage tube and other head drainage tubes, Cervical plasma drainage tube, Breast plasma drainage tube; Oronasal endotracheal intubation	1/2/3/4
Fixation mode of tubes	Suture/Holder, water bag, airbag, or tie wrap/Adhesive tape	1/2/3
Activity ability	Autonomous activity/Using walking aids, unstable walking, or need help/Absolute bed rest	0/1/2

PICC: Peripherally inserted central catheter; CVC: Central venous catheter.

number of tubes was one (54.85%) (Table 2).

A total of 26 unplanned extubation events occurred during hospitalization. Table 3 shows the basic information of unplanned extubation events.

Reliability analysis of the HUERAS

Cronbach's α coefficient was used to evaluate the internal consistency reliability and was found to be 0.815 in this study. Correlation analysis was used to evaluate the internal correlation of the scale. The correlation coefficients between each characteristic and the total score ranged from 0.183 to 0.843 (Table 4).

Validity analysis of the HUERAS

The patients' HUERAS scores were between 11 and 30, with an average score of 17.25 ± 3.73. The scores of patients with or without unplanned extubation were 22.85 ± 3.28 and 17.25 ± 3.73, respectively. The score of patients with unplanned extubation was higher than that of those without unplanned extubation ($P < 0.001$).

The AUC of HUERAS was 0.851, and the 95% confidence interval was 0.783-0.919, $P < 0.001$.

The sensitivity and specificity corresponding to different cutoff values of the HUERAS are shown in Table 5. The results showed that a score of 20.5 was the best cutoff value, the sensitivity of the scale was 84.6%, and the specificity was 81.4%.

Considering that the risk assessment score was an integer, the cutoff was determined to be 21 points. Thus, ≥ 21 points indicated the high-risk state of unplanned extubation. According to this standard, there were 14135 patients with a high risk of unplanned extubation, accounting for 18.59%. The sensitivity, specificity, positive predictive rate, and negative predictive rate of HUERAS were 84.62%, 81.43%, 0.16%, and 99.99%, respectively.

DISCUSSION

Universality of the risk assessment scale

Whether a scale is a specific scale or a universal scale has an important impact on the popularization of the use of the scale. In the past, scale development research for the risk assessment of unplanned extubation often developed and tested specific populations or specific catheters, which had a good effect on the risk assessment of unplanned extubation of specific populations or specific tubes.

Several studies[1,9,20] comprehensively used the CAM- intensive care unit (ICU)[21], the Richmond Agitation Sedation Scale[22], the Glasgow Coma Scale, the Bloomsbury sedation score, and other scales

Table 2 The characteristics of participants (*n* = 76033)

Character	Category	*n*	Percentage (%)
Sex	Male	39559	52.03
	Female	36474	47.97
Admission mode	Emergency admission	8009	10.53
	Outpatient admission	68024	89.47
Education	Master and above	1477	1.94
	University	10226	13.45
	College	9715	12.78
	Senior school, or Secondary specialized school	13240	17.41
	Junior high school	20063	26.39
	Primary school	14810	19.48
	Preschool, or illiteracy	6502	8.55
Marital status	Unmarried	8538	11.23
	Married	62902	82.73
	Divorced	1682	2.21
	Widowed	1894	2.49
	Others	1017	1.34
Number of tubes	1	41707	54.85
	2-3	22781	29.96
	> 3	11545	15.18
Discharge mode	Discharged according to doctor's order	69284	91.12
	Voluntary discharge	2216	2.91
	Death	1041	1.37
	Transfer to another hospital	3326	4.37
	Others	166	0.22

to comprehensively assess the risk of unplanned extubation. However, no special assessment tool has been developed for unplanned extubation risk assessment. Vats *et al*[13] developed a tool for unplanned extubation risk assessment of children with endotracheal intubation in the ICU and divided the risk of patients into low-, medium-, high- and very high-risk groups according to the score; however, the reliability and validity of the assessment tool were not described in their study. A tool had been developed to assess the risk of unplanned extubation for patients with endotracheal tubes in the ICU [14], but its scope of application was only for patients with endotracheal tubes. Furthermore, there was no actual data pertaining to risk assessment in patients; therefore, its actual predictive validity and application value were limited. Although Wang *et al*[12] developed a universal risk assessment tool for unplanned extubation in patients with different types of tubes and in different types of departments, patients < 14 years of age were not included, and the specific number of cases and relevant basic information of unplanned extubation were not reported in their research report; thus, their predictive validity and popularization were limited to a certain extent. Previous studies often focused on adult or pediatric patients in the ICU and the endotracheal catheters, while less attention was given to patients in other departments and other types of tubes. However, for hospitalized patients treated with tubes, the type of tubes and departments are different, and patients with tubes belong to various age groups. All these factors should be considered by medical staff.

Therefore, at the beginning of the design of this study, a universal unplanned extubation risk assessment scale suitable for all age groups and various types of tubes was developed. Thus, this study also included various types of wards, such as adult internal/surgical wards, pediatric surgery wards, and pediatric and adult ICUs. Furthermore, the tube types included central venous catheters, gastric tubes, urinary tubes, various drainage tubes, tracheal tubes, and other common clinical types of tubes to verify the universality of the scale. A total of 76033 hospitalized patients with tubes were included in this study, in whom 26 unplanned extubation events occurred. Among the patients with unplanned extubation, 46.15% had > 3 tubes; 92.31% unplanned extubations occurred on working days. Regarding

Table 3 Basic information of unplanned extubation events (*n* = 26)

Characteristic	Category	*n*	Percentage (%)
Sex	Male	22	84.62
	Female	4	15.38
Number of indwelling tubes	1	5	19.23
	2-3	9	34.62
	> 3	12	46.15
Date type	Weekdays	24	92.31
	Weekend & holidays	2	7.69
Department type	Internal medicine	13	50.00
	Surgery	11	42.31
	ICU	2	7.69
Occurrence time	Day (8:00-18:00)	7	26.92
	Night (18:00-next day 8:00)	19	73.08
Type of tube extubation	Deep venous catheter (PICC & CVC)	8	30.77
	Urinary catheter	5	19.23
	Drainage tube	5	19.23
	Orogastric tube/Nasointestinal canal	4	15.38
	Endotracheal intubation	3	11.54
	Nasogastric tube & drainage tube	1	3.85
Circumstance of unplanned extubation events	In bed	20	76.92
	During transportation	3	11.54
	Moving out of bed	2	7.69
	Improper operation by medical staff	1	3.85

PICC: Peripherally inserted central catheter; CVC: Central venous catheter; ICU: Intensive care unit.

Table 4 The correlation coefficient between each characteristic and the total score

Characteristic	*r*	*P* value
Age	0.299	0.000
State of consciousness	0.632	0.000
Degree of understanding	0.814	0.000
Emotional state	0.780	0.000
Degree of cooperation	0.843	0.000
Tolerance degree of tubes	0.653	0.000
Number of tubes	0.724	0.000
Type of tubes	0.684	0.000
Fixation mode of tubes	0.435	0.000
Activity ability	0.183	0.000

the distribution of departments, medical, surgical, and ICU departments accounted for 50%, 42.31%, and 7.69% of unplanned extubations, respectively. Among the tube types, central venous catheter, urinary catheter, drainage tube, orogastric tube/nasogastric tube, and endotracheal tube accounted for 30.77%, 19.23%, 19.23%, 15.38%, and 11.54% of unplanned extubations, respectively. In addition, a patient had the gastric tube and drainage tube removed at the same time. Although previous studies have tended to

Table 5 Sensitivity and specificity corresponding to each cutoff value of Huaxi Unplanned Extubation Risk Assessment Scale

Cutoff	Sensitivity	1-specificity	Specificity	Youden index[a]
10.0000	1.000	1.000	0	0
11.5000	1.000	1.000	0	0
12.5000	1.000	0.996	0.004	0.004
13.5000	1.000	0.932	0.068	0.068
14.5000	0.962	0.735	0.265	0.227
15.5000	0.962	0.601	0.399	0.361
16.5000	0.923	0.448	0.552	0.475
17.5000	0.885	0.335	0.665	0.55
18.5000	0.885	0.260	0.74	0.625
19.5000	0.846	0.219	0.781	0.627
20.5000	**0.846**	**0.186**	**0.814**	**0.66**
21.5000	0.769	0.157	0.843	0.612
22.5000	0.692	0.122	0.878	0.57
23.5000	0.500	0.093	0.907	0.407
24.5000	0.346	0.066	0.934	0.28
25.5000	0.115	0.045	0.955	0.07
26.5000	0.077	0.032	0.968	0.045
27.5000	0.038	0.018	0.982	0.02
28.5000	0.000	0.007	0.993	-0.007
29.5000	0.000	0.001	0.999	-0.001
31.0000	0.000	0.000	1	0

[a]Youden index = sensitivity + specificity - 1.

focus more on patients with endotracheal intubation in ICU, these data suggest that a larger number of patients with other types of tubes in the general ward also deserve our research and attention.

In terms of the occurence time, 73.08% unplanned extubation occurred in the evening (18:00-the next day 8:00), which was related to the lower nurse-patient ratio in the evening[4,9] and patients' confusion condition during sleep[23]. From the perspective of sex, males accounted for 84.62% of patients with unplanned extubation, which was consistent with previous studies[9,23] showing that male patients were more prone to unplanned extubation. Because the patients in this study were not limited to the ICU, their activity scenes were not limited to bed. In this study, the scenes of unplanned extubation were also analyzed. A total of 76.92% of cases occurred in bed, 11.54% occurred in the process of transportation, 7.69% occurred in out-of-bed activities, and 3.85% were caused due to improper operation by medical staff. Patients with unplanned extubation were relatively seriously ill and were in a state of sedation, limited bed rest, or physical restraint[23]. During transportation and out-of-bed activities, patients were also prone to unplanned extubation due to the large range of activities or pipeline traction.

Reliability and validity of HUERAS

Internal consistency is an important feature of the reliability of the scale. In this study, the Cronbach's α was 0.815, which indicated that the scale had good reliability. Correlation analysis is a method to test the structural validity of the scale. The correlation coefficients between each characteristic and the total score in this study ranged from 0.183 to 0.843 ($P < 0.001$), which indicated that there was a significant correlation between each characteristic and the total score. The above results showed that the risk assessment tool of this study had good reliability and validity.

Predictive value of HUERAS

In the past, only few studies have reported the predictive value of their unplanned extubation risk assessment tool; thus, the practical use was difficult with low popularity. In this study, the HUERAS

score in patients with unplanned extubation was 22.85 ± 3.28, which was higher than the score in the group without unplanned extubation (17.25 ± 3.73). It can be seen that the higher the score, the higher the risk of unplanned extubation. The AUC of HUERAS was 0.851. According to the classification standard of AUC, the scale had high accuracy in screening for the risk of unplanned extubation in hospitalized patients with tubes.

Cutoff of the HUERAS

In this study, the Youden Index was used to determine the cutoff of the unplanned extubation risk assessment tool. The statistical results showed that the best cutoff score on the scale was 20.5 points. Considering that the risk assessment score of unplanned extubation was an integer, the judgment standard of high risk of unplanned extubation was set at ≥ 21 points. Thus, the sensitivity and specificity of HUERAS were 84.62% and 81.43%, respectively, indicating that the assessment tool had a strong and balanced ability to identify high-risk groups of unplanned extubation. In this study, the positive predictive value was 0.16%, and the negative predictive value was 99.99%, indicating that in patients assessed as having a high risk of unplanned extubation, the proportion of patients with unplanned extubation was low. Considering that patients with unplanned extubation accounted for only 0.034% (26 cases) of the patients in this study, the low positive predictive value was in line with the actual situation. Among the low-risk patients with unplanned extubation, patients without unplanned extubation accounted for 99.99%, indicating that the exclusion rate of the scale for low-risk patients with unplanned extubation was very high and had good prediction ability for the low-risk population.

Limitations

Although this study was based on the risk assessment results of a large number of hospitalized patients with tubes, only 26 unplanned extubation events were actually reported, which was not really high enough to support all the research results based on statistical analyses in this study. Because the number of events were small compare to number of patients in the study, thus the fragility index was quite high. The possible causes, on the one hand, this study was concerned about the various types of tubes in patients, training nurses to conduct risk assessment could also improve nurses' attention to the prevention of unplanned extubation. Nurses also better performed the preventive measures of unplanned extubation, such as secondary fixation, effective communication between nurse and patient, pain and sedation management. On the other hand, the effect of reporting bias cannot be ruled out. But this was a good beginning in research of this important topic. In the follow-up research, the team will continue to conduct in-depth study on this topic.

CONCLUSION

The HUERAS had good predictive validity and could effectively identify hospitalized patients with a high risk of unplanned extubation. This scale may help clinical nurses and nursing managers to accurately identify high-risk patients and take effective preventive measures in time to prevent the occurrence of unplanned extubation in hospitalized patients with tubes.

ARTICLE HIGHLIGHTS

Research background

Critical patients often had various types of tubes, unplanned extubation of any kind of tube may cause serious injury to the patient, but previous reports mainly focused on endotracheal intubation. The limitations or incorrect use of the unplanned extubation risk assessment tool may lead to improper identification of patients at a high risk of unplanned extubation and cause delay or non-implementation of unplanned extubation prevention interventions.

Research motivation

Previous studies about unplanned extubation risk assessment lacked the support of clinical data. The reliability and validity of the previous risk assessment scales and their practicability and popularization cannot be confirmed. To effectively identify and manage the risk of unplanned extubation, a comprehensive, universal, and effective unplanned extubation risk assessment tool is needed.

Research objectives

To assess the predictive value of the Huaxi Unplanned Extubation Risk Assessment Scale in inpatients.

Research methods

We performed a retrospective validation study. For patients with tubes during hospitalization, the

patient characteristic, whether unplanned extubation occurred and the Huaxi Unplanned Extubation Risk Assessment Scale (HUERAS) score were extracted. The best cut-off value and the area under the curve (AUC) of the Huaxi Unplanned Extubation Risk Assessment Scale were been identified.

Research results

A total of 76033 inpatients with indwelling tubes were included in this study, and 26 unplanned extubations occurred. The best cut-off value was 21, and the Cronbach's α, sensitivity, specificity, positive predictive value, and negative predictive value of the HUERAS were 0.815, 84.62%, 81.43%, 0.16%, and 99.99%, respectively. The AUC of HUERAS was 0.851 (95%CI: 0.783-0.919, $P < 0.001$). The prediction validity and generalization of the HUERAS need to be further confirmed by multi center research.

Research conclusions

The HUERAS has good reliability and predictive validity. It can effectively identify inpatients at a high risk of unplanned extubation and help clinical nurses carry out risk screening and management.

Research perspectives

Larger studies with multiple centers are needed to further confirm the prediction validity and generalization of the HUERAS.

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FOOTNOTES

Author contributions: Liu K and Zhu H contributed to the conception and design of the work, and to data acquisition and interpretation, data analysis and drafted the paper; Liu Z and Deng XX contributed to data acquisition and interpretation; Li LQ and Zhang M contributed to data analysis and assisted in interpretation and drafting the paper; All authors contributed to the critical reversion of the paper and approved the final manuscript for publication; All authors have agreed to be accountable for all aspects of the work. Liu K and Zhu H are responsible for the overall content as guarantors.

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ORIGINAL ARTICLE

Retrospective Study

Classification of rectal cancer according to recurrence types - comparison of Japanese guidelines and Western guidelines

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Abstract

BACKGROUND

Rectal cancer is characterized by more local recurrence (LR) and lung metastasis than colon cancer. However, the diagnosis of rectal cancer is not standardized as there is no global consensus on its definition and classification. The classification of rectal cancer differs between Japanese and Western guidelines.

AIM

To clarify the characteristics of rectal cancer by comparing the tumor location and characteristics of rectal cancer with those of colon cancer according to each set of guidelines.

METHODS

A total of 958 patients with Stage II and III colorectal cancer were included in the analysis: 607 with colon cancer and 351 with rectal cancer. Localization of rectal cancers was assessed by enema examination and rigid endoscopy. According to Japan guidelines, rectal cancer is classified as Rb (below the peritoneal inversion), Ra (between the inferior margin of second sacral vertebrae and Rb) or RS (between Ra and sacral promontory).

RESULTS

There were no significant differences between RS rectal cancer and colon cancer in the rates of liver and lung metastasis or LR. Lung metastasis and LR were significantly more common among Rb rectal cancer (in Japan) than in colon cancer (P = 0.0043 and P = 0.0002, respectively). Lung metastases and LR occurred at significantly higher rates in rectal cancer measuring ≤ 12 cm and ≤ 10 cm than in colon cancers (P = 0.0117, P = 0.0467, P = 0.0036, P = 0.0010). Finally, the rates of liver metastasis, lung metastasis, and LR in rectal cancers measuring 11 cm to 15 cm were 6.9%, 2.8%, and 5.7%, respectively. These were equivalent to the rates in colon cancer.

CONCLUSION
High rectal cancer may be treated with the same treatment strategies as colon cancer. There was no difference in the classification of colorectal cancer between Japan and Western countries.

Key Words: Colon cancer; Metastasis; Local recurrence; Classification of rectal cancer; Western guidelines; Japanese guideline

Core Tip: Local recurrence and lung metastasis are more common in rectal cancer than in colon cancer. However, the diagnosis of rectal cancer is not standardized as there is no global consensus on its definition and classification. The classification of rectal cancer differs between Japanese and Western guidelines. High rectal cancer may be treated with the same treatment strategies as colon cancer. There was no difference in the classification of colorectal cancer between Japan and Western countries.

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INTRODUCTION

Colorectal cancer is the third major cause of death in the United States and has the third highest rate of new cases[1]. Similar numbers are observed in Japan, where colorectal cancer is the third major cause of mortality and the highest cause of morbidity among cancers[2]. Due to its anatomical characteristics, rectal cancer has significantly higher rates of local recurrence (LR) than colon cancer. However, the diagnostic criteria for rectal cancer have not been globally standardized. In Japan, rectal cancer is classified into Rb (below the peritoneal inversion), Ra (between the inferior margin of second sacral vertebrae and Rb) and RS (between Ra and sacral promontory) categories, and the localization of the bulk of the tumor is determined by enema examination[3]. According to guidelines in Western countries, such as the National Comprehensive Cancer Network (NCCN) and American Joint Committee on Cancer (AJCC) guidelines, rectal cancers are defined as lesions within ≤ 12 cm of the anal verge and are assessed by rigid endoscopy[4,5]. According to the European Society for Medical Oncology (ESMO), lesions from 0 cm to 5 cm of the anal verge are defined as low rectal cancer, and those from 5 cm to 10 cm of the anal verge are defined as mid-rectal cancer; indeed, none of the definitions are standardized[6].

In Europe, according to the ESMO guidelines, the standard therapy for patients with mid- or low rectal cancer is total mesorectal excision (TME) after chemoradiotherapy[6]. Cancers located more orally to this location are generally treated as colon cancer. Following the NCCN guidelines, in North America, patients with rectal cancer ≤ 12 cm from the anal verge undergo chemoradiotherapy followed by TME surgery[4,5]. In Japan, the standard therapy for rectal cancers located orally to Ra cancers is TME monotherapy. Moreover, rectal cancers located more anally than Rb cancers are treated by TME surgery and lateral lymph node dissection (LLND)[7,8]. This presents a further lack of standardization in the treatment of rectal cancer. Abdelsattar *et al*[9] noted inconsistencies in the guidelines for rectal cancer diagnosis and treatment. Although similar comparisons of guidelines for colorectal cancer have been made, a consensus on the topic has yet to be reached[10].

Although 80% of Ra and Rb rectal cancers are reported to correspond to mid- and low rectal cancer, respectively, the diagnoses of Ra and Rb rectal cancers are not necessarily compatible with those of mid-rectal and low rectal cancer, respectively[11]. Furthermore, tumors diagnosed as RS rectal cancer in Japan may also include tumors that correspond to cancers of the mid-rectum.

This study thus aimed to elucidate how rectal cancer is managed by investigating the relationship between rectal cancer localization in patients treated with radical resection at our facility using the various guidelines and their recurrence type and by subsequently comparing them with patients with colon cancer.

MATERIALS AND METHODS

This study was approved by the institutional review board of our university (20R-238), and all patients were provided written informed consent.

Patients

A total of 958 patients with Stage II and III colorectal cancer who underwent radical surgery between January 2005 and December 2014 were included in the analysis. A total of 607 patients that had colon cancer and 351 patients that had rectal cancer. A total of 217 patients with rectal cancer underwent preoperative chemoradiotherapy (CRT). Rectal cancer was treated surgically by TME monotherapy and none of the patients underwent LLND.

Classification

The segments of the colon including the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon can all be involved in colon cancer. Rectal cancer was classified into RS, Ra, and Rb categories according to the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma (JCCRC)[3]. The localization of rectal cancer was assessed by enema examination and rigid endoscopy. The type of recurrence was evaluated by comparing the rates of liver and lung metastasis as well as LR. LR included intrapelvic recurrences.

*Enema examinatio*n

A double-contrast barium enema was performed by radiologists in all patients to determine the rectal division in which the main part of the tumor was located in accordance with the JCCRC guidelines (second English edition translated from the 7th Japanese edition of the general rules)[3,12,13]. Tumors that involved two divisions, such as "Rb-Ra," were assigned to the major division, *i.e.* the one in which the bulk of the tumor was located. The tumor size was measured as the vertical extension on the lateral view of the barium enema. The location of the tumor in the bowel wall was described as involving the anterior, lateral, or posterior quadrants.

Statistical analysis

Fisher's exact test or the χ^2 test was used to analyze categorical variables, and the Mann-Whitney U test or Kruskal-Wallis test and the Wilcoxon signed rank sum test were used for continuous variables. In all analyses, $P < 0.05$ was considered statistically significant. The software package JMP10 (SAS Institute Inc., NC, United States) was used for statistical analysis.

RESULTS

Patient characteristics

Of the 958 patients, 580 were men and 378 were women, with a median age of 68 years. Of these, 607 had colon cancer, 351 patients had rectal cancer, and 281 underwent CRT. Overall, 482 patients had Stage II disease, and 379 had Stage III disease; 38 had ypStage 0 disease, and 59 had ypStage I disease. These were patients with rectal cancer who underwent CRT and for whom down staging was achieved (Table 1).

Distance to the lower border of the tumor according to localization by rigid endoscopy and enema examination

Rigid endoscopy was performed on 104 of the 351 patients with rectal cancer, and an enema examination was performed on all patients; the results are displayed in Table 2. The mean (SD) distance for RS, Ra, and Rb rectal cancer on rigid endoscopy was 10.3 cm, 7.7 cm, and 3.5 cm, respectively; and that for RS, Ra, and Rb rectal cancer on enema examination was 12.3 cm, 7.2 cm, and 3.2 cm respectively. There was almost no difference between the distances measured by rigid endoscopy and enema examination for Ra and Rb tumors, but there was a 2 cm difference for rectal cancers in the RS segment (Table 2).

Table 2 presents the distances from the anal verge to the lower border of the tumor in various segments measured by enema examination. The tumor was located ≥ 11 cm from the anal verge in 77 patients (73.2%) with RS cancer and ≤ 10 cm from the anal verge in 28 (26.6%) patients. For Ra and Rb cancers, tumors were located ≤ 10 cm from the anal verge in 84 (93.2%) patients and 156 (100%) patients, respectively.

Tumor localization and recurrence type

The recurrence type was classified according to colon cancer and rectal cancer. Rectal cancer was distinguished by CRT administration as it is associated with the LR rate, and they were classified according to the JCCRC, NCCN, AJCC, and ESMO guidelines. Since local recurrence is affected markedly by CRT, it

Table 1 Patients' characteristics

Variable	*n* (%)
Male	579 (60)
Female	379 (40)
Age	22-93
Median	68
Location of the tumor RC	323 (33.7)
LC	284 (29.6)
R	351 (36.6)
Neoadjuvant CRT Yes	217 (61.8)
No	134 (38.2)
Histological type wel-mod	868 (90.6)
Muc	37 (3.8)
Por or Sig	21 (2.2)
PCR	26 (2.7)
Unknown	6 (0.6)
T factor 0	37 (3.8)
1	40 (4.2)
2	83 (8.6)
3	610 (63.6)
4	188 (19.6)
N factor positive	379 (39.5)
Negative	579 (60.4)
Lymphatic invasion positive	655 (68.3)
Negative	302 (31.5)
Unknown	1 (0.1)
Venous invasion positive	647 (67.5)
Negative	310 (32.3)
Unknown	1 (0.1)
Pathological Stage 0	38 (4)
I	59 (6.1)
II	482 (50.3)
III	379 (39.5)

RC: Right sided colon; LC: Left sided colon; R: Rectum; CRT: Chemoradiotherapy; wel: well differentiated adenocarcinoma; Mod: moderated differentiated adenocarcinoma; muc: mucinous adenocarcinoma; Por: Poorly differentiated adenocarcinoma; Sig: Signet cell adenocarcinoma; PCR: Pathological complete response.

was compared to patients who did not undergo CRT.

The rates of colon cancer with liver metastasis, lung metastasis, and LR were 12.6%, 5.4% and 3.4%, respectively. The rates of liver and lung metastasis in patients with rectal cancer who underwent CRT were 8.7% and 10.1%, respectively. The LR rate was 5.5% among patients who underwent CRT and 8.2% in patients who were treated with surgery alone.

Recurrence pattern according to the JCCRC guidelines

The rates of liver metastasis, lung metastasis, and LR in RS cancers according to the JCCRC guidelines were 7.5%, 4.7% and 5.7%, respectively. In Ra and Rb cancers, including in patients who underwent CRT, the liver metastasis, lung metastasis, and LR rates were 9.3%, 10.5% and 6.9%, respectively. The LR

Table 2 Distance to the lower border of the tumor according to localization by rigid endoscopy and enema examination

Classification	Rigid endoscope				Enema examination		
	mean ± SD	Range	*n*		mean ± SD	Range	*n*
RS	10.3 ± 2.3	6-13.5	12 (11.8)		12.3 ± 2.8	7-21	105 (29.9)
Ra	7.7 ± 1.6	5-12	38 (37.6)		7.2 ± 2.3	3-18	90
Rb	3.5 ± 1.8	0-7	54 (53.4)		3.2 ± 2.3	0-10	156
	0-5 cm	6-10 cm	11-15 cm	> 15 cm	Total		
RS	0	28 (26.6)	66 (62.8)	11 (10.4)	105		
Ra	17 (18.8)	67 (74.4)	5 (4.4)	1 (1.1)	90		
Rb	132 (84.6)	24 (15.3)	0	0	156		

Classifications: Rb (below the peritoneal inversion), Ra (between the inferior margin of second sacral vertebrae and Rb) and RS (between Ra and sacral promontory). SD: Standard deviation.

rate was 17.2% among patients who underwent surgery alone and 5.5% among patients who also underwent CRT. There were no significant differences between the rates of liver metastasis, lung metastasis, and local recurrence between RS cancer and colon cancer (P = 0.1491, P = 0.7737, and P = 0.2657, respectively) (Table 3).

Patients with Ra and Rb rectal cancer had significantly higher rates of lung metastasis than those with colon cancer (P = 0.0043). Ra and Rb cancer treated by surgery alone had significantly higher rates of local recurrence than colon cancer (P = 0.0002).

Recurrence pattern according to the NCCN and AJCC guidelines

According to the NCCN and AJCC guidelines, rectal cancer located ≤ 12 cm from the anal verge showed rates of liver and lung metastasis of 8.3% and 10.7%, respectively. The rate of liver and lung metastasis was significantly higher in rectal cancer ≤ 12 cm from the anal verge than in colon cancer (P = 0.0631, P = 0.0117). The LR rate was 8.5% in rectal cancer located ≤ 12 cm from the anal verge treated with surgical monotherapy. Therefore, the LR rate was significantly higher than that in colon cancers located orally less than 12 cm from the anal verge (P = 0.0467) (Table 4).

Recurrence pattern according to the ESMO guidelines

According to the ESMO guidelines, tumors ≤ 15 cm from the anal verge are classified as rectal cancer. Mid- or low rectal cancers are treated surgically, whereas lesions located more orally than ≥ 10 cm from the anal verge are generally treated the same as colon cancer. Consequently, comparisons were made based on rectal cancers located ≤ 10 cm from the anal verge. The rates of liver and lung metastasis of rectal cancer located ≤ 10 cm from the anal verge were 8.9% and 10.4%, respectively. Rectal cancer located ≤ 10 cm from the anal verge had significantly higher rates of liver and lung metastasis than colon cancer (P = 0.1752, P = 0.0036). The LR rate in rectal cancer located ≤ 10 cm from the anal verge treated with surgical monotherapy was 13.2%. This was significantly higher than the LR rate of colorectal cancer located more than 10 cm oral to the anal verge (P = 0.0010) (Table 5).

The rates of liver metastasis, lung metastasis, and LR in rectal cancer located 11 cm to 15 cm from the anal verge were 6.9%, 2.8%, and 5.7%, respectively. There was no significant association with the liver metastasis, lung metastasis, and LR rates of colon cancer (P = 0.1714, P = 0.3357, and P = 0.3400, respectively).

DISCUSSION

Lung metastases and LR were more common in rectal cancer than in colon cancer, and TME is performed for rectal cancer as a common operative method to reduce LR[14-16]. Furthermore, although therapeutic strategies for colon cancer are standardized worldwide, those for rectal cancer vary from CRT and LLND to post-CRT watch and wait. Among these treatments, the indications for CRT are notably different between classification systems; while the NCCN and AJCC guidelines recommend this procedure for advanced rectal cancer located ≤ 12 cm from the anal verge, the ESMO guidelines recommend it for advanced rectal cancer ≤ 10 cm from the anal verge, and the JCCR guidelines only make a weak recommendation in cancers that are T3 or deeper or are cN+ with a high risk of LR. In addition, the localization of the lesion for this recommendation is not specified[3-6].

Table 3 Reccurence pattern according to Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma guidelines

	Liver (%)			Lung (%)			Local (%)		
	Metastasis	*n*	*P* value	Metastasis	*n*	*P* value	Metastasis	*n*	*P* value
Colon cancer	77 (12.6)	530 (87.4)		33 (5.4)	574 (94.6)		21 (3.4)	586 (96.6)	
RS	8 (7.5)	97 (92.5)	0.1491	5 (4.7)	100 (94.3)	0.7737	6 (5.7)	99 (94.3)	0.2657
Ra and Rb	23 (9.3)	223 (90.7)	0.3049	26 (10.5)	220 (89.5)	0.0043	5 (17.2)	24 (82.8)	0.0002
Total		958			958			740	

Table 4 Recurrence pattern according to National Comprehensive Cancer Network and American Joint Committee on Cancer guidelines

	Liver (%)			Lung (%)			Local (%)		
	Metastasis	*n*	*P* value	Metastasis	*n*	*P* value	Metastasis	*n*	*P* value
Colon cancer	77 (12.6)	530 (87.4)		33 (5.4)	574 (94.6)		21 (3.4)	586 (96.6)	
> 12 cm	6 (11.5)	46 (88.5)		2 (3.8)	50 (96.2)		4 (8.3)	48 (91.7)	
≤ 12 cm	25 (8.3)	274 (91.4)	0.0631	29 (10.7)	270 (89.3)	0.0117	7 (8.5)	75 (91.5)	0.0467
Total		958			958			740	

Table 5 Recurrence pattern according to European Society for Medical Oncology guidelines

	Liver (%)			Lung (%)			Local (%)		
	Metastasis	*n*	*P* value	Metastasis	*n*	*P* value	Metastasis	*n*	*P* value
Colon cancer	77 (12.6)	530 (87.4)		33 (5.4)	574 (94.6)		21 (3.4)	586 (96.6)	
> 15 cm	2 (16.6)	10 (83.4)		1 (8.3)	11(91.7)		0 (0)	12 (100)	
11-15 cm	5 (6.9)	66 (93.1)	0.1714	2 (2.8)	69 (97.2)	0.3357	4 (5.7)	65 (94.3)	0.3400
≤ 10 cm	24 (8.9)	244 (91.1)	0.1752	28 (10.4)	240 (89.6)	0.0036	7(13.2)	46 (86.8)	0.0010
Total		958			958			740	

This study compared the recurrence type of rectal cancer according to various diagnostic criteria.

Approximately 26.6% of the tumors diagnosed as RS were located between 6 cm and 10 cm from the anal verge. They likely include more mid- and low rectal cancers that should be treated with CRT rather than tumors classified according to other guidelines. However, according to our current findings, the LR rates of RS cancers and rectal cancers considered "high rectal" cancers (*i.e.* those located more orally than 12 cm, 10 cm from the anal verge) after surgical monotherapy were 5.7%, 8.3% and 5.7%, respectively. These results were similar to the results for colon cancer. There was no significant difference in the recurrence type between RS and colon cancers. In light of its characteristic recurrence types (*i.e.* LR and lung metastasis), rectal cancer can be treated similarly to high rectal and colon cancers as presented by other guidelines. This suggests that the Japanese convention is as reliable as its Western counterparts.

The LR rates of RS cancers, tumors located ≤ 12 cm from the anal verge, and those located ≤ 10 cm from the anal verge after surgical monotherapy were 17.2%, 8.5% and 13.2%, respectively. These results were significantly higher than those for colon cancer ($P = 0.0002$, $P = 0.0467$, and $P = 0.0010$). However, the LR rate of rectal cancers decreased to 5.5% when CRT was added. This value is equivalent to the recurrence rate of colon cancer. Unlike other guidelines, the JCCRC criteria classify rectal cancers according to the location of the tumor relative to the sacrum and the peritoneal reflection[3]. A large proportion of Rb rectal cancers are defined as tumors located below the peritoneal reflection. Measurements performed in this study according to these guidelines showed that 84.6% of Rb cancers were located within 0 cm to 5 cm of the peritoneal reflection. However, Najarian *et al*[17] reported that the mean distance between the anal verge and the peritoneal reflection was 9.7 cm in men and 9.0 cm in women. Although differences in the relationships between peritoneal reflection locations and Ra cancer and Rb cancers are possible, the findings of our investigation on recurrence types generally seemed to suggest that Ra cancer and Rb cancers had higher local recurrence rates according to the JCCRC guidelines than according to other guidelines. In addition, this study found that this diagnosis should be

considered valid for caution in rectal cancer. In terms of therapeutic modalities, the findings of this study showed that in Western countries, nCRT is administered for the majority of tumors located below the peritoneal reflection, whereas in Japan, LLND is only performed for tumors diagnosed as Rb. This suggests that tumors diagnosed as Ra may include tumors for which LLND should be performed, assuming that CRT and LLND are performed as treatments for local control.

In conclusion, based on recurrence types, rectal cancers diagnosed as RS according to the JCCRC guidelines can be treated as colon cancer in terms of therapeutic strategies, similar to other guidelines. Rectal cancers diagnosed as Ra and Rb generally correspond to rectal cancer as defined by the NCCN and AJCC guidelines and to mid-rectal and low rectal cancer as defined by the ESMO guidelines. However, the retrospective, single-center design is a limitation of this study, and further research of patients in a multi-center study is warranted for more detailed investigations.

CONCLUSION

Our findings suggest that rectal cancers classified as RS under the JCCRC guidelines and rectal cancers classified as high rectal cancer under ESMO guidelines can be treated in the same way as colon cancer. The recurrence types of various lesions that require treatment as rectal cancer under the different guidelines were generally consistent; no major differences were found.

ARTICLE HIGHLIGHTS

Research background

Rectal cancer is characterized by more local recurrence and lung metastasis than colon cancer. However, the diagnosis of rectal cancer is not standardized as there is no global consensus on its definition and classification. The classification of rectal cancer differs between Japanese and Western guidelines.

Research motivation

To clarify the characteristics of rectal cancer by comparing the tumor location and characteristics of rectal cancer with those of colon cancer according to each set.

Research objectives

To make the management of rectal cancer a common understanding and to help determine the optimal treatment strategy. To that end, each guideline was compared.

Research methods

A total of 958 patients with Stage II and III colorectal cancer were included in the analysis: 607 with colon cancer and 351 with rectal cancer. Localization of rectal cancers was assessed by enema examination and rigid endoscopy.

Research results

Rectal cancer, which is indicated for chemoradiotherapy in the Western country, is consistent with middle-lower rectal cancer in Japan, and the recurrence rate was characterized by local recurrence and lung metastasis more than colon cancer.

Research conclusions

High rectal cancer may be treated with the same treatment strategies as colon cancer. There was no difference in the classification of colorectal cancer between Japan and Western countries.

Research perspectives

Chemoradiotherapy and lateral lymph node dissection are available for rectal cancer. Although many studies are being conducted around the world, clarifying the correct diagnosis will help in selecting the optimal treatment.

FOOTNOTES

Author contributions: Miyakita H designed the research; Miakita H and Chan LF performed the research; Miyakita H and Kamei Y contributed new reagents/analytic tools; Miyakita H, Okada K and Kayano H analyzed the data; Miyakita H and Yamamoto S wrote the paper.

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ORIGINAL ARTICLE

Retrospective Study

Risk of critical limb ischemia in long-term uterine cancer survivors: A population-based study

Min-Chi Chen, Jung-Jung Chang, Miao-Fen Chen, Ting-Yao Wang, Cih-En Huang, Kuan-Der Lee, Chao-Yu Chen

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Abstract

BACKGROUND

The risk of critical limb ischemia (CLI) which causes ischemic pain or ischemic loss in the arteries of the lower extremities in long-term uterine cancer (UC) survivors remains unclear, especially in Asian patients, who are younger at the

diagnosis of UC than their Western counterparts.

AIM

To conduct a nationwide population-based study to assess the risk of CLI in UC long-term survivors.

METHODS

UC survivors, defined as those who survived for longer than 5 years after the diagnosis, were identified and matched at a 1:4 ratio with normal controls. Stratified Cox models were used to assess the risk of CLI.

RESULTS

From 2000 to 2005, 1889 UC survivors who received surgery alone or surgery combined with radiotherapy (RT) were classified into younger (onset age < 50 years, n = 894) and older (onset age ≥ 50 years, n = 995) groups. While compared with normal controls, the younger patients with diabetes, hypertension, and receiving hormone replacement therapy (HRT) were more likely to develop CLI. In contrast, the risk of CLI was associated with adjuvant RT, obesity, hypertension, and HRT in the older group. Among the UC survivors, those who were diagnosed at an advanced age (> 65 years, aHR = 2.48, P = 0.011), had hypertension (aHR = 2.18, P = 0.008) or received HRT (aHR = 3.52, P = 0.020) were at a higher risk of CLI.

CONCLUSION

In this nationwide study, we found that the risk factors associated with CLI were similar in both cohorts except for adjuvant RT that was negligible in the younger group, but positive in the older group. Among the survivors, hypertension, advanced age, and HRT were more hazardous than RT. Secondary prevention should include CLI as a late complication in UC survivorship programs.

Key Words: Uterine cancer; Critical limb ischemia; Radiotherapy; Survivorship

Core Tip: The risk of critical limb ischemia (CLI) in long-term uterine cancer (UC) survivors remains unclear, especially in Asian patients. In this nationwide study, a total of 1889 UC survivors were classified into younger and older groups. We found that the risk factors associated with CLI were similar in both cohorts except for adjuvant radiotherapy (RT) that was negligible in the younger group, but positive in the older group. Among these survivors, hypertension, advanced age, and hormone replacement therapy were more hazardous than RT. Secondary prevention should include CLI as a late complication in UC survivorship programs.

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INTRODUCTION

Uterine cancer (UC) is the most common gynecologic malignancy in developed areas[1]. The incidence of UC is increasing at a rate of 1%-2% per year in Western and Asian countries[2,3]. In Western populations, 15% of UC patients are under the age of 50 years[4,5], however, around 40% of UC patients in Taiwan are younger than 50 years of age[3]. The patients with loco-regional disease in the United States, which comprises 89% of all cases of UC, have a great prognosis since the 5-year survival rates for local disease and regional disease are 95.3% and 67.5%, respectively[4,5]. Due to the high survival rate, UC survivorship care should include the management of many health issues, such as late side effects in post-treatment cancer survivors. The long-term survivors are commonly defined as patients who are alive for more than 5 years after diagnosis[6]. The well-being of long-term cancer survivors may be as well as persons with similar age and demographic characters[7]. However, even 5 years or more after diagnosis, patients can continue to face the physical effects related to treatment. Thus, concerns have been raised about the detrimental impact of late complications owing to treatment in their survivorship [7,8].

Surgery is the principal treatment for local-regional UC, and radiotherapy (RT) has become the standard adjuvant treatment of choice for patients with high-risk factors[9]. Major pelvic surgery may result in lympho-vascular complications such as deep vein thrombosis or lymph edema[10,11]. In addition, RT can cause local inflammation, oxidative stress, fibrosis and in-field cardiovascular disease [12]. Several studies have reported that RT increased the risk of ischemic stroke in patients with head and neck cancers[13,14].

Peripheral arterial disease (PAD) is a cardiovascular disease that encompasses all chronic arterial occlusive diseases of the arteries other than coronary arteries and the aorta caused by atherosclerosis. The most prevalent sites of PAD are the lower extremities, which may cause leg or pelvic pain, intermittent claudication, and limited mobilization. Women with PAD have been reported to have an increased prevalence of coexisting coronary artery disease and ischemic stroke, and higher all-cause mortality[15]. The risk of PAD has been reported in cervical cancer patients[16,17], however few studies have investigated the risk of PAD in UC survivors. A study from the US using the SEER Utah Cancer Registry revealed that among the UC patients treated with surgery alone or surgery with adjuvant RT, the risk of PAD was 24% higher in the patients with RT than in those who received surgery alone during the first 5 years of follow-up. However, no long-term effect of adjuvant RT was observed 5 years after the diagnosis[2].

These previous studies took a broad definition of PAD, however, delayed diagnoses are common in the PAD patients especially when the symptoms are mild. In this study, we focused on critical limb ischemia (CLI) which presents a relatively severe clinical syndrome related to PAD and causes ischemic pain or ischemic loss in the arteries of the lower extremities. Furthermore, Asian patients with UC are younger on average, the risk of PAD in younger survivors may be different from that in Western patients. Therefore, a nationwide population-based study was conducted to assess the risk of CLI in UC long-term survivors, defined as patients who survived for more than 5 years after diagnosis. We also assessed whether age, treatment modality, income level, comorbidities, and hormone replacement therapy (HRT) are associated with the risk of CLI.

MATERIALS AND METHODS

Data sources

The data used in this study were sourced from the Registry of Catastrophic Illness (RCI) and Longitudinal Health Insurance Database 2005 (LHID2005), which are two subsets of records from the Taiwan National Health Insurance Research Database (NHIRD). The NHIRD is a nationwide database containing longitudinal medical records of beneficiaries enrolled in the National Health Insurance (NHI) program, which provides comprehensive health care coverage for over 98% of the Taiwanese population. The evaluation process for patients in the RCI database is conducted by a panel of specialists who follow a strict process of reviewing medical records, imaging, and pathology reports, therefore, it was used to identify patients with UC or other cancers. The LHID2005 contains original claims data for 1000000 beneficiaries randomly sampled from the entire population in 2005. All information on comorbidities and treatment modalities (for UC cases) from 1995-2012 was available for analysis from inpatient and outpatient records. This retrospective study was approved by the Institutional Review Board (IRB) of Chang Gung Medical Foundation (201600205B0). This study is based in part on data from the NHIRD provided by the NHI Administration, Ministry of Health and Welfare and managed by National Health Research Institutes. This is a secondary use of individuals' healthcare data and all personal information has been removed by de-identification, so that specific persons and their identities cannot be re-identified or be linked to other database. In accordance with the Declaration of Helsinki, this study did not increase the risk of participants, and the IRB approves the waiver of the informed consent form.

Study design

The primary endpoint of this study was the development of CLI during the follow-up period (2005-2012). CLI was identified if the patients were hospitalized with a major or minor diagnosis of the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: 440.0x, (atherosclerosis of the aorta), 440.2x (atherosclerosis of native arteries of the extremities), 440.8x (atherosclerosis of other specified arteries), 440.9x (generalized and unspecified atherosclerosis), 443.9x (peripheral vascular disease, unspecified), 444.0x (arterial embolism and thrombosis of the abdominal aorta), 444.2x (arterial embolism and thrombosis of other specified arteries), 447.8x (other specified disorders of arteries and arterioles), 447.9x (unspecified disorders of arteries and arterioles).

To evaluate the risk of CLI in UC survivors (ICD-9-CM code: 179 or 182), subgroup analysis was performed according to the age at the diagnosis of UC: < 50 years (younger group) and ≥ 50 years (older group). For each group, two study cohorts were compared: a UC survivor group and a matched control group. The survivors were defined as those who survived for longer than 5 years after the diagnosis of UC, and the first day after 5 years of survivorship was defined as the index date. Originally, the UC group comprised 4022 patients who were diagnosed between 2000 and 2005. However, 2133 patients

were excluded due to any one of the following criteria: aged < 20 or > 80 years at diagnosis of UC, survived for less than 5 years, developed second cancers during follow-up or CLI before the index date, incomplete individual information, and received treatment modalities other than surgery alone and surgery with adjuvant RT. Finally, 894 younger and 995 older survivors were eligible for this study. Normal controls were matched using propensity score, calculated as the probability of being a case (UC) according to baseline variables, including age at the index date, sex, urbanization level, and income-related insurance payment. At a ratio of 1:4, four corresponding controls were selected for each UC case based on the closest propensity score. Thus, a total of 7556 controls aged 25-85 years without any history of cancers or CLI before the index date were selected from the LHID2005. The index date of each control was assigned to be the same as that of the corresponding UC survivor. The survival time for all groups was defined as the number of years from the index date to a new diagnosis of CLI, withdrawal from the NHI program (mostly due to death, and a few cases owing to immigration, imprisonment, and others), or December 31st, 2012, whichever occurred first. Comorbidities related to CLI including hypertension, diabetes, atrial fibrillation, hyperlipidemia, chronic kidney disease, morbid obesity and smoking-related diseases, and diagnoses of these comorbidities were confirmed by at least three clinical visits or at least one hospitalization during the 12 mo prior to the index date. We identified HRT (G03C, G03F) according to the Anatomical Therapeutic Chemical Classification system, and retrieved prescription data from NHI files. The dosage of HRT was defined as the average number of days of taking HRT per year from the diagnosis of UC to the date of last follow-up.

Statistical analysis

Baseline characteristics are presented as means with standard deviations or frequencies with percentages. Comparisons between UC survivors and controls were performed using generalized estimating equations[18] which takes into account correlations within each cluster (1 UC case and 4 matched controls). Similarly, stratified Cox proportional hazards models were used to assess the risk of CLI between two groups, and the results are presented as crude hazard ratios (HRs) and adjusted HRs (aHRs) with *P* values. In addition, the cumulative incidence rates of CLI were calculated and compared between groups by applying a competing risk model proposed by Kalbfleisch and Prentice[19] and Gray[20]. Among the UC survivors, risk factors related to CLI were assessed using a Cox proportional hazards models. Data were managed and analyzed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, United States). All statistical tests were two-sided at 0.05 Level of significance.

RESULTS

Characteristics of the study participants

From 2000 to 2005, a total of 1889 eligible UC 5-year survivors were identified from the RCI, and 7556 controls were selected from the LHID2005. The baseline characteristics are listed and two cohorts were comparable with respect to sex, age, and income-related insurance payment (all $P \geq 0.600$) for both age groups (Table 1). In the younger group, the UC survivors had higher rates of comorbidities including hypertension (27.39% *vs* 14.15%, $P < 0.001$), diabetes (18.34% *vs* 5.54%, $P < 0.001$), hyperlipidemia (10.63% *vs* 5.87%, $P < 0.001$), obesity (4.92% *vs* 3.19%, $P = 0.010$) and duration of HRT (percentage of > 1 mo: 15.44% *vs* 6.10%, $P = 0.033$) than the matched controls. However, the controls had a higher rate of smoking-related diseases than the survivors (9.82% *vs* 4.36%, $P < 0.001$). In contrast, compared with the older controls, the UC survivors had similar prevalence rates of all comorbidities, except for lower rates of morbid obesity (1.81% *vs* 3.09%, $P = 0.031$) and smoking-related diseases (7.33% *vs* 18.52%, $P < 0.001$), and a higher rate of diabetes (23.72% *vs* 20.50%, $P = 0.026$).

Risk factors for a CLI event in the younger survivors

The crude incidence rates of CLI were higher in the younger survivors than in the matched controls, but the difference was not significant (198.21 *vs* 117.17 per 100000 person-years, $P = 0.212$, Table 1). In univariate analysis, those who received HRT for longer than 1 mo (HR ≥ 3.67, $P \leq 0.027$) or had any one of the following comorbidities were at a higher risk of developing CLI: diabetes (HR = 4.49, $P = 0.002$), hypertension (HR = 2.89, $P = 0.007$), hyperlipidemia (HR = 3.12, $P = 0.010$) (left panel, Table 2). The adjusted HRs also revealed that the younger patients with diabetes (aHR = 2.93, $P = 0.033$), hypertension (aHR = 2.93, $P = 0.033$), and receiving HRT (aHR ≥ 2.89, $P \leq 0.038$) were more likely to develop PAD (right panel, Table 2). In contrast, both the surgery alone and surgery + RT subgroups had a similar risk to the normal controls (aHR = 0.75 and 0.34, respectively, both $P \leq 0.083$).

Risk factors for a CLI event in the older survivors

In the older group, the crude incidence rates of CLI were not different between two groups (436.25 *vs* 380.54 per 100000 person-years, $P = 0.599$, Table 1). Consistently, univariate analysis also showed that the survivors were at a higher but not significant risk of CLI compared with the controls (HR = 1.17, $P = 0.503$). However, obesity, diabetes, hypertension and receiving HRT for longer than 6 mo increased the

Table 1 Characteristics of uterine cancer survivors and matched normal controls

Characteristic	UC survivors, onset age < 50 years (*n* = 894)	Normal controls (*n* = 3576)	*P* value	UC survivor, onset age 50 years (*n* = 995)	Normal controls (*n* = 3980)	*P* value
Age at index date (yr)	48.00 ± 5.63	47.82 ± 5.74		63.09 ± 6.83	63.23 ± 7.25	
25-40	88 (9.84)	352 (9.84)	1.00			1.00
40-45	121 (13.53)	484 (13.53)				
45-50	251 (28.08)	1004 (28.08)				
50-55	434 (48.55)	1736 (48.55)				
55-60				391 (39.30)	1564 (39.30)	
60-65				267 (26.83)	1068 (26.83)	
65-70				155 (15.58)	620 (15.58)	
> 70				182 (18.29)	728 (18.29)	
Urbanization						
1 (least urbanized)	174 (19.46)	696 (19.46)	0.768	229 (23.01)	996 (23.01)	1.00
2	216 (24.16)	867 (24.24)		223 (22.41)	1184 (22.41)	
3	300 (33.56)	1197 (33.47)		296 (29.75)	892 (29.75)	
4	204 (22.82)	816 (22.82)		247 (24.82)	908 (24.82)	
Income-related insurance payment						
1 (lowest)	449 (50.22)	1793 (50.14)	0.600	665 (66.83)	2660 (66.83)	1.00
2	214 (23.94)	856 (23.94)		153 (15.38)	612 (15.38)	
3	146 (16.33)	587 (16.41)		132 (13.27)	528 (13.27)	
4 (highest)	85 (9.51)	340 (9.51)		45 (4.52)	180 (4.52)	
Morbid obesity[1]	44 (4.92)	111 (3.10)	0.010	18 (1.81)	123 (3.09)	0.031
Smoking-related diseases[2]	39 (4.36)	351 (9.82)	< 0.001	73 (7.33)	737 (18.52)	< 0.001
HRT[3]			0.033			0.108
0	548 (61.30)	2200 (61.52)		663 (66.63)	(69.87)	
1-30 d	208 (23.27)	1158 (32.38)		229 (23.02)	774 (19.45)	
31-180 d	113 (12.64)	192 (5.37)		90 (9.05)	350 (8.79)	
> 180 d	25 (2.80)	26 (0.73)		13 (1.31)	75 (1.88)	
Comorbidity						
Hypertension	244 (27.39)	506 (14.15)	< 0.001	473 (47.54)	1779 (44.70)	0.094
Diabetes	164 (18.34)	198 (5.54)	< 0.001	236 (23.72)	816 (20.50)	0.026
Atrial fibrillation	5 (0.56)	11 (0.31)	0.268	12 (1.21)	65 (1.63)	0.312
Hyperlipidemia	95 (10.63)	210 (5.87)	< 0.001	179 (17.99)	750 (18.84)	0.532
Chronic kidney disease	7 (0.78)	15 (0.42)	0.173	11 (1.11)	35 (0.88)	0.511
CLI	8 (0.89)	19 (0.53)		19 (1.91)	66 (1.66)	
Mean follow-up after index date (yr)	4.515	4.535		4.377	4.358	
Incidence per 100000 person-years[4]	198.21	117.17	0.212	436.25	380.54	0.599
Treatment modality						
Surgery alone	727 (81.32)			694 (69.75)		

Surgery + RT	167 (18.68)	301 (30.25)

[1]Morbid obesity (ICD-9 code: 278, 278.00, 278.01, and V778).
[2]Smoking related diagnoses (ICD-9 code: 305.1, 491.2, 492.8, 496, 523.6, 959.84, 649.0, and V15.82).
[3]Number of days of taking hormone replacement therapy (HRT) per year during the follow-up period. HRT was identified according to the Anatomical Therapeutic Chemical classification system and included estrogen only (G03C) and an estrogen-progesterone combination (G03F).
[4]Incidence per 100000 person-years. Data are presented as *n* (%) or mean ± SD.
UC survivors and the comparison group were matched by 5-year age group, sex, urbanization level, and income-related insurance payment. All *P* values were obtained from generalized estimating equations models. UC: Uterine cancer; RT: Radiotherapy; HRT: Hormone replacement therapy; CLI: Critical limb ischemia.

Table 2 Crude and adjusted hazard ratios for the occurrence of critical limb ischemia in the younger group using a stratified Cox model with withdrawal as a competing risk

	Crude HR (95%CI)		*P* value	Adjusted HR[1] (95%CI)		*P* value
Group (controls)	1		0.150	1		0.395
UC survivors[2]	1.68	(0.83-3.43)		0.66	(0.25-1.72)	
Surgery alone[3]				0.75	(0.25-2.22)	0.601
Surgery + RT[3]				0.34	(0.10-1.15)	0.083
Morbid obesity	1.36	(0.35-5.37)	0.659			
Smoking	1.83	(0.62-5.35)	0.271			
Diabetes	4.49	(1.76-11.44)	0.002	2.93	(1.09-7.92)	0.033
Hypertension	2.89	(1.33-6.27)	0.007	3.61	(1.43-9.08)	0.006
Hyperlipidemia	3.12	(1.31-7.46)	0.010			
Chronic kidney disease	4.00	(0.40-39.83)	0.237			
HRT						
0 d	1			1		
1-30 d	1.98	(0.82-4.75)	0.127	2.89	(1.06-7.91)	0.038
30-180 d	3.67	(1.16-11.58)	0.027	5.65	(1.62-19.65)	0.006
> 180 d	22.36	(3.43-145.80)	0.001	25.75	(4.72-155.24)	< 0.001

[1]Adjusted HRs and *P* values were obtained from a multiple stratified Cox model, which included treatment modality and significant explanatory variables only.
[2]All UC survivors, regardless of treatment modality.
[3]Treatment modalities (surgery alone and surgery with RT) were examined in the Cox model.
UC: Uterine cancer; RT: Radiotherapy; HRT: Hormone replacement therapy; HR: Hazard ratio; CI: Confidence interval; CLI: Critical limb ischemia.

risk of CLI (HR = 6.00, *P* = 0.001; HR = 1.67, *P* = 0.021; HR = 2.24, *P* = 0.002; HR = 5.24, *P* = 0.002, respectively) (left panel, Table 3). Furthermore, the aHRs revealed that the older UC survivors who received RT after surgery had at least a 2-fold higher risk of CLI compared to the matched controls after adjusting for confounders (aHR = 2.12, *P* = 0.019) (right panel, Table 3). In addition, obesity (aHR = 5.55, *P* = 0.003), hypertension (aHR = 2.06, *P* = 0.005) and HRT for ≥ 180 d (aHR = 4.54, *P* = 0.013) were still positively associated with the risk of developing CLI.

The risk of CLI in the UC survivors

Among the 1889 UC survivors, a comparison between treatment modalities revealed that RT increased the risk of CLI by 39%, but this was not significant after adjusting for other confounders (aHR = 1.39, *P* = 0.247). However, the risk of CLI was significantly increased among the survivors who were older (age at the index year > 65 years; aHR ≥ 2.48, *P* < 0.011), had hypertension (aHR = 2.18, *P* = 0.008), and received HRT for longer than 6 mo per year from the diagnosis of UC (aHR = 3.52, *P* = 0.020) (Table 4).

Table 3 Crude and adjusted hazard ratios for the occurrence of critical limb ischemia in the older group using a stratified Cox model with withdrawal as a competing risk

	Crude HR (95%CI)		*P* value	Adjusted HR[1] (95% CI)		*P* value
Group (controls)	1		0.503	1		
UC survivors[2]	1.17	(0.74-1.85)		1.29	(0.80-2.07)	0.299
Surgery alone[3]				0.93	(0.47-1.84)	0.832
Surgery + RT[3]				2.12	(1.13-3.95)	0.019
Morbid obesity	6.00	(2.08-17.29)	0.001	5.55	(1.82-16.94)	0.003
Smoking	0.92	(0.52-1.62)	0.769			
Comorbidity						
Diabetes	1.67	(1.08-2.59)	0.021			
Hypertension	2.24	(1.36-3.68)	0.002	2.06	(1.24-3.43)	0.005
Hyperlipidemia	1.59	(0.98-2.57)	0.062			
Chronic kidney disease	0.800	(0.11-5.63)	0.823			
HRT						
0 d	1			1		
1-30 d	0.68	(0.38-1.24)	0.208	0.60	(1.06-7.91)	0.100
30-180 d	1.01	(0.47-2.15)	0.979	0.82	(1.62-19.65)	0.615
> 180 d	5.24	(1.81-15.23)	0.002	4.54	(1.38-14.91)	0.013

[1]Adjusted hazard ratios and *P* values were obtained from a multiple stratified Cox model, which included treatment modality and significant explanatory variables only.
[2]All UC survivors, regardless of treatment modality.
[3]Treatment modalities (surgery alone and surgery with RT) were examined in the Cox model.
UC: Uterine cancer; RT: Radiotherapy; HRT: Hormone replacement therapy; HR: Hazard ratio; CI: Confidence interval; CLI: Critical limb ischemia.

DISCUSSION

In this nationwide study, we found that the risk factors associated with CLI were similar in both cohorts except for adjuvant RT that was negligible in the younger group, but positive in the older group. In our study population, the younger patients accounted for 47% of the total (894/1889), which is much higher than that reported in Western populations[2,5]. Among the survivors, hypertension, advanced age, and HRT for longer than 180 d per year were more hazardous than RT.

PAD in the general population usually appears after the age of 50 years, and the prevalence then increases with age[21]. This trend was also observed in the UC survivors with CLI in the present study. RT is a known cause of cardiovascular morbidity and mortality. The long-term effects on vascular endothelial damage and the possible mechanism of ionizing radiation on the progression of atherosclerotic plaque have been reported[22,23]. Although studies on the late vascular effects induced by RT have been performed in preclinical models, no clear correlations between individual changes and their time course after conventional fractionated RT have been identified. Accordingly, further studies are needed to investigate whether RT for UC increases the risk of CLI. In our analysis, RT did not cause CLI to occur earlier, but it increased the incidence of CLI in the older patients. People over 65 years of age often have multiple cardiovascular risk factors, and atherosclerosis can be accelerated by radiation[24].

In this study, we found that HRT was more associated with an increased risk of CLI than RT. A previous study reported that estrogen can regulate injury-induced chemokines and oxidative stress and that it has a vascular protective effect, but that it has no vascular protective effects on aging blood vessels[25]. The "timing hypothesis" suggests that because the estrogen signaling pathway in older women has changed, estrogen has no vascular protective effect in patients with subclinical vascular diseases[25]. Compared with the slow decline of estrogen levels in natural menopause over time, bilateral oophorectomy for UC treatment can lead to a sudden decrease in estrogen and menopause. This dramatic decline in estrogen has been associated with a higher cardiometabolic risk[26,27]. This may explain why HRT does not have a protective effect in UC patients, and even showed toxic effects on blood vessels in this study.

In this study, the UC survivors all had common risk factors for CLI, such as smoking, obesity, hypertension, and diabetes. Previous studies have reported that hypertension is a major risk factor for

Table 4 Adjusted hazard ratios for the occurrence of critical limb ischemia in the uterine cancer survivors using a Cox proportional hazards model (*n* = 1889)

	Adjusted HR	95%CI	*P* value
Treatment modality			
Surgery alone	1		0.247
Surgery with RT	1.39	(0.80-2.42)	
Age at index year (yr)			
< 55	1		
55-65	0.72	(0.35-1.48)	0.372
65-75	2.48	(1.23-4.99)	0.011
> 75	3.63	(1.55-8.47)	0.003
Hypertension	2.18	(1.23-3.88)	0.008
HRT			
0 d	1		
1-30 d	0.53	(0.25-1.15)	0.108
30-180 d	1.08	(0.45-2.58)	0.864
> 180 d	3.52	(1.22-10.13)	0.020

Adjusted hazard ratios and *P* values were obtained from a multiple Cox model, which included treatment modality and significant explanatory variables only. UC: Uterine cancer; RT: Radiotherapy; HRT: Hormone replacement therapy; HR: Hazard ratio; CI: Confidence interval; CLI: Critical limb ischemia.

PAD regardless of age[2]. In addition, the prevalence of PAD has been shown to increase with age and to be higher in people with metabolic syndrome and diabetes[15]. We also found that the influence of diabetes and hyperlipidemia was more prominent in the younger group. This may be due to the fact that younger UC patients usually have type I endometrial cancer, which is associated with obesity and metabolic syndrome. These are common risk factors for symptomatic PAD and can lead to chronic atherosclerosis[4,15].

The UC survivors in this study were defined as those who were diagnosed with UC between 2000 and 2005, and who survived for longer than 5 years. Although details of the surgical methods were not available in the dataset, we believe that they all underwent traditional surgery. At present, current surgical methods including a laparoscopic or robotic approach and sentinel lymph node evaluation are considered to be minimally invasive surgery which can improve the short-term quality of life. However, no significant difference in overall survival according to the initial surgical management has been reported between traditional laparotomy and these minimally invasive techniques[28]. In addition, sentinel lymph nodes can reduce the risk of lower limb lymphedema, which may influence circulation in the lower limbs. Further studies to evaluate differences in treatment techniques are suggested. In addition, compared with Western women, Asian women have a higher grade of histology, more advanced stage and worse 5-year survival rate. Therefore, Asian women are more likely to receive lymphadenectomy, which may result in more aggressive surgery leading to a higher risk of complications[29,30].

There are several strengths to this study. It is the first study examining RT effect on long-term UC survivors, and the use of a nationwide database allowed for a large sample size, homogeneous population, and long follow-up period. In addition, we could evaluate the temporal relationship regarding the use of HRT. Nevertheless, the major limitation is that data on other covariates including body mass index, use of contraceptives, self-pay medications, reproductive history, smoking status, details of treatment such as volume of radiation are not provided in NHIRD. We also lacked information of histology and staging at the initial diagnosis, which are major factors for survival. However, endometrial adenocarcinoma comprises approximately 90% of all UC[4] and we only included patients who had surgery alone or surgery combined with adjuvant RT, which are the main treatments for loco-regional disease. Finally, limited incidences due to restrict criteria of CLI may cause overfitting in statistical modeling. Using a public dataset for research has inevitable limitations, and therefore we aim to use other data sources for more persuasive comparisons in the future.

CONCLUSION

We used a nationwide population-based database to explore the risk of CLI among long-term UC survivors. Among them, the correlation between adjuvant RT and CLI was far weaker than the correlations of hypertension, diabetes, and long duration of HRT. Therefore, younger patients should pay special attention to monitoring CLI when using HRT. The development of CLI is an important risk factor for severe vascular diseases, such as ischemic stroke and coronary artery disease. Consequently, future survivorship care should include CLI as a late complication to ensure proper prevention and management.

ARTICLE HIGHLIGHTS

Research background

Uterine cancer (UC) is the most common gynecologic malignancy in developed areas. The long-term survivors are commonly defined as patients who are alive for more than 5 years after diagnosis. Peripheral arterial disease (PAD) is a cardiovascular disease and the most prevalent sites of PAD are the lower extremities. In this study, we focused on critical limb ischemia (CLI) which presents a relatively severe clinical syndrome related to PAD.

Research motivation

The risk of CLI which causes ischemic pain or ischemic loss in the arteries of the lower extremities in long-term UC survivors remains unclear, especially in Asian patients, who are younger at the diagnosis of UC than their Western counterparts.

Research objectives

A nationwide population-based study was conducted to assess the risk of CLI in UC long-term survivors, defined as patients who survived for more than 5 years after diagnosis. We also assessed whether age, treatment modality, income level, comorbidities, and hormone replacement therapy (HRT) are associated with the risk of CLI.

Research methods

UC survivors, defined as those who survived for longer than 5 years after the diagnosis, were identified and matched at a 1:4 ratio with normal controls. Stratified Cox models were used to assess the risk of CLI. The data used in this study were sourced from the records from the Taiwan National Health Insurance Research Database.

Research results

From 2000 to 2005, a total of 1889 eligible UC 5-year survivors were identified from the RCI, and 7556 controls were selected. In the younger group, the UC survivors had higher rates of comorbidities including hypertension, diabetes, hyperlipidemia, obesity and duration of HRT than the matched controls. In the younger survivors, the adjusted hazard ratios (aHRs) also revealed that the younger patients with diabetes (aHR = 2.93, P = 0.033), hypertension (aHR = 2.93, P = 0.033), and receiving HRT (aHR ≥ 2.89, P ≤ 0.038) were more likely to develop PAD. Furthermore, the aHRs revealed that the older UC survivors who received radiotherapy (RT) after surgery had at least a 2-fold higher risk of CLI compared to the matched controls. The risk of CLI was significantly increased among the survivors who were older (age at the index year > 65 years; aHR ≥ 2.48, P < 0.011), had hypertension (aHR = 2.18, P = 0.008), and received HRT for longer than 6 mo per year from the diagnosis of UC (aHR = 3.52, P = 0.020).

Research conclusions

We found that the risk factors associated with CLI were similar in both cohorts except for adjuvant RT that was negligible in the younger group, but positive in the older group. Among UC cancer survivors, the correlation between adjuvant RT and CLI was far weaker than the correlations of hypertension, diabetes, and long duration of HRT. Therefore, younger patients should pay special attention to monitoring CLI when using HRT.

Research perspectives

Using a public dataset for research has inevitable limitations, and therefore we aim to use other data sources for more persuasive comparisons in the future.

FOOTNOTES

Author contributions: Chen MC, Chang JJ, Chen CY, and Lee KD designed the research study; Chen MC and Lee KD performed the study concept and collected data; Chen MC analyzed the data; Chen MC, Chang JJ, and Chen CY drafted the manuscript; Chang JJ and Chen CY interpreted the data; Lee KD, Chen MF, Wang TY, and Huang CE edited and reviewed the manuscript; Chen MC and Chang JJ contributed equally to this paper; Lee KD and Chen CY contributed equally to this paper; all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Serum Spondin-2 expression, tumor invasion, and antitumor immune response in patients with cervical cancer

Ling-Li Zhang, Song Lin, Yan Zhang, Dong-Mei Yao, Xin Du

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Abstract

BACKGROUND

Cervical cancer is a gynecological malignancy common in middle-aged and older patients, with a high mortality rate. Spondin-2 is an extracellular matrix protein that involved in innate and acquired immune responses. Herein, we investigated the relationship between serum Spondin-2 expression, tumor invasion and infiltration, and immune response in patients with cervical cancer and provided a theoretical basis for clinical practice.

AIM

To investigate the relationship between serum Spondin-2 expression and cervical cancer-related indicators.

METHODS

Overall, 147 patients with cervical cancer who were admitted to our institution between January 2019 and August 2019 were assigned to the cervical cancer group, and 92 patients with benign uterine lesions and 86 healthy individuals were assigned to the benign and control groups, respectively. In each group, serum Spondin-2 expression was measured, and the receiver operating characteristic (ROC) curve was determined. Patients with cervical cancer were classified into high or low Spondin-2 groups depending on the Spondin-2 threshold value used for diagnosing cervical cancer. Patient's clinical data were collected to compare the clinicopathologic characteristics, immune cytokine levels, and prognosis of patients with varying Spondin-2 expression levels.

RESULTS

The expression level of serum Spondin-2 was significantly higher in the cervical cancer group than in the benign and control groups ($P < 0.05$). According to the ROC curve, the cutoff value of Spondin-2 used in the diagnosis of cervical carcinoma was 25.68 ± 7.11 μg/L. The proportion of patients with Federation of Gynecology and Obstetrics stage III, nerve invasion, vascular invasion, and lymph node metastasis was higher in the high Spondin-2 group than in the low Spondin-2 group ($P < 0.05$). Interleukin-5 (IL-5) and IL-4 Levels were higher in the high Spondin-2 group than in the low Spondin-2 group. In contrast, IL-2 and tumor necrosis factor-α levels were lower in the high Spondin-2 group than in the low Spondin-2 group ($P < 0.05$). After 3 years of follow-up, progression-free survival and overall survival were significantly shorter in the high Spondin-2 group than in the low Spondin-2 group ($P < 0.05$).

CONCLUSION

The expression of serum Spondin-2 is upregulated in patients with cervical carcinoma and is related to tumor invasion and infiltration, antitumor immune response, and prognosis.

Key Words: Cervical cancer; Spondin-2; Invasion and infiltration; Immune response; Prognosis; Malignant tumor

Core Tip: We measured the expression of Spondin-2 in the sera of patients with cervical cancer, patients with benign uterine lesions, and healthy individuals. Spondin-2 expression was regulated in patients with cervical cancer and was related to tumor invasion and infiltration, antitumor immune response, and prognosis.

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INTRODUCTION

Cervical cancer is a gynecological malignancy that is common in middle-aged and older patients; in recent years, it reportedly occurs in younger patients and seriously endangers patient health[1]. Relevant studies have indicated that cervical cancer is associated with high-risk human papillomavirus (HPV) infection and abnormal immune response, among other factors. Among these, an abnormal immune response may not be helpful in HPV clearance. It may interfere with the body's normal antitumor response, leading to invasion and metastasis, which are important factors that cause high mortality[2,3]. Molecular markers that significantly affect the immune function in cervical cancer should be identified from the molecular biology perspective to guide patients' treatment and increase their survival. Spondin-2 is an extracellular matrix protein that plays a role in innate and acquired immune responses. Its expression is currently associated with the development and spreading of several malignant tumors, including prostate cancer[4] and lung adenocarcinoma[5]. This study aimed to examine the association between serum Spondin-2 expression, tumor invasion and infiltration, and immune response in patients with cervical cancer to provide a theoretical basis for clinical practice.

MATERIALS AND METHODS

General information

We enrolled 147 patients with cervical cancer who were admitted to our hospital between January 2019 and August 2019 for this study. Inclusion criteria included patients: (1) Diagnosed with cervical cancer by postoperative pathological examination according to the clinical practice guidelines for cervical cancer proposed by the National Comprehensive Cancer Network in 2019[6]; (2) aged ≥18 years; (3) with serum samples obtained preoperatively; and (4) who signed an informed consent form. Exclusion criteria included patients: (1) Who did not receive chemoradiotherapy or antitumor treatment prior to the study enrollment; (2) who developed endometriosis, uterine fibroids, or other serious uterine lesions along with cervical cancer; (3) with other primary malignant tumors, immune system abnormalities,

liver and kidney decompensation, or serious infection; and (4) with incomplete clinical data and follow-up data. Additionally, 92 patients with benign uterine disease and 86 healthy individuals were enrolled into the benign and control groups, respectively. Patients in the cervical cancer group were aged 37–69 (51.62 ± 5.87) years; had a body mass index (BMI) of 19–25 (22.75 ± 1.63) kg/m^2; had a disease duration of 1–3 (2.17 ± 0.65) years; had the following pathological types: squamous cell carcinoma in 101 cases, adenocarcinoma in 25 cases, and adenosquamous carcinoma in 21 cases; had the following Federation of Gynecology and Obstetrics (FIGO)[7] stages: stage I in 42 cases, stage II in 49 cases, and stage III in 56 cases; had nerve invasion in 92 cases and no nerve invasion in 55 cases; had vascular invasion in 69 cases and no vascular invasion in 78 cases; and had lymph node metastasis in 87 cases and no lymph node metastasis in 60 cases. Patients in the benign group were aged 40–65 (51.12 ± 6.21) years; had a BMI of 19–25 (22.61 ± 1.82) kg/m^2; had a disease duration of 1–3 (2.24 ± 0.59) years; and developed endometriosis in 42 cases, uterine fibroids in 36 cases, and adenomyosis in 14 cases. Patients in the control group were 35–65 (52.04 ± 5.48) years and had a BMI of 20–25 (22.84 ± 1.59) kg/m^2. Among the three groups, no significant differences were observed in age or BMI ($P > 0.05$).

Method

Detection of serum Spondin-2 and immune cytokine levels: Before surgery, blood samples were collected and centrifuged at 3,000 rpm for 10 min to separate the upper serum. An enzyme-linked immunosorbent assay was used to determine the serum levels of Spondin-2, interleukin (IL)-2, IL-4, tumor necrosis factor (TNF-α), and IL-5. The human factor antibody was added to approximately 100 μL of the standard samples and 100 μL of the test samples, and the reaction was performed at 37 °C for 90 min. After the reaction was completed, horseradish peroxidase enzyme was added to each well and incubated at 37 °C for 30 min, followed by the addition of substrate solution and the termination of the reaction. The optical density values were measured at 450 nm using a microplate reader, and the factor levels to be measured were compared using the standard curve.

All patients with cervical cancer underwent extensive hysterectomy and bilateral pelvic lymphadenectomy. Their clinicopathological data, including pathological type, FIGO stage, nerve invasion, vascular invasion, and lymph node metastasis, were collected. A receiver operating characteristic (ROC) curve was used to analyze the cutoff value for serum Spondin-2 Levels used in the diagnosis of cervical cancer, and the patients were divided into high Spondin-2 and low Spondin-2 groups to analyze the differences in the clinicopathological characteristics of patients with different expression levels.

Follow-up: The patients were followed up every 3 mo until July 30, 2022 or death. Progression-free survival (PFS) and overall survival (OS) were assessed. PFS was defined as the time until confirmed tumor recurrence or metastasis, whereas OS was defined as the time until confirmed death.

Statistical analysis

The data were analyzed using SPSS 22.0, and the formula mean ± SD was used to represent the measurement data in accordance with the normal distribution. A one-way analysis of variance was applied for comparison between groups, the Student–Newman–Keuls-*q* test was applied for pairwise comparison between groups, and an independent sample *t*-test was used for comparison between two groups. The enumeration data were expressed as percentages (%). The χ^2 test was utilized for comparison between groups. The ROC curve was developed to determine the cutoff value of serum Spondin-2 expression for diagnosing cervical cancer. The Kaplan–Meier curve was used to analyze the PFS and OS. A *P* value of < 0.05 was considered statistically significant.

RESULTS

Serum Spondin-2 expression in each group

The serum Spondin-2 expression level was considerably higher in the cervical cancer group ($P < 0.05$) than in the benign and control groups (Table 1).

Determination of cutoff values for Spondin-2

ROC curves were established, and the maximum Youden's index was used as the cutoff value of Spondin-2 expression in patients with cervical cancer (21.20 μg/L). The sensitivity and specificity values were 71.1% and 95.3%, respectively, and the area under the curve value was 0.866 (95%CI: 0.827-0.905; $P < 0.001$) (Figure 1).

Serum Spondin-2 expression in patients with different clinicopathological characteristics of cervical cancer

According to the cutoff value, patients with Spondin-2 expression levels greater than the cutoff value were assigned to the high expression group and those with lower levels were assigned to the low expression group. The proportion of patients with FIGO stage III, vascular invasion, nerve invasion, and lymph node metastasis was higher in the high Spondin-2 group than in the low Spondin-2 group (*P* <

Table 1 Serum Spondin-2 expression in each group (mean ± SD)

Group	*n*	Spondin-2 (μg/L)	*F*	*P* value
Cervical cancer group	147	25.68 ± 7.11	105.790	0.000
Benign group	92	17.52 ± 5.76		
Control group	86	14.16 ± 4.96		

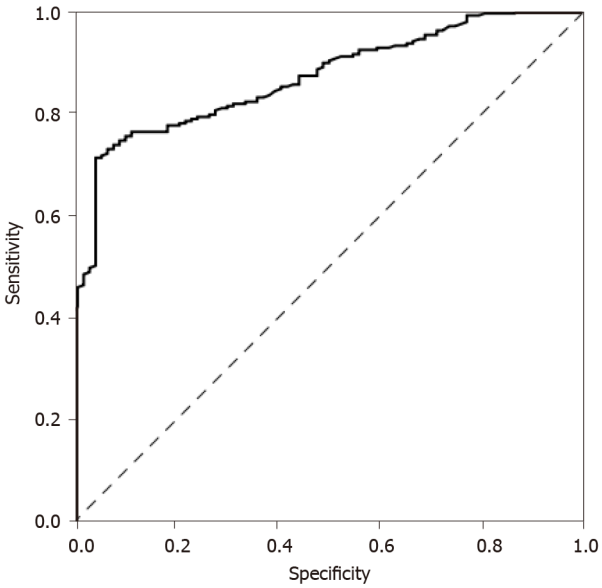

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Figure 1 Receiver operating characteristic curve of Spondin-2 in the diagnosis of cervical cancer.

0.05). No significant difference was observed in the pathogenic categories between the two groups (P > 0.05) (Table 2).

Relationship between serum Spondin-2 expression and immune response in patients with cervical cancer

The high Spondin-2 group had higher IL-4 and IL-5 levels than the low Spondin-2 group, whereas the low Spondin-2 group had higher IL-2 and TNF-α levels than the high Spondin-2 group (P < 0.05) (Table 3).

Relationship between serum Spondin-2 expression and prognosis in patients with cervical cancer

After 3 years of follow-up, PFS and OS were shorter in the high Spondin-2 group than in the low Spondin-2 group (P < 0.05) (Table 4, Figure 2A and B).

DISCUSSION

Cervical cancer has a complicated etiology, and HPV infection is a recognized risk factor[8]. Tumor cells often have the ability to evade immune recognition[9]. Disturbed immune responses not only facilitate HPV infection but also cause persistent infection and increase the risk of epithelial malignant transformation[10,11]. In addition, cervical cancer is prone to peripheral nerve invasion and invasive metastasis, which are important factors that result in a poor prognosis[12]. Therefore, it is imperative to analyze the factors related to invasion and infiltration and the antitumor immune response to improve cervical cancer prognosis.

Spondin-2 is a secreted protein, which was originally discovered in ovarian cancer cells, and is linked to innate and acquired immunity as a pattern-recognition molecule and integrin ligand for pathogenic microorganisms[13]. Spondin-2 is reportedly a critical indicator of the initial response to innate immunity, but its expression levels differ in tumor and non-tumor cells[14]. Moreover, Spondin-2 expression levels were elevated in the sera of patients with prostate cancer[15], hepatocellular carcinoma[16], and pancreatic cancer[17], and high levels were associated with bone metastasis and lymph node metastasis, suggesting that Spondin-2 was also involved in tumor invasion and metastasis.

Table 2 Serum Spondin-2 expression in patients with different clinicopathological features of cervical cancer

Clinical pathology	High Spondin-2 group (*n* = 101)	Low Spondin-2 group (*n* = 46)	χ^2 value	*P* value
Pathological type				
Squamous cell carcinoma	70	31	0.595	0.743
Adenocarcinoma	18	7		
Adenosquamous carcinoma	13	8		
FIGO stage				
Stage I–II	50	41	10.501	0.001
Stage III	51	5		
Nerve invasion				
Yes	72	20	10.438	0.001
No	29	26		
Vascular invasion				
Yes	57	12	11.688	0.001
No	44	34		
Lymph node metastasis				
Yes	66	21	5.075	0.024
No	35	25		

FIGO: Federation of Gynecology and Obstetrics.

Table 3 Relationship between serum Spondin-2 expression and immune response in patients with cervical cancer (mean ± SD)

Group	*n*	IL-2 (pg/mL)	TNF-α (ng/mL)	IL-4 (pg/mL)	IL-5 (pg/mL)
High Spondin-2 group	101	3.52 ± 0.83	10.62 ± 1.80	2.98 ± 0.53	4.43 ± 1.08
Low Spondin-2 group	46	4.12 ± 1.13	13.83 ± 2.56	2.45 ± 0.76	3.18 ± 0.72
t value	-	3.614	8.735	4.879	7.153
P value	-	0.000	0.000	0.000	0.000

IL: Interleukin; TNF: tumor necrosis factor.

Table 4 Relationship between serum Spondin-2 expression and prognosis in patients with cervical cancer (mean ± SD)

Group	*n*	PFS (mo)	OS (mo)
High Spondin-2 group	101	23.2 ± 9.3	26.8 ± 8.7
Low Spondin-2 group	46	28.9 ± 10.4	30.1 ± 9.7
t value	-	3.319	2.056
P value	-	0.001	0.042

PFS: Progression free survival; OS: Overall survival.

This study found that serum Spondin-2 expression was significantly higher in the cervical cancer group than in the benign and control groups, suggesting that Spondin-2 expression is elevated in the sera of patients with cervical cancer and may play a role in the development of cervical tumors and their microenvironment. An ROC curve was used to determine the cutoff value for serum Spondin-2 diagnosis, and patients with cervical cancer were divided into high Spondin-2 and low Spondin-2 groups. The results showed that the number of patients with FIGO stage III, nerve invasion, vascular invasion, and lymph node metastasis was higher in the high Spondin-2 group than in the low Spondin-2

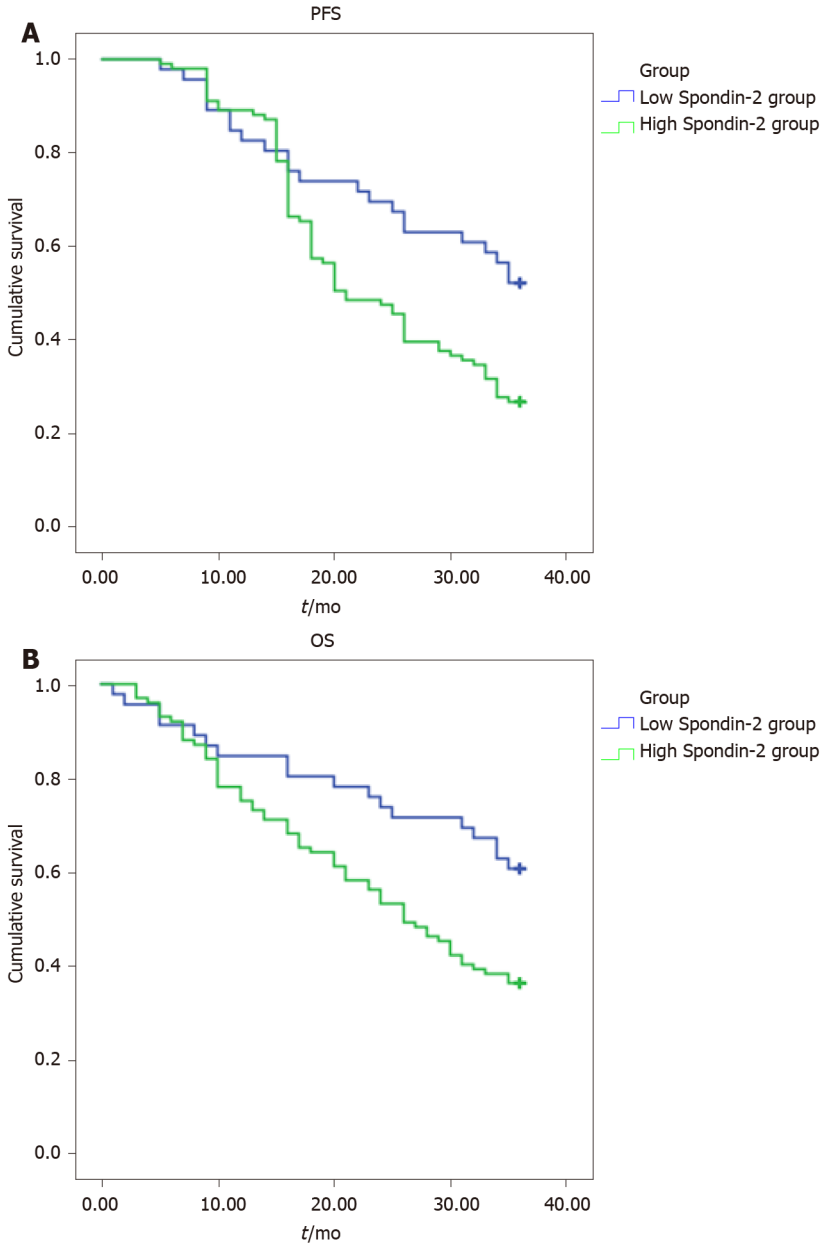

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Figure 2 Comparison of progression-free and overall survival in patients with different serum Spondin-2 expression levels. A: Progression-free survival; B: Overall survival. PFS: Progression-free survival; OS: Overall survival.

group, implying that serum Spondin-2 expression is related to these aspects progression of cervical cancer; thus, its high expression indicates disease progression. Tumor cells can induce neovascularization in surrounding non-malignant tissues, which not only supports tumor growth but also provides a pathway for metastasis[18]. Nerve invasion is also one of the routes of tumor metastasis and mainly refers to neurotropic invasion and peripheral spread of the tumor[19]. It involves the detachment of tumor cells into the stroma and vascular system and the formation of tumor thrombi around the lesion and other tissues and organs, forming the basis of tumor metastasis; these are high-risk indicators affecting the recurrence rate of cervical cancer and patient survival[20]. Spondin-2 influences the proliferation, invasion, and metastasis of cancer cells by regulating the Wnt signaling pathway, which may be related to the invasion and infiltration of cervical cancer cells[21]. Moreover, the susceptibility of cervical cancer to invasion and infiltration may be related to immune dysfunction[14], and Spondin-2 may influence cancer cell invasion and infiltration by participating in the body's specific and non-specific immune responses. T lymphocytes mediate the body's antitumor immune response, which is crucial for HPV elimination and monitoring of abnormal growing cells; when the immune function is abnormal, malignant cervical cells cannot be recognized and removed in time, which triggers the development and progression of cervical cancer. Spondin-2 acts as an integrin ligand in the extracellular matrix and can interfere with the body's normal immune response by recruiting inflammatory cells[22]. This study revealed that IL-4 and IL-5 in high Spondin-2 group were higher than those in low Spondin-2

group, while IL-2 and TNF- α level lower than low Spondin-2 group, suggesting that Spondin-2 is involved in the antitumor immune response. CD4+ is the primary cell type that exerts specific immune effects, including T helper type 1 (Th1) and Th2 subtypes, with the former secreting IL-2 and TNF-α. In contrast, the latter secretes IL-4 and IL-5, which play an immunosuppressive role. The findings of this study indicate that Spondin-2 can inhibit the antitumor immune response and promote the immune escape of tumor cells, thus affecting the progression of the disease. After 3 years of follow-up, PFS and OS were shorter in the high Spondin-2 group than in the low Spondin-2 group, indicating that high serum Spondin-2 expression is associated with a poor prognosis of cervical cancer and further validating the involvement of Spondin-2 in the development of cervical cancer.

CONCLUSION

In conclusion, the serum level of Spondin-2 is elevated in patients with cervical cancer and is linked to tumor invasion and infiltration, antitumor immune response, and prognosis. Thus, it is a potential novel diagnostic marker and treatment target for cervical cancer. However, this study did not investigate its specific mechanism of action in depth, and further studies should be conducted.

ARTICLE HIGHLIGHTS

Research background

Cervical cancer is a gynecological malignancy that is common in middle-aged and older patients, with a high mortality rate; it seriously endangers the health of patients. Spondin-2 is an important molecular marker that is involved in innate and acquired immune responses. This study focused on the relationship between serum Spondin-2 expression, tumor invasion and infiltration, and immune response in patients with cervical cancer to provide a theoretical basis for clinical practice.

Research motivation

The motivation of this study was to investigate the differences in serum Spondin-2 expression levels in patients with cervical cancer, patients with benign uterine lesions, and healthy subjects, as well as the relationship between serum Spondin-2 Levels, tumor invasion and infiltration, and antitumor immune response.

Research objectives

This study aimed to investigate the relationship between serum Spondin-2 expression, tumor invasion and infiltration, and antitumor immune response in patients with cervical cancer.

Research methods

We detected Spondin-2 expression in the sera of patients with cervical cancer or benign uterine lesions and in those of healthy subjects. According to the threshold of Spondin-2 used in cervical cancer diagnosis, patients with cervical cancer were divided into high Spondin-2 and low Spondin-2 groups. Clinicopathological features, immune cytokine levels, and prognosis of patients with different levels of Spondin-2 expression were compared.

Research results

The serum Spondin-2 expression level was significantly higher in the cervical cancer group than in the benign and control groups. The proportion of patients with Federation of Gynecology and Obstetrics stage III, nerve invasion, vascular invasion, and lymph node metastasis was higher in the high Spondin-2 group than in the low Spondin-2 group. The levels of interleukin (IL)-5 and IL-4 were higher in the high Spondin-2 group than in the low Spondin-2 group, whereas the levels of IL-2 and tumor necrosis factor-α were lower in the high Spondin-2 group than in the low Spondin-2 group. After 3 years of follow-up, progression-free survival and overall survival were significantly lower in the high Spondin-2 group than in the low Spondin-2 group.

Research conclusions

The expression of Spondin-2 in patients with cervical cancer was upregulated, and it was associated with tumor invasion and infiltration, antitumor immune response, and prognosis.

Research perspectives

Serum Spondin-2 Levels can be used as a new diagnostic marker and therapeutic target for cervical cancer, providing a theoretical basis for clinical diagnosis and disease evaluation.

FOOTNOTES

Author contributions: Zhang LL wrote this article, Lin S provided experimental ideas, Yao DM and Du X performed data collection, and Lin S and Zhang Y performed data sorting and analysis.

Institutional review board statement: This study was approved by the Ethics Committee of the Maternal and Child Health Hospital of Hubei Province.

Informed consent statement: All study participants signed an informed consent form before participating in the study.

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ORIGINAL ARTICLE

Retrospective Study

Thoracic para-aortic lymph node recurrence in patients with esophageal squamous cell carcinoma: A propensity score-matching analysis

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Abstract

BACKGROUND

Thoracic para-aortic lymph node (TPLN) recurrence in esophageal squamous cell carcinoma (ESCC) is rare and its impact on survival is unknown. We studied survival in patients with ESCC who developed TPLN recurrence.

AIM

To study the survival in patients with ESCC who developed TPLNs recurrence.

METHODS

Data were collected retrospectively for 219 patients who had undergone curative surgery for ESCC during January 2012 to November 2017 and who developed recurrences (36.29% of 604 patients who had undergone curative surgeries for ESCC). The patients were classified into positive (+) and negative (-) TPLN metastasis subgroups. We also investigated TPLN recurrence in 223 patients with ESCC following definitive chemoradiotherapy during 2012-2013. Following propensity score matching (PSM) and survival estimation, factors predictive of overall survival (OS) were explored using a Cox proportional hazards model.

RESULTS

Among the patients with confirmed recurrence, 18 were TPLN (+) and 13 developed synchronous distant metastases. Before PSM, TPLN (+) was associated with worse recurrence-free (P = 0.00049) and OS [*vs* TPLN (-); P = 0.0027], whereas

only the intergroup difference in recurrence-free survival remained significant after PSM (P = 0.013). The Cox analysis yielded similar results. Among the patients who had received definitive chemoradiotherapy, 3 (1.35%) had preoperative TPLN enlargement and none had developed recurrences.

CONCLUSION
TPLN metastasis is rare but may be associated with poor survival.

Key Words: Esophageal cancer; Surgery; Thoracic para-aortic lymph node; Overall survival; Metastasis

Core Tip: Lymph node recurrence is common in resected esophageal squamous cell carcinoma (ESCC). However, thoracic para-aortic lymph nodes (TPLNs) recurrence in ESCC is rare and its impact on survival is unknown. Our study identified the incidence of TPLNs recurrence in ESCC after curative surgery and revealed TPLNs recurrence negatively associated with the overall survival.

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INTRODUCTION

Esophageal cancer is the fourth most common cause of cancer-related deaths in China[1]. Although the incidence of esophageal squamous cell carcinoma (ESCC) has decreased in Western countries[2], this subtype accounts for more than 90% of the esophageal cancer diagnoses in China. Currently, surgical resection is the mainstay of curative treatment, and preoperative chemoradiotherapy followed by esophagectomy is considered the standard treatment for locally advanced esophageal cancer based on the accumulated evidence over the past 15 years[3-5].

Lymph node metastasis is among the most crucial negative prognostic factors affecting cancer patients[6]. Thoracic para-aortic lymph node (TPLN) metastasis, a rare complication of esophageal cancer, has only been described in a few case reports[7,8], although in one case report, it was observed that there was a higher incidence of metastasis with recurrent disease[9]. Generally, two-field lymphadenectomy is commonly performed in Western countries and China[3-5], whereas extended three-field lymphadenectomy is performed in Japan[10]. A Chinese consensus recommends the dissection of nine stations of mediastinal lymph nodes to achieve better local control and survival outcomes[11]. However, extensive lymph node dissection increases the number of postoperative complications[12]. Nevertheless, the established guidelines in China and Western countries do not specify dissection of the TPLNs, likely because of the low incidence of TPLN metastasis.

In this study, we reviewed the outcomes of patients who had undergone curative surgery for ESCC at our center to determine the incidence of TPLN metastasis and its impact on survival outcomes. We also reviewed patients who had received definitive chemoradiotherapy for ESCC and compared the effects of different treatment modalities on TPLN metastasis.

MATERIALS AND METHODS

This was a retrospective cohort study of anonymized data extracted from medical records. Approval for the use of medical records was obtained from the Ethics Committees of Shantou Central Hospital, China, prior to the study. All study protocols were approved by this committee.

We reviewed the medical records of consecutive patients who had undergone curative esophagectomy for pathologically proven ESCC between January 2012 and November 2017 at our Department of Surgery. The following information was extracted: Patient age, sex, work-up, treatments, and follow-up. Patients who met the following inclusion criteria were considered eligible: (1) Pathological diagnosis of squamous cell carcinoma; (2) Disease stage I-III; and (3) Surgical treatment with curative intent. The main exclusion criteria were a diagnosis of adenocarcinoma or other pathological type and stage IV disease. We further reviewed the records of consecutive patients who had received definitive chemoradiotherapy between January 2012 and December 2013 at the

Department of Radiation Oncology. The inclusion criteria were as follows: (1) Pathological diagnosis of squamous cell carcinoma; (2) Disease stage I-III; and (3) Radiochemotherapy with curative intent.

At our center, the operative procedure for ESCC comprised *en bloc* esophagectomy with two-field (mediastinal and upper abdominal) lymphadenectomy, gastric tube reconstruction, and cervical anastomosis. Mediastinal lymphadenectomy was performed *via* a right thoracic approach and included the left and right recurrent, paraesophageal, paratracheal, and subcarinal regions and the inferior pulmonary ligament, as per the Chinese expert consensus on mediastinal lymph node dissection[11]. The pathological tumor stage was determined according to the seventh edition of the American Joint Committee on Cancer TNM classification (2009).

The location of the TPLN was defined as previously described[13], namely, the posterior mediastinum surrounded by the descending thoracic aorta, inferior pulmonary vein, pericardium, and thoracic duct. Positive recurrent TPLN was determined based on any of the following computed tomography (CT) findings: (1) Presence of lymph nodes in an area where they were not detected preoperatively, irrespective of size; and (2) Enlargement of preexisting lymph nodes in this area.

Recurrence was defined as the first documented radiographic evidence of disease relapse. The recurrence-free survival (RFS) and overall survival (OS) rates were estimated using the Kaplan-Meier method and compared using the log-rank test. Comparisons of categorical data were performed using the chi-squared test. A P value < 0.05 indicated statistical significance.

A Cox regression model was used to identify prognostic factors, and logistic regression was used to explore the relationships between clinicopathological factors and TPLN recurrence. We performed a propensity score-matching analysis (with variables including age, sex, tumor location, tumor grade, T stage, nodal status, and type of adjuvant therapy) based on the one-to-many nearest neighbor method (caliper width: 0.1)[14]. All P values were two-sided, and all statistical analyses were performed using R software (version i386 3.3.2; R Project for Statistical Computing, Vienna, Austria).

RESULTS

Between January 2012 and November 2017, 604 patients who had been diagnosed with pathologically proven ESCC underwent curative esophagectomy and lymphadenectomy at our center. The R0 reaction rate was 98.34% (594/604). Regarding perioperative mortality, no deaths occurred within 30 d after surgery. A median of 20 lymph nodes were harvested, and positive lymph nodes were observed in 294 (48.68%) of the 604 patients. The median follow-up was 38.63 mo. Among the patients (Supplementary Table 1), we recorded 89 (14.74%) deaths without a known cause, 39 (6.46%) patients lost to follow-up, 257 (42.55%) patients who remained alive without radiographic evidence of recurrence, and 219 (36.26%) patients who developed recurrences. The patients with recurrence were separated into two groups based on the presence of TPLN recurrence: TPLN (+) and TPLN (-). Eighteen of the six hundred and four patients (2.98%) had TPLN recurrence, and 13 of these patients developed synchronous distant metastases.

Figure 1 shows an example of TPLN recurrence after surgery in a representative patient. In the TPLN (+) group, 4 (4/604, 0.66%) patients presented with small TPLNs before surgery. The diameters of these small TPLNs ranged from 5.5 to 8.2 mm (mean, 6.73 mm). The TPLNs in these 4 patients were not dissected during surgery. Two patients received adjuvant chemoradiotherapy postoperatively, and two received no adjuvant treatment.

Of the 223 patients diagnosed with thoracic ESCC who had undergone definitive chemoradiotherapy between January 2012 and December 2013, 3 (1.35%) presented with enlarged TPLNs before treatment (diameters: 5.4, 6.2, and 11.0 mm). After definitive therapy, all the TPLNs shrank and did not relapse during follow-up. No other TPLN recurrences were observed in this group. The characteristics of the two groups are shown in Table 1. The groups were well balanced before and after propensity score matching, and the logistic regression analysis did not indicate that any of these characteristics contributed to TPLN metastasis.

Before matching, the median RFS duration was significantly longer in the TPLN (-) group than in the TPLN (+) group [12.83 mo, 95% confidence interval (CI): 11.5-14.6 *vs* 6.35 mo, 95%CI: 3.4-15.4, P = 0.00049; Figure 2A). Similarly, the median OS duration was significantly longer in the TPLN (-) group than in the TPLN (+) group (21.47 mo, 95%CI: 19.37-26.60, *vs* 15.30 mo, 95%CI: 11.90-28.30, P = 0.0027; Figure 2B).

After matching, the median RFS duration remained significantly longer in the TPLN (-) group than in the TPLN (+) group (12.00 mo, 95%CI: 9.8-14.0 *vs* 6.35 mo, 95%CI: 3.4-15.4, P = 0.013; Figure 2C). However, the difference in OS duration between the TPLN (-) and TPLN (+) groups was only borderline significant, despite the longer duration in the former group (18.25 mo, 95%CI: 16.7-24.1 *vs* 15.30 mo, 95%CI: 11.90-28.30, P = 0.051; Figure 2D). A Cox model analysis of potential prognostic factors similarly indicated the presence of TPLN metastasis as a risk factor for OS before matching but not after matching.

Table 1 Main characteristics

	TPLN (+)	Before matching		After matching	
		TPLN (-)	*P* value (df)	TPLN (-)	*P* value (df)
Age, median, yr	56.5	59	0.19	57.5	0.76
Sex			1.00 (1)		1.00 (1)
Male	14	156		78	
Female	4	45		20	
Location			0.73 (2)		0.87 (2)
Upper	0	6		1	
Middle	10	115		50	
Lower	8	80		47	
Grade			0.31 (3)		0.50 (3)
I	0	21		5	
II	11	133		68	
III	6	39		23	
Unknown	1	8		2	
T stage			0.85 (3)		0.82 (3)
T1	0	5		1	
T2	3	33		11	
T3	14	157		83	
T4	1	6		1	
N stage			0.43 (3)		0.76 (3)
N0	4	75		25	
N1	6	61		28	
N2	7	48		32	
N3	1	17		13	
Adjuvant therapy			0.70 (2)		0.91 (2)
Chemoradiotherapy	3	24		14	
Chemotherapy	8	109		49	
None	7	68		35	

df: Degree of freedom; TPLN: Thoracic paraaortic lymph node.

DISCUSSION

Globally, the treatment of esophageal cancer remains challenging. For patients with locally advanced esophageal cancer, neoadjuvant chemoradiotherapy or chemoradiotherapy followed by surgery has led to significant improvements in survival relative to surgery alone[15]. However, in some scenarios, surgery represents mainly a curative method, along with definitive chemoradiotherapy.

As noted previously, lymph node metastasis is a strong prognostic factor in cancer cases. A higher number of dissected lymph nodes and increased station clearance are associated with more precise staging, better local control, and perhaps better OS, although these benefits may come at the cost of an increased risk of complications[16]. Consequently, efforts to enhance the radical dissection of lymph nodes include the progression from two-field to three-field lymphadenectomy[17] and a shift from a limited left thoracic approach to an extended right thoracic approach[18]. Despite these advances, surgeons might neglect stations associated with a low incidence of lymph node metastasis, such as TPLN. Few reports have described TPLN recurrence in cases of resectable esophageal cancer.

To the best of our knowledge, our study is the largest cohort study of TPLN recurrence, and our findings demonstrate that TPLN recurrence is associated with poor RFS and OS. We observed a TPLN

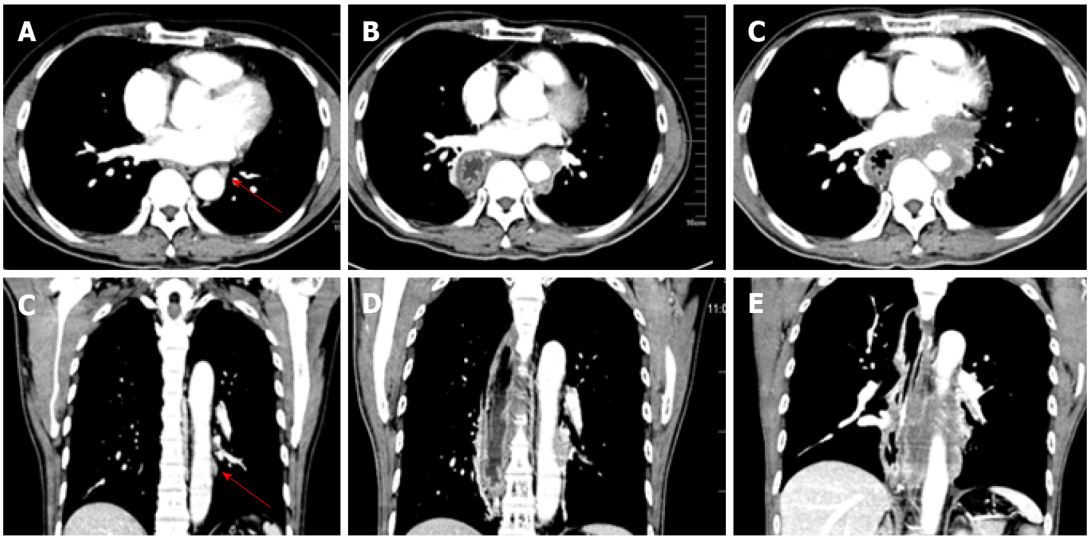

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Figure 1 Computed tomography scan results. A and B: Small thoracic paraaortic lymph node (TPLN, arrow) in a patient before surgery; C and D: TPLN recurrence 3 mo after surgery; E and F: TPLN recurrence 5 mo after surgery.

recurrence rate of approximately 3%. In our cohort, TPLN recurrence did not occur in tumors located in the upper thoracic esophagus, in low-grade tumors (grade 1), or in tumors that had invaded the lamina propria, muscularis mucosae, or submucosa (T1 stage). However, we failed to identify any parameters significantly predictive of TPLN recurrence.

Despite our inability to identify predictive factors, our results have several implications for clinical practice. Previously, Shishido *et al*[8] reported on 2 patients with enlarged TPLNs (10 mm) that were confirmed pathologically after dissection. In contrast, we identified small TPLNs (longest transverse diameter < 10 mm) in 4 patients *via* CT scans. Although such small TPLNs had not been previously considered indicative of a metastasis-positive status[19], all 4 of the TPLNs in our patients were swollen after surgery, indicating that the lymph nodes in the thoracic para-aortic area should be treated cautiously, irrespective of the transverse diameter. Moreover, in cases of esophageal cancer, we always intraoperatively harvest small lymph nodes that are pathologically proven to be positive after surgery. However, the value of positron emission tomography/CT scans has not been validated, and therefore, this imaging technique is not routinely applied at our center.

As mentioned above, TPLN is not included in the description of standard lymph node dissection in the guidelines used in China or Western countries, and the extent of LN station nine (*i.e.*, the pulmonary ligament area) does not necessarily include TPLNs[20]. Although we have performed esophageal surgery in more than 1700 cases at our center, we do not routinely clear this area. Moreover, some small lymph nodes in this area are often overlooked, which might explain the poor survival outcomes among our patients with TPLN recurrence.

In Japan, TPLNs are further classified as anterior or posterior. Posterior TPLNs are associated with worse RFS and OS outcomes than anterior TPLNs[13]. Currently, a left thoracic approach is recommended for the eradication of TPLNs. As reported, the posterior TPLNs were successfully dissected *via* this approach in 3 cases[7,8]. We support the recommendation for the left approach to posterior TPLNs; however, we consider the right thoracic approach to anterior TPLN dissection to be feasible.

Our study had several limitations. First, this was a retrospective study of a small sample of patients at a single treatment center, which had an inherent risk of bias by the nature of the study design. To overcome this limitation, we are currently building a database dedicated to capturing data on TPLNs. Second, before 2017, nearly all the patients with resectable esophageal cancer at our center were offered surgery as an initial treatment. This practice contrasts with the preferred initial treatment options in Western countries. However, most patients in Western countries present with esophageal adenocarcinoma, but the majority of patients in China have ESCC. Additionally, the benefit of neoadjuvant chemoradiotherapy in Chinese patients with ESCC has been confirmed only recently[5]. A further evaluation of TPLN is needed once this treatment paradigm has been fully introduced into clinical practice.

CONCLUSION

Our study results confirm the low incidence of TPLN metastasis and reveal a potential relationship between this complication and survival outcomes.

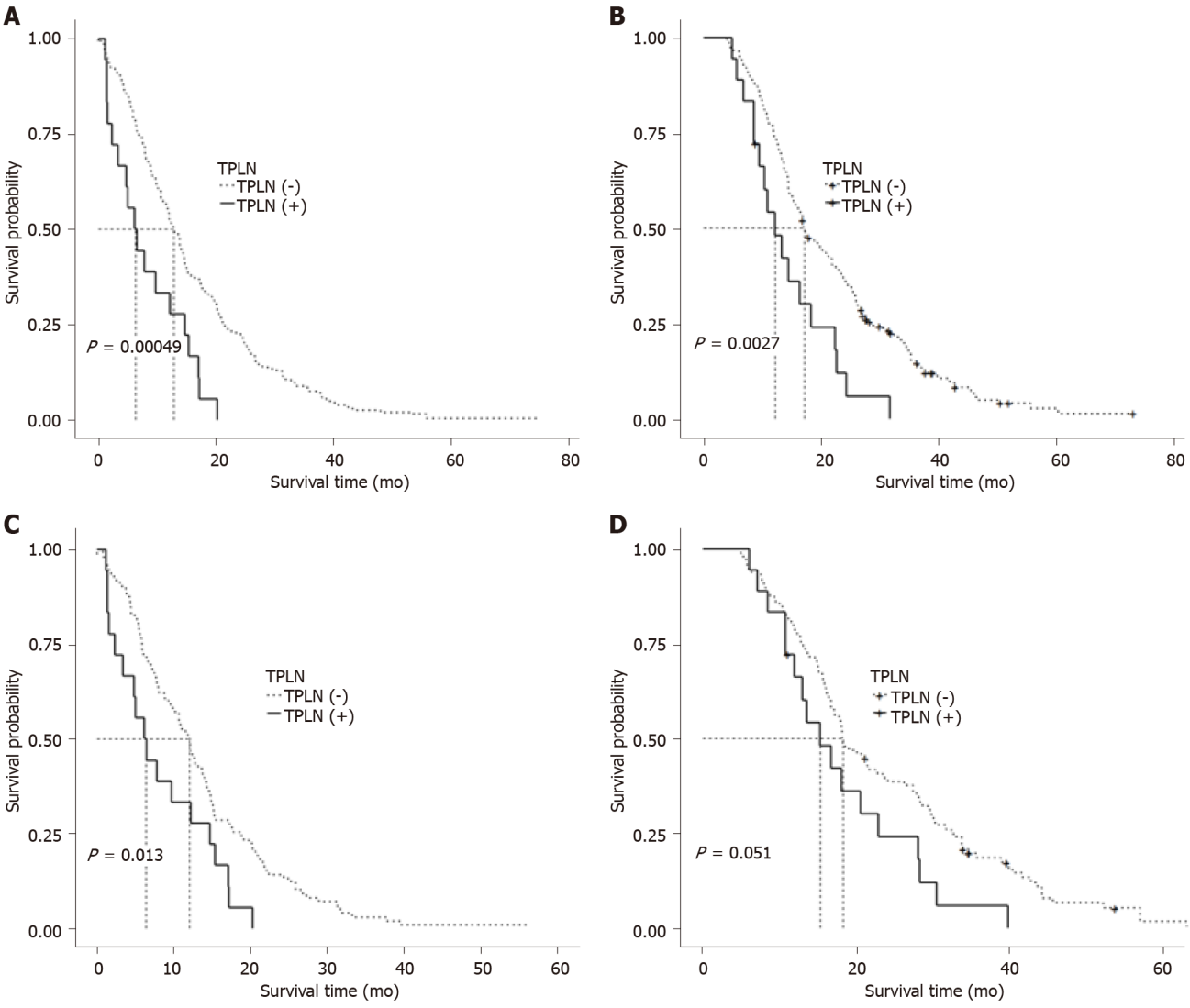

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Figure 2 Comparison of recurrence-free survival and overall survival before propensity score matching. A: Comparison of recurrence-free survival (RFS) before propensity score matching; B: Comparison of overall survival (OS) before propensity score matching; C: Comparison of RFS after propensity score matching; D: Comparison of OS after propensity score matching. TPLN: Thoracic paraaortic lymph node.

ARTICLE HIGHLIGHTS

Research background

Thoracic para-aortic lymph nodes (TPLNs) recurrence in esophageal squamous cell carcinoma (ESCC) is rare but with poor survival outcomes in clinical observation.

Research motivation

TPLNs recurrence had negative impact on survival outcomes in patients with ESCC.

Research objectives

TPLN (+) was associated with worse recurrence-free and overall survival (OS) in patients with ESCC.

Research methods

The propensity score-matching and survival estimation were applied, and factors predictive of OS were explored using a Cox proportional hazards model.

Research results

To study survival in patients with ESCC who developed TPLNs recurrence.

Research conclusions

To determine TPLNs recurrence rate and its impact on survival.

Research perspectives

TPLNs recurrence in ESCC is rare but with poor survival outcomes in clinical observation.

FOOTNOTES

Author contributions: Li XY and Huang LS contributed equally to this work; Li XY designed the research study; Xie D and Yu SH performed the research; Li XY, Huang LS, Xie D and Yu SH analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Anastomotic leakage in rectal cancer surgery: Retrospective analysis of risk factors

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Abstract

BACKGROUND

Anastomotic leakage (AL) after restorative surgery for rectal cancer (RC) is associated with significant morbidity and mortality.

AIM

To ascertain the risk factors by examining cases of AL in rectal surgery in this retrospective cohort study.

METHODS

To identify risk factors for AL, a review of 583 patients who underwent rectal resection with a double-stapling colorectal anastomosis between January 2007 and January 2022 was performed. Clinical, demographic and operative features, intraoperative outcomes and oncological characteristics were evaluated.

RESULTS

The incidence of AL was 10.4%, with a mean time interval of 6.2 ± 2.1 d. Overall mortality was 0.8%. Mortality was higher in patients with AL (4.9%) than in patients without leak (0.4%, $P = 0.009$). Poor bowel preparation, blood transfusion, median age, prognostic nutritional index < 40 points, tumor diameter and intraop-

erative blood loss were identified as risk factors for AL. Location of anastomosis, number of stapler cartridges used to divide the rectum, diameter of circular stapler, level of vascular section, T and N status and stage of disease were also correlated to AL in our patients. The diverting ileostomy did not reduce the leak rate, while the use of the transanastomic tube significantly did.

CONCLUSION
Clinical, surgical and pathological factors are associated with an increased risk of AL. It adversely affects the morbidity and mortality of RC patients.

Key Words: Anastomosis; Leak; Anterior resection; Morbidity; Mortality; Rectal surgery

Core Tip: Anastomotic leakage (AL) after rectal cancer surgery is associated with significant morbidity and mortality. A review of 583 patients who underwent rectal resection with a double-stapling colorectal anastomosis in a 15-year period was performed. The overall incidence of AL was 10.4%. Mortality was higher in patients with AL than in patients without leak. Prognostic nutritional index < 40 points and intraoperative blood loss were identified as risk factors for AL. Location of anastomosis, number of stapler cartridges used to divide the rectum, diameter of circular stapler and level of vascular section were also correlated to AL in our patients.

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INTRODUCTION

Complications after rectal cancer (RC) surgery are still inevitable[1-3]. Anastomotic leakage (AL) is one of the most severe complications for RC surgery owing to its negative impact on both short- and long-term outcomes[1,4,5]. The incidence reported in the literature has not significantly changed in recent decades despite constant improvements in the preoperative assessment of the patient as well as in the surgical technique. The incidence of AL varies widely depending on the anastomosis type and the distance from the anal verge. AL rate after anterior resection varies from 0% to 36.3% and is associated with a 2%-10% mortality rate and with a 10%-100% risk of permanent stoma[2,6,7].

AL is typically diagnosed 5-8 d post RC surgery. It can be classified as "early" and "late" AL according to whether it and AL-related complications were diagnosed within or after 30 d from surgery [8]. An early-onset AL is usually associated with severe peritonitis, emergency relaparotomy and increased mortality rate. By contrast, an AL that occurs late is associated with a long-lasting pelvic abscess[9]. An early dehiscence is frequently related to technical failure of the anastomosis due to surgical disruption of the blood supply or tension at the anastomotic site[10]. Late AL is related to patient conditions, such as local sepsis, poor nutrition, immunosuppression, morbid obesity and radiation exposure[11].

Clinical, surgical and pathological factors are associated with an increased risk of AL. Cancer patients with poor physical health, including several comorbidities, may not be able to cope with the physiological insult when AL occurs. Different studies have documented that sex, location of the anastomotic site, preoperative albumin level and several other factors are closely related to the occurrence of AL[1,3].

Furthermore, we have observed an increased rate of AL after end-to-end anastomosis (29.2%) compared to the end-to-side anastomosis technique (5%, $P < 0.005$)[6]. In consideration of these results, we did not use the end-to-end technique, preferring to perform the double-stapling technique for rectal anastomosis, as indicated by Knight *et al*[12] and known as the Knight-Griffen procedure. This procedure has good results, even if its effectiveness is still debated[13-16], particularly regarding the safety of the double suture technique. It has been documented that the number of linear stapler firings during rectal division, the intersecting lateral suture lines (dog-ears) and the intersections of the stapling lines could be associated with AL[13,17].

In this study, we retrospectively reviewed our RC surgery cases and investigated the frequency of AL, surgical procedures and clinical and pathological features to identify the risk factors for AL.

MATERIALS AND METHODS

A retrospective analysis of clinical data, surgical features and pathological characteristics was conducted on patients with RC treated at the General Surgery Operative Unit, Policlinico Universitario "A Gemelli" from January 2007 to December 2015, at the General Surgery Operative Unit, Azienda Sanitaria Provinciale Crotone from January 2016 to May 2020 and at the Department of Surgery, Fondazione Policlinico Universitario A Gemelli IRCCS from June 2020 to January 2022. Patient demographics, perioperative variables, tumor characteristics and postoperative mortality and morbidity were extracted from medical records after formal approval by the institutional medical ethics committee was obtained. All patients provided written consent before the surgical procedures. The study was conducted according to the STROCSS criteria[18].

Inclusion criteria and staging procedures

Patients with a histological diagnosis of RC were included in the study. All patients underwent a complete clinical evaluation, including laboratory tests, with complete blood cell count and serum chemistry. In all the patients, a preoperative staging of the neoplasm was performed, which encompassed lower digestive endoscopy with biopsy, a carcinoembryonic antigen (CEA) serum test, chest X-ray and abdominopelvic computed tomography (CT) scan. High-resolution magnetic resonance imaging or transrectal ultrasound were subsequently performed to assess tumor height. RC was defined as tumors with distal extension 15 cm from the anal margin[19,20]. Cancers were categorized as low (up to 5 cm), middle (from > 5 to 10 cm) or high (from > 10 up to 15 cm). Tumors were staged according to the latest version of the pathologic classification (pTNM) of the American Joint Committee on Cancer [21]. All patients were treated with elective procedures for uncomplicated disease at clinical presentation.

Exclusion criteria

Patients with colonic cancer and tumors histologically different from adenocarcinoma were excluded from the analysis. Patients with positive surgical resection margins, patients with peritoneal carcinomatosis and/or distant metastatic disease, patients with ≥ 1 missing data point and patients who underwent a nonrestorative surgery, such as Hartmann's procedures or Miles' operation, were not included in the study.

Diagnosis of AL

An AL was defined as a defect of the intestinal wall integrity at the colorectal anastomosis site leading to a communication between the intra- and extraluminal compartments as reported by the International Study Group of Rectal Cancer (ISREC)[22]. The perianastomotic presence of a pelvic abscess was also considered dehiscence. Abdominal pain, fever, tachycardia, the appearance of peritonitis or purulent discharge from pelvic drainage or when anastomotic fluid collections or fistulae were detected by CT with rectal water-soluble contrast agent were all elements used to make the diagnosis[23]. To assess severity of AL, ISREC grading was used[22]. AL is graded according to the therapeutic management it requires (type A: no management; type B: non-operative management; type C: operative management).

Study variables

Patient-, disease- and treatment-related variables were analyzed. The clinical variables evaluated were age, sex, serum albumin and CEA levels, hemoglobin values, the presence of concomitant pathologies, weight loss, smoking and alcohol intake and the prognostic nutritional index (PNI). Other variables considered were the quality of mechanical bowel preparation, need for blood transfusions and execution of neoadjuvant treatments. The surgical parameters evaluated were type of surgical approach, site of the colorectal anastomosis, complete or partial excision of the mesorectum, site of vascular section, number of stapler cartridges used to dissect the rectum, diameter of the circular stapler used and the presence of the ileostomy or placement of a transanastomotic decompression tube (TDT). The pathological variables taken into consideration were the T status, the N status and the stage of the disease. Mean age, mean operative time, intraoperative blood loss, mean tumor size, distance of the tumor from the anal verge and mean length of postoperative hospital stay were also evaluated.

Weight loss was defined as the loss of 10% or more of habitual body weight over the prior 6 mo. Prespecified subgroup analyses were defined according to age (65 years or > 65 years), serum albumin (< 3.5 g/dL or ≥ 3.5 g/dL), CEA levels (< 5 ng/mL or ≥ 5 ng/mL) and hemoglobin values (< 10 g/dL or ≥ 10 g/dL), in agreement with other findings in the literature. The cutoff used in this study was age > 65 years. It was considered a significant risk factor for postoperative complications in RC surgery, in accordance with a definition of age limits for elderly patients. The PNI was calculated using serum albumin and the peripheral lymphocyte count, using the following formula: PNI = serum albumin level (g/dL) + 5 × total lymphocyte count. The cutoff value of PNI was 40, based on an original investigation by Onodera *et al*[24]. Reoperation was defined as reintervention within 30 d after the primary operation.

Preoperative treatments

Patients underwent neoadjuvant treatment or upfront surgery based on the clinical stage of the cancer. The therapeutic decision was made after a multidisciplinary evaluation. Neoadjuvant treatment was long course in all patients with administration of a dose of 45-50 Gy associated with 5-fluorouracil or capecitabine. The ERAS protocol was not used in any patient.

Surgical procedure

All patients were prepared with the same protocol. This involved intestinal preparation (polyethylene glycol electrolytic solution performed 12 h before surgery), thrombotic prophylaxis (enoxaparin 4000 IU) and antibiotic prophylaxis (metronidazole 500 mg and ciprofloxacin 400 mg administered intravenously at the beginning of the surgery). After surgery, all patients received enoxaparin (4000 IU sc once daily for 30 d). In the postoperative period, antibiotic treatment was initiated in patients with fever and leucocytosis, first empirically and then modified based on microbiological findings.

Surgery following neoadjuvant treatment was performed within 8-12 wk as all patients underwent long course radiotherapy and chemotherapy. The vascular section was performed at the level of the origin of the inferior mesenteric artery or the superior hemorrhoidal artery. The splenic flexure was taken down routinely to achieve maximal colonic mobilization. The type of procedure was defined by the anatomical site of anastomosis. In low anterior resection the anastomosis was about 5 to 8 cm above the anal verge. In "ultra-low" anterior resection the anastomosis was performed at the level of the anorectal junction, at about 3-5 cm from the anal verge.

The hydropneumatic test was used to assess the integrity of the anastomosis. Doughnuts were inspected for integrity after removal of the stapler. Each surgeon decided at his own discretion to create a protective ileostomy, based on his own criteria of measuring the risk of AL in each specific patient, and to place a TDT after performing the colorectal anastomosis. Two perianastomotic extraperitoneal drains were placed. The drains were left in place until the stool passed. In all patients, the anastomosis was excluded from the abdominal cavity with the suture of the pelvic peritoneum. The type of approach adopted was classified in open surgery or laparoscopic surgery.

Main outcomes

Patients were classified into two groups: Patients with AL and patients without AL. This subdivision was made on the basis of their clinical course. The primary endpoint of the study was the detection of any independent risk factors for AL. Secondary endpoints include the overall rate of AL in the study population, the relationship with the factors considered and the distribution of AL according to ISREC clinical severity grading[22]. In addition, 30-d mortality and morbidity and reoperation in patients with and without AL was evaluated.

Statistical analysis

The results were expressed as mean ± SD or as percentage. All statistical elaborations were obtained by using Student's *t* test and Fisher's exact test. Data were processed using GraphPad Prism software (GraphPad, San Diego, CA, United States). All *P* values were two tailed. *P* values of less than 0.05 were considered statistically significant.

RESULTS

Data of 583 patients (301 males and 282 females, mean age 63.7 ± 19.4 years) were analyzed (Table 1). Among them, 58.5% of patients (341 cases) were ≥ 65 years of age and 50.9% (301 cases) had at least one concomitant disease. Weight loss was present in 98 patients (16.8%). We observed that 80% of patients had normal serum albumin levels. CEA levels were increased in 336 cases (57.6%) and values of hemoglobin < 10 g/dL were observed in 49.9% of patients. The PNI was < 40 points in 130 patients (22.3%).

Complete and adequate bowel preparation was achieved in 361 patients (61.9%); 44.9% of patients (262 cases) received blood transfusions in the perioperative period due to their anemic condition. Regarding the disease stage, 122, 185 and 276 patients were found to be in stage I, II and III, respectively. A neoadjuvant treatment was needed in 393 patients (67.4%).

All patients studied underwent anterior rectal resection with a mean operative time of 130.1 ± 36.1 min and intraoperative blood loss of 210.0 ± 30.0 mL. In 76.7% of cases (447 patients) the surgical approach was open. The inferior mesenteric artery was tied up in 277 patients (47.5%). The excision of the mesorectum occurred in 311 patients and partial in the remaining 272 cases. The distal rectum was divided with a single 60 mm purple or black cartridge (EndoGIA, Medtronic, MN, United States) in 351 patients (60.2%) and with multiple cartridges in the remaining patients. Colorectal anastomosis was performed in the middle rectum in 49.4% of cases (288 patients) and in the lower rectum in the remaining cases (295 patients). The circular stapler was introduced through the anus. A 25 mm diameter circular stapler (Covidien, Premium Plus CEEA or EEA with DST series technology, Medtronic, MN,

Table 1 Clinical, demographic and pathological characteristics in 583 rectal cancer patients

	Patients, *n*	%
Age, yr		
< 65	242	41.5
≥ 65	341	58.5
Sex		
M	301	51.6
F	282	48.4
Albumin, g/dL		
< 3.5	117	20.0
≥ 3.5	466	80.0
CEA, ng/mL		
< 5	247	42.4
≥ 5	336	57.6
Hemoglobin, g/dL		
< 10	291	49.9
≥ 10	292	50.1
Prognostic nutritional index points		
< 40	130	22.3
≥ 40	453	77.7
Concomitant diseases		
Yes	297	50.9
No	287	49.1
Weight loss		
Yes	98	16.8
No	485	83.2
Smoking habits		
Yes	227	38.9
No	356	61.1
Alcohol habits		
Yes	75	12.9
No	508	87.1
Bowel preparation		
Complete/adequate	361	61.9
Poor	222	38.1
Blood transfusions		
No	321	55.1
≥ 1 Unit	262	44.9
Neoadjuvant treatment		
Yes	393	67.4
No	190	32.6
Type of approach		
Open	447	76.7

Laparoscopy	136	23.3
Location of anastomosis		
Medium rectum	288	49.4
Low rectum	295	50.6
Mesorectal excision		
Total	311	53.3
Partial	272	46.6
Site of vascular ligation		
Inferior mesenteric artery	277	47.5
Superior hemorrhoidal artery	306	52.5
No. stapler cartridges used		
1	351	60.2
> 1	232	39.8
Diameter of circular stapler in mm		
25	128	21.9
28	455	78.1
Diverting ileostomy		
Present	297	51.0
Absent	286	49.0
Transanastomotic decompression tube		
Present	196	33.6
Absent	387	66.4
T status		
T1	73	12.5
T2	104	17.8
T3	306	52.5
T4	100	17.2
N status		
N+	321	55.1
N-	262	44.9
Stage		
I	122	20.9
II	185	31.7
III	276	47.4

CEA: Carcinoembryonic antigen; M: Male; F: Female.

United States) was used in 128 cases (21.9%), and a 28 mm diameter circular stapler (Covidien, Premium Plus CEEA or EEA with DST series technology, Medtronic, MN, United States) was adopted in 455 patients (78.1%). A diverting ileostomy was performed in 297 patients, and a TDT tube was placed in 196 patients.

Regarding the T status, 73, 104, 306 and 100 patients were T1, T2, T3 and T4, respectively. Positive lymph nodes were found in 321 patients (55.1%). The mean postoperative hospital stay was 8.7 ± 3.7 d.

The overall incidence of AL was 10.4% (61/583 patients), with a mean time interval of 6.2 ± 2.1 d (range 3-27 d). Clinical features at the time of the diagnosis were a median temperature of 38.4 °C (range 36.8-39.5 °C), a median heart rate of 105 bpm (range 70-140) and a median blood pressure of 110 mmHg (range 55-180 mmHg). A type C AL was identified in 35 patients (57.4%).

Patients were divided into two groups based on the absence or presence of AL. Clinical and demographic characteristics of the included patients are shown in Table 2. Patients who developed AL were significantly older (68.2 ± 10.7 years) than patients without AL (59.7 ± 17.2 years, $P = 0.0002$). A higher incidence of AL was documented in patients with low serum albumin (15.2% *vs* 7.9% in serum albumin ≥ 3.5 g/dL, $P = 0.006$) and low hemoglobin levels (11.8% *vs* 7.0% in level ≥ 10 g/dL, $P = 0.02$). A higher incidence of AL was also reported in patients with a PNI score < 40 points (18.2% *vs* 6.6% with ≥ 40 points, $P = 0.0001$). AL was more frequent in patients who experienced weight loss before the operation (17.3% *vs* 9.1%, $P = 0.01$). No differences between the two groups were found for sex ($P = 0.08$), age < 65 years or ≥ 65 years ($P = 0.09$), presence of concomitant diseases ($P = 0.1$), smoking habits ($P = 0.5$) or use of alcohol ($P = 0.1$). A higher incidence of AL was observed in patients with poor bowel preparation (16.2%) compared to those with complete and appropriate bowel preparation (6.9%, $P = 0.0007$) and in patients receiving blood transfusions (14.8%) compared to those who did not require this therapy (6.8%, $P = 0.002$). As for neoadjuvant treatments, the adoption of a long course of radiochemotherapy did not lead to a statistically significant AL rate compared to patients treated who underwent upfront surgery (11.2% *vs* 8.9%, $P = 0.4$).

The treatment related variables are listed in Table 3. The surgical approach adopted showed no influence on the incidence of AL (10.2% in open surgery *vs* 11% in laparoscopic approach, $P = 0.8$). The mean duration of surgery was longer in patients who developed AL (186.0 ± 40.2 min) than in patients without AL (115.0 ± 47.8 min, $P = 0.0001$). A similar difference was found for intraoperative blood loss (365.0 ± 50.0 mL in patients with AL *vs* 175.5 ± 45.0 mL in patients without AL, $P = 0.0001$). Significant differences between the two groups were found to be related to the site of the anastomosis (6.9% middle rectum *vs* 13.9% low rectum, $P = 0.006$), stapled rectal resection firing more than one cartridge (5.4% one stapler cartridge *vs* 18.1% > 1 cartridges, $P = 0.0001$), the diameter of the circular stapler used (5.4% 25 mm *vs* 11.8% 28 mm, $P = 0.03$), the vascular ligation site (14% inferior mesenteric artery *vs* 7.1% superior hemorrhoidal artery, $P = 0.009$) and type of mesorectal excision (13.1% in total excision *vs* 7.3% in partial excision, $P = 0.02$). The presence of a diverting ileostomy had no influence on the AL rate (10.1% with ileostomy *vs* 10.8% without ileostomy, $P = 0.7$), while the use of a TDT resulted in a lower incidence of AL rate (6.1%) compared to patients in whom this device was not used (12.6%, $P = 0.01$).

Regarding pathological data, all the considered variables showed significant differences between the two groups (Table 4). The mean RC size was larger in patients with AL (47.9 ± 16.1 mm) than in patients without AL (39.0 ± 21.1 mm, $P = 0.001$). The distance of the tumor from the anal margin was less in patients with AL (71.0 ± 32.0 mm) than in patients without AL (89.0 ± 21.0 mm, $P = 0.0001$). A higher incidence of AL was documented in patients with more advanced RC (11.0%) than in those with early cancer (5.8%, $P = 0.02$). Lymph node involvement and stage of disease were both significantly related to the risk of AL (Table 4).

The mean postoperative hospital stay was 7.0 ± 2.1 d in patients without AL and 29.2 ± 13.4 d in those with AL ($P = 0.0001$).

Overall, the mortality rate was 0.8% (5/583 patients). Mortality was statistically higher in patients with AL (4.9%, 3/61 cases) than in patients without AL (0.4%, 2/522 cases, $P = 0.009$). Postoperative mortality in patients without AL was determined by massive pulmonary embolism on the 6th postoperative day and by acute myocardial infarction in severe enteric bleeding on the 3rd postoperative day. Three patients with AL died from sepsis and multiple organ failure.

Observed complications are listed in Table 5. In the AL group, 35 patients (type C AL) were reoperated; all patients underwent stoma formation. Of these 35 patients, 15 had the anastomosis taken down and repackaged. Ten patients with AL were subjected to conservative treatments. Four patients were treated with a course of intravenous antibiotics only, and 6 patients underwent radiological drainage of postoperative collections. All patients were without ileostomy and had type B AL. In 16 patients (7 with ileostomy performed at the time of anterior resection surgery) an endoluminal vacuum therapy (EndoSponge, B.Braun Surgical S.A., Barcelona, Spain) was used with closure of the AL (27.8 ± 12.7 d), with an average replacement of sponges of 11.2 ± 5.7. Patients with AL showed a higher incidence of pelvic sepsis ($P = 0.0001$), wound dehiscence ($P = 0.003$) and wound infection ($P = 0.0008$). No differences were shown regarding the incidence of urinary infection or pneumonia.

DISCUSSION

One of the most serious postoperative complications after RC surgery is AL. This is also the leading cause of mortality[25]. AL affects the outcome of surgery, worsening the short- and long-term outcomes and increasing the times and costs of hospitalization[4,5,26,27]. The mortality rate after AL ranges from 25% to 66% after all colorectal surgery procedures. Morbidity is also high, and the risk of receiving a definitive ostomy can exceed 25%[28]. The present study showed an AL incidence of 10.4%, consistent with the current published data. Overall mortality was 0.8%. It was higher in patients with AL (4.9%) than in patients without leak (0.4%, $P = 0.009$). As already reported, we have observed a significant increase in the mean postoperative hospital stay (7.0 ± 2.1 d *vs* 29.2 ± 13.4 d in patients with AL, $P = 0.0001$) and the incidence of severe complications.

Table 2 Clinical and demographic characteristics, *n* (%)

Patients, *n*	Leakage		*P* value
	Absent, *n* = 522	Present, *n* = 61	
Mean age, yr	59.7 ± 17.2	68.2 ± 10.7	0.0002
Age, yr			
< 65	223 (92.2)	19 (7.8)	0.09
≥ 65	299 (87.7)	42 (12.3)	
Sex			
M	263 (87.4)	38 (12.6)	0.08
F	259 (91.9)	23 (8.1)	
Albumin, g/dL			
< 3.5	117 (84.8)	21 (15.2)	0.006
≥ 3.5	466 (92.1)	40 (7.9)	
CEA, ng/mL			
< 5	247 (89.5)	29 (10.5)	0.4
≥ 5	336 (91.3)	32 (8.7)	
Hemoglobin, g/dL			
< 10	291 (88.2)	39 (11.8)	0.02
≥ 10	292 (93.0)	22 (7.0)	
Prognostic nutritional index points			
< 40	130 (81.8)	29 (18.2)	0.0001
≥ 40	453 (93.4)	32 (6.6)	
Concomitant diseases			
Yes	259 (87.6)	37 (12.4)	0.1
No	263 (91.7)	24 (8.3)	
Weight loss			
Yes	81 (82.7)	17 (17.3)	0.01
No	441 (90.9)	44 (9.1)	
Smoking habits			
Yes	201 (88.6)	26 (11.4)	0.5
No	321 (90.2)	35 (9.8)	
Alcohol habits			
Yes	71 (94.7)	4 (5.3)	0.1
No	451(88.8)	57 (11.2)	
Bowel preparation			
Complete/adequate	336 (93.1)	25 (6.9)	0.0007
Poor	186 (83.8)	36 (16.2)	
Blood transfusions			
No	299 (93.2)	22 (6.8)	0.002
≥ 1 unit	223 (85.2)	39 (14.8)	
Mean tumor distance from anal verge in mm	89.0 ± 21.0	71.0 ± 32.0	0.0001
Neoadjuvant treatment			
Yes	349 (88.8)	44 (11.2)	0.4

No	173 (91.1)	17 (8.9)	
Mean hospital stays in d	7.0 ± 2.1	29.2 ± 13.4	0.0001

CEA: Carcinoembryonic antigen; F: Female; M: Male.

Table 3 Treatment related variables, *n* (%)

Patients, *n*	Leakage		*P* value
	Absent, *n* = 522	Present, *n* = 61	
Mean operative time, min	115.0 ± 47.8	186.0 ± 40.2	0.0001
Intraoperative blood loss, mL	175.5 ± 45.0	365.0 ± 50.0	0.0001
Type of approach			
Open	401 (89.8)	46 (10.2)	0.8
Laparoscopy	121 (89.0)	15 (11.0)	
Location of anastomosis			
Medium rectum	268 (93.1)	20 (6.9)	0.006
Low rectum	254 (86.1)	41 (13.9)	
Mesorectal excision			
Total	270 (86.9)	41 (13.1)	0.02
Partial	252 (92.7)	20 (7.3)	
Site of vascular ligation			
Inferior mesenteric artery	238 (86.0)	39 (14.0)	0.009
Superior hemorrhoidal artery	284 (92.9)	22 (7.1)	
No. stapler cartridges used			
1	332 (94.6)	19 (5.4)	0.0001
> 1	190 (81.9)	42 (18.1)	
Diameter of circular stapler, mm			
25	121 (94.6)	7 (5.4)	0.03
28	401 (88.2)	54 (11.8)	
Diverting ileostomy			
Present	267 (89.9)	30 (10.1)	0.7
Absent	255 (89.2)	31 (10.8)	
Transanastomotic decompression tube			
Present	184 (93.9)	12 (6.1)	0.01
Absent	338 (87.4)	49 (12.6)	

Risk assessment of AL is crucial. An early decision-making process must consider several factors. We have observed results that do not completely match with the current literature. A Cochrane review confirmed that male sex is an independent risk factor[28]. Male sex is significantly related to increased AL risk after laparoscopic surgery for RC[10], probably due to the narrower male pelvis as well as androgens that may affect the bowel microcirculation acting on intestinal endothelial function. In the present study, no differences in sex, age, presence of concomitant diseases, smoking habits or use of alcohol were found between the two groups of patients.

Our patients who developed AL were significantly older. Furthermore, a higher incidence of AL was documented in patients with low serum albumin (P = 0.006), low hemoglobin levels (P = 0.02) and a PNI score of less than 40 points (P = 0.0001). Our findings were consistent with the current published data. Advanced age was associated with mortality after AL[29] as well as low perioperative albumin[30]. Weight loss, malnutrition, fluid and electrolyte disorders were also associated with a higher risk of AL as documented by a multivariate analysis[31]. Hemoglobin is related to perfusion and oxygenation of

Table 4 Staging and pathological data, *n* (%)

Patients, *n*	Leakage		*P* value
	Absent, *n* = 522	Present, *n* = 61	
Mean tumor diameter, mm	39.0 ± 21.1	47.9 ± 16.1	0.001
T status			
T1-2	177 (94.2)	11 (5.8)	0.02
T3-4	406 (89.0)	50 (11.0)	
N status			
N+	279 (86.9)	42 (13.1)	0.02
N-	243 (92.8)	19 (7.2)	
Stage			
I	115 (94.3)	7 (5.7)	0.01[1]
II	171 (92.4)	14 (7.6)	0.02[2]
III	236 (85.5)	40 (14.5)	

[1]Stage I *vs* Stage III.
[2]Stage II *vs* Stage III.

Table 5 Mortality and morbidity in-hospital or 30 d, *n* (%)

Patients, *n*	Leakage		*P* value
	Absent, *n* = 522	Present, *n* = 61	
Mortality	2 (40.0)	3 (60.0)	0.009
Reoperation	0	35 (100)	0.0001
Peritonitis/abdominal sepsis	1 (4.6)[1]	21 (95.4)	0.0001
Pelvic sepsis	2 (3.7)[1]	53 (96.3)	0.0001
Wound dehiscence	3 (42.9)	4 (57.1)	0.003
Wound infection	10 (52.8)	7 (41.2)	0.0008
Urinary infection	10 (76.9)	3 (23.1)	0.1
Urinary retention[2]	3 (33.4)	6 (66.6)	0.0001
Pneumonia	3 (60.0)	2 (40.0)	0.08

[1]Due to blood collections with secondary infection from contamination during primary surgery in patients without anastomotic leakage.
[2]Catheter at discharge.

the anastomotic margins, an essential factor for anastomotic healing. Currently, a hemoglobin level less than 11 g/dL increased the risk for AL[32]. We observed a higher incidence of AL in patients with PNI < 40 points. Different cutoff points have been used in the literature. Several published studies found a relationship between PNI, cancer prognosis and complication rate after surgery for colorectal cancer [33]. Tokunaga *et al*[34] found that a low index was associated to higher postoperative morbidity. We believe that this index represents an additional useful tool when estimating the state in which our patients go to surgery, which can help us evaluate each case and grade their risk of developing complications. For high-risk patients (PNI < 40), the possibility of delaying a procedure could be considered, whenever it is possible, with the intention of improving their nutritional status. In addition, we might regard a more conservative approach during the postoperative period and the possibility of a diverting stoma to protect a colorectal anastomosis.

Moreover, we noticed a higher incidence of AL in patients undergoing blood transfusions compared to those who did not require this therapy and in patients with poor bowel preparation compared to those with complete and appropriate bowel preparation. Several randomized trials have found that omitting mechanical bowel preparation does not increase the risk of AL[35,36]. A systematic review including over 5000 patients found no evidence that patients benefit from bowel preparation (either

orally or by enema)[37]. Furthermore, data from registry analysis showed a beneficial effect of local decontamination with polymyxin, tobramycin, vancomycin and amphotericin B in the prevention of AL in RC surgery[38,39,40].

As for neoadjuvant treatments, the adoption of a long course of radiochemotherapy did not lead to a statistically significant AL rate compared to patients who underwent upfront surgery. Neoadjuvant treatment was not found to be associated with AL in this study. While some authors showed a relationship between preoperative radiochemotherapy and AL occurrence[41-43], several others could not confirm this connection[10]. A recent meta-analysis of literature from 1980 to 2015 demonstrated no significant correlation between increased incidence of AL and neoadjuvant therapy[44].

We observed that the risk of AL rises in advanced stage RC and in metastatic nodes. Our results are consistent with previous studies. This may be explained by the more technical complexity of such cases [2]. An additional identified risk factor for AL is tumor distance from the anal verge. Data of the present study (71.0 ± 32.0 mm in AL patients *vs* 89.0 ± 21 mm in patients without AL, $P = 0.0001$) is consistent with literature evidence. RC diameter greater than 3 cm and advanced local disease at the time of surgical treatment were identified by Zhu *et al*[45] as an independent risk factor. Our data are congruous with these findings.

To date, even though the minimally invasive approach for RC surgery is spreading worldwide, the non-inferiority of laparoscopy compared with open surgery with respect to postoperative complications is still debated[46,47]. We did not observe any difference between the two surgical approaches. Many randomized controlled trials have confirmed equivalent oncological outcome and long-term survival, with no differences for postoperative mortality and complications[46,48-51]. Laparoscopy has distinct differences from open surgery, such as the need for multiple stapler firings when transecting the rectum, which is associated with an increased AL rate, although this is likely to be reduced with advances in stapler technology. The duration of the procedure and the number of stapling cartridges influence AL appearance. These intraoperative risk factors often determine a challenging surgery for locally advanced RC. Operative time longer than 3 h has also been described in the literature as being associated with a higher incidence of AL[52,53]. Several studies showed that multiple applications of linear stapler cartridges increased the leak risk due to an unduly long stapling line with an oblique angle in the lower locations[17], making an ileostomy mandatory in these cases[14,17] after both open and laparoscopic surgery for RC. Our results are consistent with the conclusions of these studies.

Moreover, a significant association between vascular ligature level and AL was observed. Our data confirm these results. An increase in the AL rate in cases of inferior mesenteric artery ligation compared to superior hemorrhoidal artery ligation has been noted. High vascular ligation probably results in reduced colonic perfusion. Trencheva *et al*[54] reported that ligation of the inferior mesenteric artery below the left colonic artery significantly decreased the incidence of AL. Tanaka *et al*[55] did not observe a significant association between the incidence of AL and the level of ligation of the inferior mesenteric artery. These results were confirmed in the multivariate analysis by Cirocchi *et al*[56], evaluating 8666 patients. In fact, they did not observe statistically significant differences in the prevalence of AL between high and low ligation groups. A promising technology is intraoperative fluorescence angiography with indocyanine green[57]. The procedure provides information on tissue perfusion[58,59]. Evidence for the impact of intraoperative fluorescence angiography in preventing AL after colorectal anastomosis is growing.

Regarding the TDT, several studies showed no difference in AL rate between the patients with and without one[60,61]. Our findings are in accordance with other literature observations that have documented a reduction in the frequency of AL in patients with TDT[62-65]. Prophylactic TDT was thought to lower the risk of AL whilst presenting less risks of complication than a diverting stoma. A systematic review and meta-analysis pooling 1772 patients undergoing anterior resection described TDT to lower the risk of AL (relative risk 0.44)[66]. However, patients receiving diverting stoma were excluded, leading to a potential underestimation of the AL rate. Another systematic review and meta-analysis followed, including patients with diverting stoma, and obtained the same conclusion (a reduction of the risk of AL in patients with TDT)[67]. Therefore, prophylactic TDT could constitute an efficient method to prevent AL in high-risk patients without exposing them to the complications of diverting stoma. A large scale randomized controlled trial comparing the two techniques still needs to be conducted.

Based on the distal section of the rectum, we divided anastomoses in two groups: anastomosis of the middle rectum and anastomosis of the low rectum. We realized 268 anastomoses for the first group and 254 for the second group. Anastomotic location was a factor related to AL development; also, we noted a significantly higher leak rate in patients who underwent a total mesorectal excision than those who underwent partial excision. We observed a reduced incidence of AL in patients who used a 25 mm circular stapler compared to those in which a 28 mm stapler was used, as reported in the literature[68].

A diverting loop ileostomy ideally protects a low colorectal anastomosis. The actual role of a protective stoma after rectal resection is still strongly debated[69]. Some authors report a reduction in the rate of dehiscence and re-interventions in patients with a protective ileostomy; others do not consider ostomy as a crucial factor in reducing the rate of AL. We believe that ostomy is useful to reduce clinical symptoms of AL by increasing the percentage of subclinical dehiscence but not changing the total percentage overall.

We acknowledge the limitations of the present study. There may be uncontrollable and unrecognized biases. These include its retrospective nature and patient sample size over a 15-year period. Furthermore, the present study lacked analysis on the role of pelvic drains in the appearance of AL after anterior resection for RC because we always use them just as we always mobilize the left colon flexure. Similarly, there is no evaluation of the emergency/urgent cases that were excluded from the study. Likewise, different ways of performing the colorectal anastomosis were not studied, as all patients underwent a double stapling technique. The evaluation of prognostic parameters such as the dosage of C-reactive protein and procalcitonin was not performed. Likewise, angiography with indocyanine green was not used, and we did not consider parameters related to the volume and expertise of the hospital. Moreover, surgeon factor was not analyzed.

CONCLUSION

AL after RC surgery is a fearsome complication. Dehiscence is responsible for the increase in mortality and morbidity. Many factors are related to the onset of AL in the postoperative period. The evaluation of the PNI is very promising. A very low PNI should lead to a diverting ileostomy, which mitigates the systemic effects of sepsis in the case of AL. The TDT is useful in preventing the formation of AL. This is a simple method that could avoid performing diverting ileostomies. The use of small diameter circular staplers should be considered in prospective randomized studies on a larger number of patients.

ARTICLE HIGHLIGHTS

Research background

Anastomotic leakage (AL) is one of the most severe complications for rectal cancer (RC) surgery owing to its negative impact on both short- and long-term outcomes. The incidence reported in the literature has not significantly changed in recent decades despite constant improvements in the preoperative assessment of the patient as well as in the surgical technique.

Research motivation

In a previous study, we observed an increased rate of AL after end-to-end anastomosis compared to the end-to-side anastomosis technique. In consideration of these results, we did not use the end-to-end technique, preferring to perform the double stapling technique for rectal anastomosis.

Research objectives

In this study, we retrospectively reviewed our RC surgery cases, investigated frequency of AL, surgical procedures and clinical and pathological features to identify the risk factors for this complication.

Research methods

Patient-, disease- and treatment-related variables were analyzed. Patients were classified into two groups: patients with AL and patients without AL. The primary endpoint of the study was the detection of any independent risk factors for leakage. Secondary endpoints included the overall rate of leakage in the study population, the distribution of AL according to clinical severity grading and 30-d mortality and morbidity.

Research results

Data of 583 patients were analyzed. Mortality rate was 0.8%. It was higher in patients with AL. The incidence of AL was 10.4%. Patients who developed leakage were significantly older than patients without AL. A higher incidence of AL has been documented in patients with low serum albumin and low hemoglobin levels and in patients with a prognostic nutritional index score < 40 points. A higher incidence of leakage was observed in patients with poor bowel preparation compared to those with complete and appropriate bowel preparation and in patients receiving blood transfusions compared to those who did not require this therapy. Significant differences between the two groups were found to be related to the site of the anastomosis, stapled rectal resection firing more than one cartridge, the diameter of the circular stapler used, the vascular ligation site and type of mesorectal excision. The use of a transanastomotic tube resulted in a lower incidence of rate of AL compared to patients in whom this device was not used.

Research conclusions

AL after RC surgery is a fearsome complication with considerable mortality and morbidity. Many factors are related to the onset of leakage in the postoperative period. The evaluation of the prognostic nutritional index is very promising.

Research perspectives

The use of the transanastomotic tube prevents the formation of AL. This is a simple method that could avoid performing diverting ileostomies. The use of small diameter circular staplers should be considered in prospective randomized studies on a larger number of patients.

FOOTNOTES

Author contributions: Brisinda G contributed to the writing-original draft; Brisinda G, Chiarello MM and Bianchi V contributed to the conceptualization, methodology and writing-reviewing and editing; Brisinda G, Pepe G, Cariati M, Fico V and Mirco P contributed to the data curation; Brisinda G and Fico V contributed to the formal analysis; Fico V and Mirco P contributed to the investigation; All the authors read and approved the final manuscript.

Institutional review board statement: The study involves the analysis of clinical data. For this reason, the approval of the Institutional Board of the Ethics Committee was not required. The study did not lead to changes in the diagnosis and treatment of the disease in the patients under analysis.

Informed consent statement: All patients were informed about the treatment modalities at the time they were observed. Regarding the study, this is a retrospective analysis of anonymous clinical data.

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META-ANALYSIS

Successful outcomes of unilateral *vs* bilateral pedicle screw fixation for lumbar interbody fusion: A meta-analysis with evidence grading

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Abstract

BACKGROUND

Whether it's better to adopt unilateral pedicle screw (UPS) fixation or to use bilateral pedicle screw (BPS) one for lumbar degenerative diseases is still controversially undetermined.

AIM

To make a comparison between UPS and BPS fixation as to how they work efficaciously and safely in patients suffering from lumbar degenerative diseases.

METHODS

We have searched a lot in the databases through 2020 with index terms such as "unilateral pedicle screw fixation" and "bilateral pedicle screw fixation." Only randomized controlled trials and some prospective cohort studies could be found, yielding 15 studies. The intervention was unilateral pedicle screw fixation; Primarily We've got outcomes of complications and fusion rates. Secondarily, we've achieved outcomes regarding total blood loss, operative time, as well as length of stay. Softwares were installed and utilized for subgroup analysis, analyzing forest plots, sensitivity, heterogeneity, forest plots, publication bias, and risk of bias.

RESULTS

Fifteen previous cases of study including 992 participants have been involved in our meta-analysis. UPS had slightly lower effects on fusion rate [relative risk (RR) = 0.949, 95%CI: 0.910 to 0.990, P = 0.015], which contributed mostly to this meta-analysis, and similar complication rates (RR = 1.140, 95%CI: 0.792 to 1.640, P = 0.481), Δ visual analog scale [standard mean difference (SMD) = 0.178, 95%CI: -0.021 to 0.378, P = 0.080], and Δ Oswestry disability index (SMD = -0.254, 95%CI: -0.820 to 0.329, P = 0.402). In contrast, an obvious difference has been observed in Δ Japanese Orthopedic Association (JOA) score (SMD = 0.305, 95%CI: 0.046 to 0.563, P = 0.021), total blood loss (SMD = -1.586, 95%CI: -2.182 to -0.990, P = 0.000), operation time (SMD = -2.831, 95%CI: -3.753 to -1.909, P = 0.000), and length of

hospital stay (SMD = -0.614, 95%CI: -1.050 to -0.179, P = 0.006).

CONCLUSION
Bilateral fixation is more effective than unilateral fixation regarding fusion rate after lumbar interbody fusion. However, JOA, operation time, total blood loss, as well as length of stay were improved for unilateral fixation.

Key Words: Unilateral pedicle screw fixation; Bilateral pedicle screw fixation; Meta-analysis; Spinal fusion surgery; Discectomy; Lumbar interbody fusion

Core Tip: This literature is not strongly conclusive regarding whether bilateral pedicle screw (BPS) fixation or unilateral pedicle screw (UPS) one is more efficacious and safe for patients with lumbar degenerative diseases. While BPS has been considered standard, it has been associated with excessive rigidity and clinically adverse effects clinically, for example, device-related osteoporosis, adjacent segment degeneration, and a higher risk of other complications. This was the first large scale meta-analysis comparing UPS and BPS. We found UPS to have a slightly more poor fusion rate, but significantly improved prognosis regarding several clinical outcomes, possibly associated with minimal invasion.

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INTRODUCTION

Lumbar interbody fusion (LIF) or spinal fusion surgery was independently proposed by Hibbs *et al*[1] in 1911. To date, this surgical procedure has been used to treat spinal disorders including degenerative vertebral disease, trauma, infection, and tumors for more than a century. The main procedures include discectomy, endplate preparation, bone grafting, cage insertion, pedicle screw placement, or standalone. Patient expectations and the increasing demand for shorter hospital stays have led to more innovative surgical techniques. There are five major surgical approaches: posterior LIF, anterior LIF, lateral LIF, transforaminal LIF, and oblique LIF or anterior to the psoas. The choice of surgical approach is often determined by surgeon preference and patient factors, as there has been no clear or strong evidence regarding which approach is superior[2-5]. The most common internal fixation method for fusion is posterior pedicle screw fixation, and bilateral pedicle screw (BPS) fixation is considered a standard procedure. However, excessive rigidity is suspected to result in clinically adverse effects, such as adjacent segment degeneration, device-related osteoporosis, and a higher risk of other complications[6]. While there is plenty of research exploring two pedicle screw fixations, most studies were limited by their retrospective nature, lack of a comparison group, or inadequate follow-up[7,8]. Previous meta-analyses also included the limitations of not including all prospective studies and incorporating many retrospective studies, and the results may be biased[8,9]. We retrieved all the literature about unilateral and BPS fixation after lumbar fusion in recent years and included the latest randomized controlled trials (RCTs) and prospective cohort studies. The results were meta-analyzed to provide a reference for future clinical work.

MATERIALS AND METHODS

Literature search

We retrieved relevant studies using "Unilateral Pedicle Screw fixation," "lumbar interbody fusion," "lumbar degenerative diseases" along with "Bilateral Pedicle Screw fixation," as key words with Boolean operators "AND" or "OR" in electronic databases, namely, EMBASE, the Cochrane Library and PubMed as of January 2020. While only prospective cohort studies and RCTs carried out upon human subjects were kept for further use. For presenting the flowchart of the trial selection, Figure 1 has been worked out. PRISMA guidelines, Cochrane Handbook and GRADE system are adopted as well for assessing qualities from involved study so as for convincing that the data herein presented were not only reliable but verifiable as well[10-12].

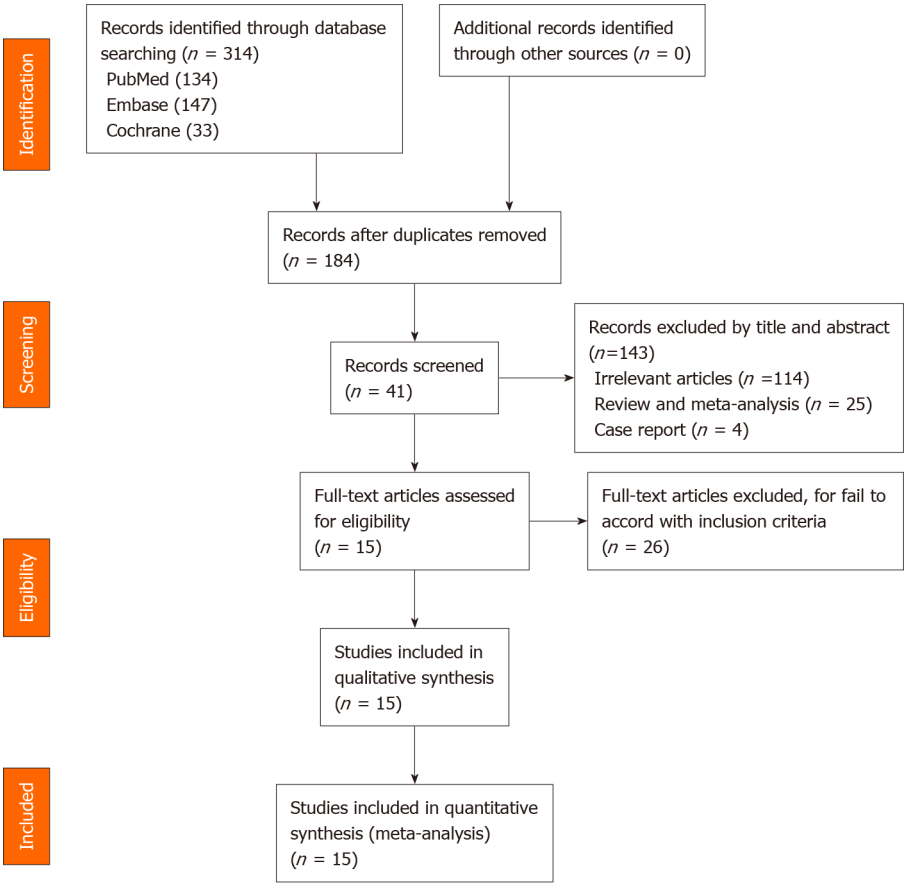

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Figure 1 Flow diagram of study searching and selection process.

Selection criteria

The PICOS (Population, Intervention, Comparison, Outcome, and Study design) outline was used for including studies in the review. Inclusion criteria: (1) RCTs or prospective cohort studies; (2) The study population was patients with BPS fixation or UPS one after lumbar interbody fusion; (3) The intervention was UPS fixation, UPS fixation was also adopted for comparison; and (4) The primary outcomes were fusion rate and complications such as screw loosening, cage migration, infection, psoas, and neural symptoms. The secondary outcomes included changes in the following: Visual Analog Scale (VAS) score, Oswestry Disability Index (ODI) score, Japanese Orthopedic Association (JOA) score, operation time, total blood loss, as well as in-hospital duration. Exclusion criteria were: (1) No report on fusion rate or complication rate; (2) Study on recurrent lumbar diseases or revision surgeries; and (3) Repeated studies.

Data extraction

Two independent researchers searched the papers independently using the same search strategy, and a third researcher resolved any disagreement. Two reviewers collected the obtainable data from the involved studies independently, and any disagreement between the two reviewers was resolved by a third reviewer. Relevant data consist of names of the authors, dates of publication, types of intervention, ages, sample sizes, outcomes, follow-up duration, and types of reference. we obtained the outcome data, or estimated statistics *via* the data provided either in tables or in figures if we could not obtain the data directly from the statements of the articles. We present the baseline characteristics of the involved trials in Table 1.

Risk of bias assessment

The methodological qualities and foundation of the involved studies were assessed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. Based on the included literature, the two researchers evaluated adequate sequence generation, allocation concealment, binding, selective reporting, and other bias as being at high, low, or unclear risks of bias. If there were any inconsistency, the third researcher would be consulted to deal with it (Figures 2 and 3).

Table 1 Characteristics of included randomized controlled trial

Ref.	Number of patients (*n*)		Gender (M/F)		Age (yr, mean ± SD)		Follow-up (mo)		Type of operation	Surgical segments	Reference type
	UPS	BPS	UPS	BPS	UPS	BPS	UPS	BPS			
Gu *et al*[13], 2015	35	39	17/18	21/18	64.5 ± 8.0	66.1 ± 7.1	32.1 ± 7.5	31.7 ± 8.0	MI-TLIF	2	Prospective cohort
Shen *et al*[14], 2014	31	34	17/14	16/18	57.3 ± 11.7	58.9 ± 10.1	26.6 ± 4.5	26.6 ± 4.5	MI-TLIF	1	RCT
Zhang *et al*[15], 2014	33	35	14/19	10/25	59.4 ± 10.2	55.7 ± 11.6	25.6 ± 4.5	25.6 ± 4.5	TLIF	2	RCT
Dong *et al*[16], 2014	20	19	6/14	6/13	54.0 ± 12.3	56.6 ± 14.7	24	24	PLIF	1	RCT
Chen *et al*[17], 2014	15	15	10/5	8/7	43.1 ± 5.8	44.9 ± 6.5	15.2 ± 3.25	15.2 ± 3.25	MI-TLIF	NG	RCT
Gologorsky *et al*[18], 2014	40	40	19/21	21/19	41.6	46.9	52 ± 6.5	52 ± 6.5	TLIF	1 or 2	Prospective
Lin *et al*[19], 2013	43	42	19/24	20/22	67	65.5	26 ± 3.5	26 ± 3.5	MI-TLIF	1	RCT
Duncan *et al*[20], 2013	46	56	20/26	20/36	53.5 ± 14.75	55.7 ± 14	25.1	25.1	TLIF	1 or 2	RCT
Dahdaleh *et al*[21], 2013	16	20	6/10	20/36	62.2 ± 13.1	57.3 ± 11.2	11.4 ± 6.1	12.4 ± 7.2	MI-TLIF	1	RCT
Choi *et al*[22], 2013	26	27	12/14	9/18	53.39 ± 14.31	56.22 ± 12.62	27.52 ± 3.3	28.85 ± 4.37	MI-TLIF	NG	RCT
Xie *et al*[23], 2012	56	52	32/24	28/24	56.2 ± 8	55 ± 8.5	36 ± 3	36 ± 3	PLIF	1 or 2	RCT
Aoki *et al*[24], 2012	25	25	8/17	12/13	66.2 ± 8.3	65.6 ± 8.8	31 ± 3.25	31.2 ± 4.5	TLIF	1	RCT
Xue *et al*[25], 2012	37	43	17/20	18/25	57.1 ± 8.1	58.2 ± 7.6	25.3 ± 3.5	25.3 ± 3.5	TLIF	1 or 2	RCT
Feng *et al*[26], 2011	20	20	12/8	10/10	53.75	53.2	24	24	TLIF	1	RCT
Fernández-Fairen *et al*[27], 2007	40	42	15/24	15/27	60.8 ± 5.33	61.42 ± 5.47	36	36	PLIF	1 or 2	RCT

F: Female M: Male; MI-TLIF: Minimally invasive transforaminal lumbar interbody fusion; TLIF: Transforaminal lumbar interbody fusion; PLIF: Posterior lumbar interbody fusion; RCT: Randomized controlled trial.

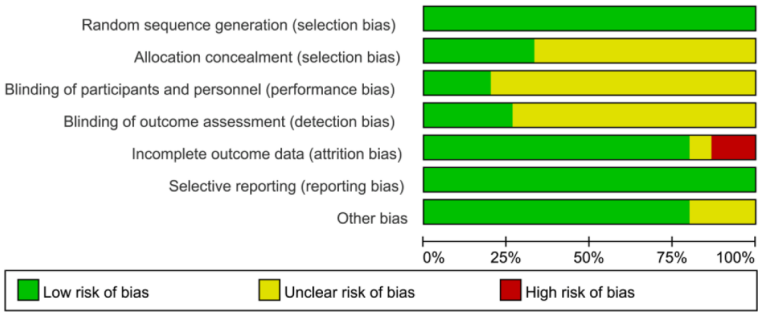

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Figure 2 Risk of bias graph.

Grading quality of evidence

The GRADE software has been used to conduct evaluation on the convincing level of evidence and strength of recommendations for the involved outcomes. Initially, RCTs were considered to have high confidence, and cohort studies low confidence as for the estimate of effect. Factors which may have decreased the level of confidence level included inconsistency, limitations, imprecision, indirectness, as well as publication bias. Factors that may have raised confidence level consisted of plausible confounding, large effect and dose-response. We present the results of GRADE analysis in Table 2.

Table 2 The GRADE evidence quality for each outcome

No of studies	Design	Decrease quality of evidence				Increase quality of evidence				Quality	Importance
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Does-response		
Fusion rate	RCT	No	No	No	No	Unlikely	No	No	No	High (++++)	Critical
Complications	RCT	No	No	No	Serious	Very likely	No	No	No	Very low (+---)	Critical
-Δ VAS	RCT	No	Serious	No	No	Likely	No	No	No	Low (++--)	Important
Δ ODI	RCT	No	Serious	No	No	Likely	No	No	No	Low (++--)	Important
Δ JOA	RCT	No	Serious	No	No	Unlikely	No	No	No	Moderate (+++-)	Important
Total blood loss	RCT	No	Serious	No	No	Very likely	No	No	No	Very low (+---)	Important
Operation time	RCT	No	Serious	No	No	Unlikely	No	No	No	Moderate (+++-)	Important
Length of hospital stay	RCT	No	Serious	No	No	Very likely	No	No	No	Very low (+---)	Important

High quality: Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: We are very uncertain about the estimate. VAS: Visual analog scale; ODI: Oswestry disability index; JOA: Japanese Orthopedic Association; RCT: Randomized controlled trial.

Statistical analysis

Meta-analyses have been conducted using RevMan 5.3 software and STATA 13.1. The Standard Mean Difference (SMD) has been applied to make assessment of consecutive outcomes, with 95% Confidence Interval (CI). Relative Risk (RR) with 95%CI was adopted to make assessments of the dichotomous outcomes. The inverse variance, Mantel-Haenszel, and DerSimonian-Laird approaches have been applied to make combination of separated statistics. The results have been considered statistically important at P values < 0.05.

Investigation of heterogeneity and publication bias

Heterogeneity out of studies has undergone evaluation *via* I^2 values and and considered high if $I^2 \geq 50\%$ or low if $I^2 < 50\%$, respectively. An fixed-effects model was adopted when $I^2 \geq 50\%$, whereas an effect model of random type was used when $I^2 < 50\%$. Subgroup analyses and sensitivity analysis ones have been conducted to figure out the heterogeneity source, while $I^2 \geq 50\%$. Stata13.1 adopted for evaluation of the publication bias.

RESULTS

Search results

According to the index words, 314 citations were identified from the electronic databases. A total of 130 citations were duplicated, and 143 citations were excluded from the title and abstract, such as irrelevant articles, reviews, and case reports. Additionally, 26 retrospective studies were excluded from the analysis. Ultimately, 15 RCTs were included[13-27]. However, the limitation is that not every study included contains every outcome of interest. We summarized the characteristics of the involved studies and presented in Table 1.

Primary outcome

The complications and fusion rate of the two internal fixations were the primary outcomes from the meta-analysis, used for evaluating efficacy and safety.

Fusion rate

Eleven studies assessed the fusion rate of 708 patients followed up for at least 12 mo. Compared with BPS, UPS had a slightly lower fusion rate (RR = 0.949, 95%CI: 0.910 to 0.990, P = 0.015, Figure 4A). The

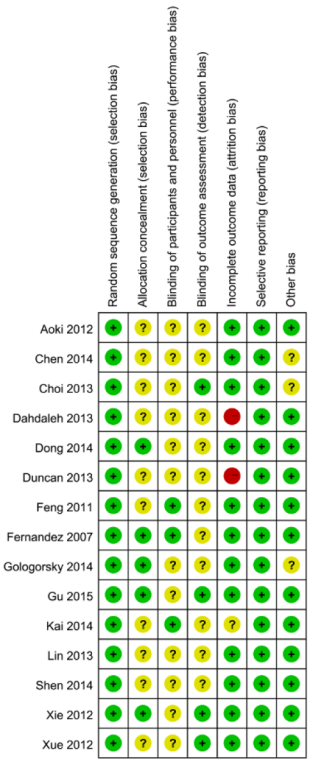

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Figure 3 Risk of bias summary.

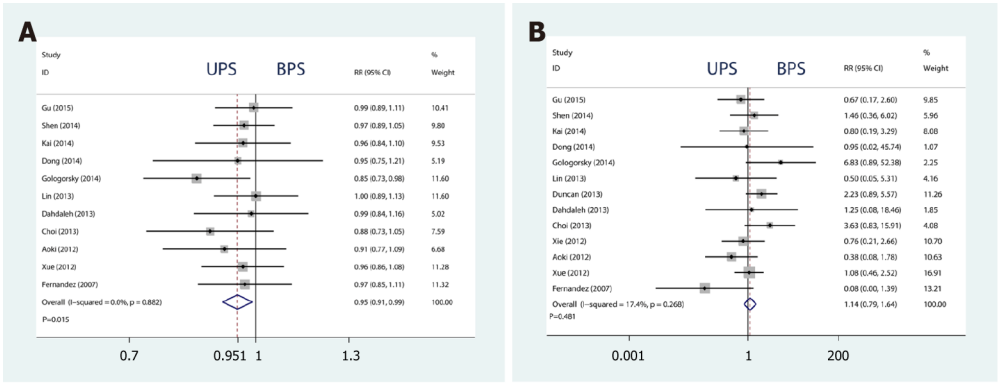

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Figure 4 Forest plots of fusion rates and complications. A: Fusion rates; B: Complications.

age subgroup analysis indicated that the significant difference disappeared in patients aged > 60 years (RR = 0.975, 95%CI: 0.914 to 1.041, *P* = 0.455, Figure 5A). The type of operation subgroup analysis showed that TLIP significantly reduced the fusion rate of the UPS (SMD = 0.921, 95%CI: 0.857 to 0.988, *P* = 0.022, Figure 5B).

Complications

Thirteen studies assessed the fusion cage migration rate of 918 patients followed up for at least 12 mo. No drastic difference has been observed between both internal fixation approaches (RR = 1.140, 95%CI: 0.792 to 1.640, *P* = 0.481, Figure 4B).

Secondary outcome

The enhancements in VAS, JOA, and ODI scores were considered subjective. To some extent, operation, blood loss, as well as in-hospital duration depended upon the surgeon's proficiency. Therefore, these outcomes are secondary but essential indicators of prognosis in clinical practice.

Improvement of VAS, ODI and JOA: There was no significant difference in ΔVAS or ΔODI (ΔVAS,

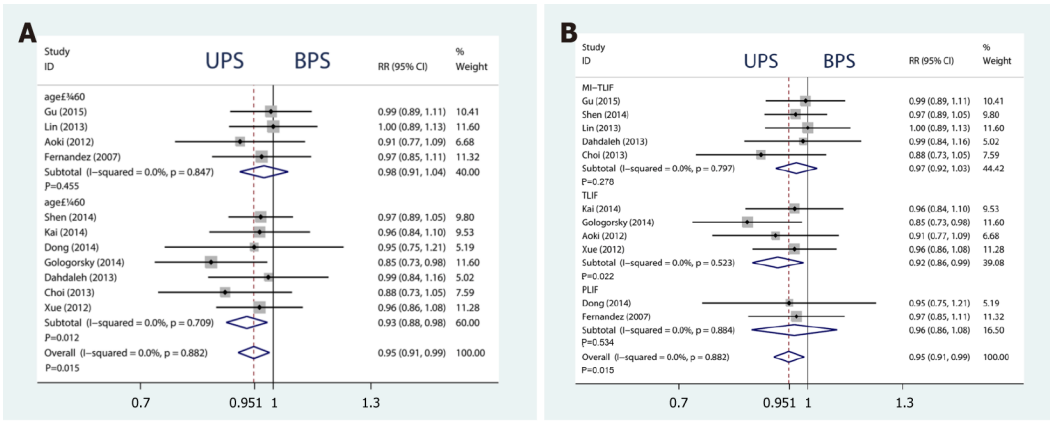

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Figure 5 Forest plots of subgroup analysis.

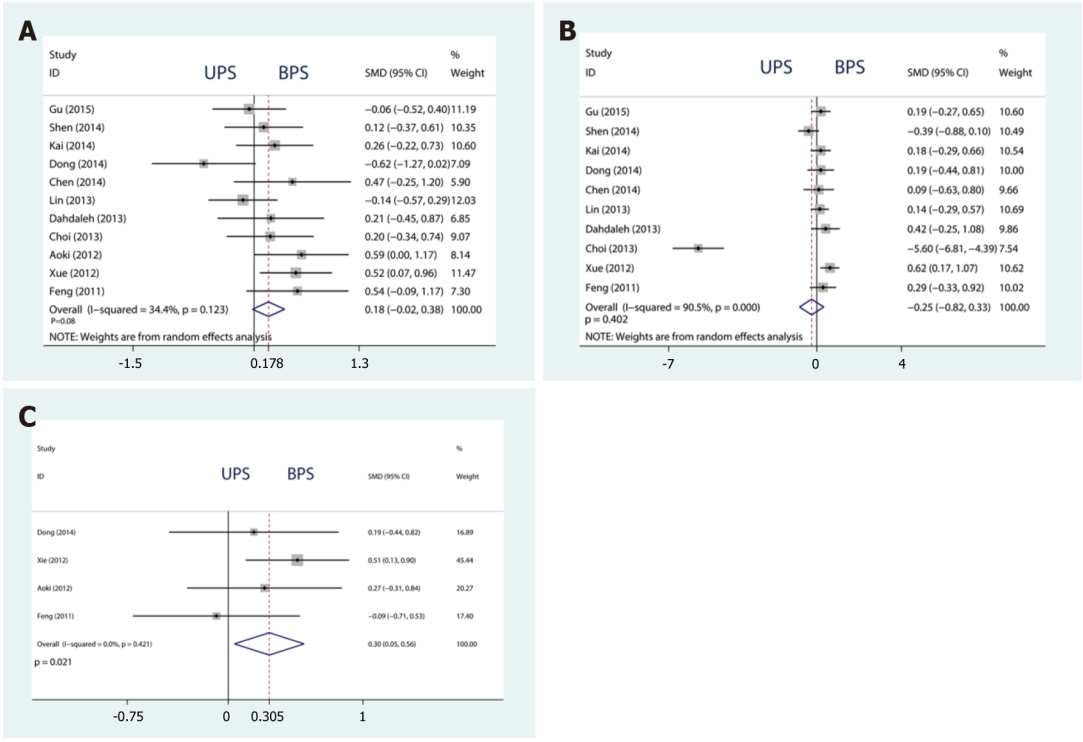

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Figure 6 Forest plots of Δ visual analog scale, Δ Oswestry disability index, and Δ Japanese Orthopedic Association. A: Δ visual analog scale; B: Δ Oswestry disability index; C: Δ Japanese Orthopedic Association.

SMD = 0.178, 95%CI: -0.021 to 0.378, *P* = 0.080; ΔODI, SMD = -0.254, 95%CI: -0.820 to 0.329, *P* = 0.402, Figure 6A and B). However, compared with BPS, UPS significantly improved ΔJOA (SMD = 0.305, 95%CI: 0.046 to 0.563, *P* = 0.021, Figure 6C).

Total blood loss, operation time, as well as in-hospital duration: Compared with BPS, UPS significantly reduced the total blood loss, operation time, and length of hospital stay (total blood loss, SMD = -1.586, 95%CI: -2.182 to -0.990, *P* = 0.000; operation time, SMD = -2.831, 95%CI: -3.753 to -1.909, *P* = 0.000; length of hospital stay, SMD = -0.614, 95%CI: -1.050 to -0.179, *P* = 0.006, Figure 7A-C).

Quality assessment

We present baseline characteristics of the involved trials in Table 1, and results of GRADE analysis are presented in Table 2. The included studies met the principles of randomized controlled trials with a high level of evidence (Figures 2 and 3). Given medical ethics and patients' informed consent rights, these RCTs rarely mention whether to adopt allocation concealment and blind methods, especially

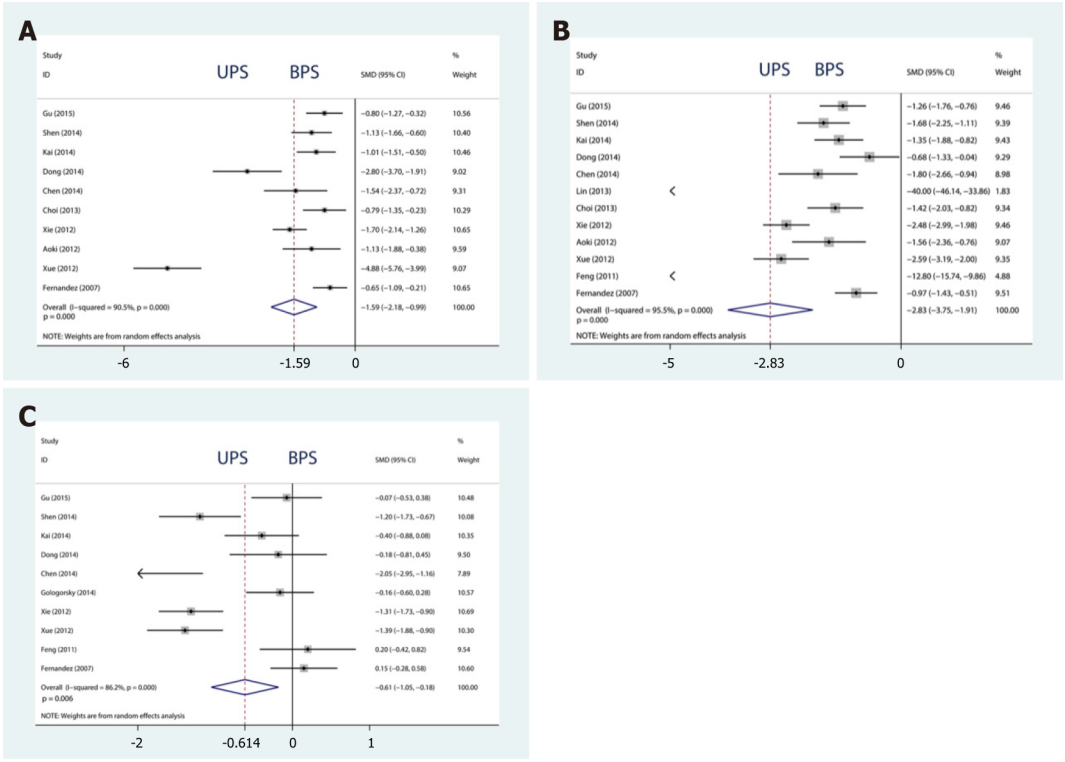

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Figure 7 Forest plots of total blood loss, operation time, and length of hospital stay. A: Total blood loss; B: Operation time; C: Length of hospital stay.

single-blind methods. We used the Harbord method and considered that no significant publication bias has been observed in the fusion rate (P = 0.710, Figure 8A). We conducted a sensitivity analysis with metatrim and metaninf and considered the included studies to be steady (Figure 8B and C).

DISCUSSION

This study suggested that UPS had a poorer fusion rate but significantly improved prognosis regarding several clinical outcomes.

However, the choice between unilateral and BPS fixation after lumbar fusion remains controversial. The BPS provides greater immediate stability, and the UPS significantly decreases the stiffness of the instrumented segment and surgical trauma. In recent years, many clinical follow-up studies and human cadaver studies have shown that UPS is as effective as BPS, and that UPS can achieve biomechanical stability comparable to that of BPS[28-32]. Computer simulation studies, such as finite element studies, also support UPS[33].

However, there are some objections to this approach. Kasai reported that UPS offers only uneven fixation in a human cadaver study, whereas BPS may allow excellent fixation in all directions[34]. Schleicher performed stiffness testing in fresh-frozen human cadaveric lumbar spine motion segments and concluded that BPS offers significantly more stability than UPS in the majority of test modes[35]. Many studies have found no significant difference in only one- or two-level interbody fusion[36]. Our study shows that there is a slightly lower fusion rate in UPS, even with short-segment fixation, which is different from those reported previously[37,38]. In terms of the rate of fusion cage migration, previous studies have found that UPS generates more cage migration than BPS[39]. After synthesizing the newly published studies, our evidence shows no difference in the rate of fusion cage migration between UPS and BPS. In terms of Improvement of VAS, ODI and JOA, there was no difference between UPS and BPS, which was consistent with the conclusion of previous studies[39]. In terms of total blood loss, operation time, and the length of hospital stay, UPS was lower than BPS, which was consistent with the actual clinical situation. Unilateral PS fixation avoided contralateral exposure and reduced trauma. Therefore, UPS fixation can not only shorten the operation time and reduce surgical trauma, but also reduce the recovery time[40]. GRADE is one of the widely adopted approaches in industries of public health and medicine to make assessment of the evidence's outcome-specific certainty through systematically conducted reviews[41]. Our results show that the level of evidence is high. Therefore, we believe that this is the main contribution of the present meta-analysis. Although UPS has many advantages, BPS

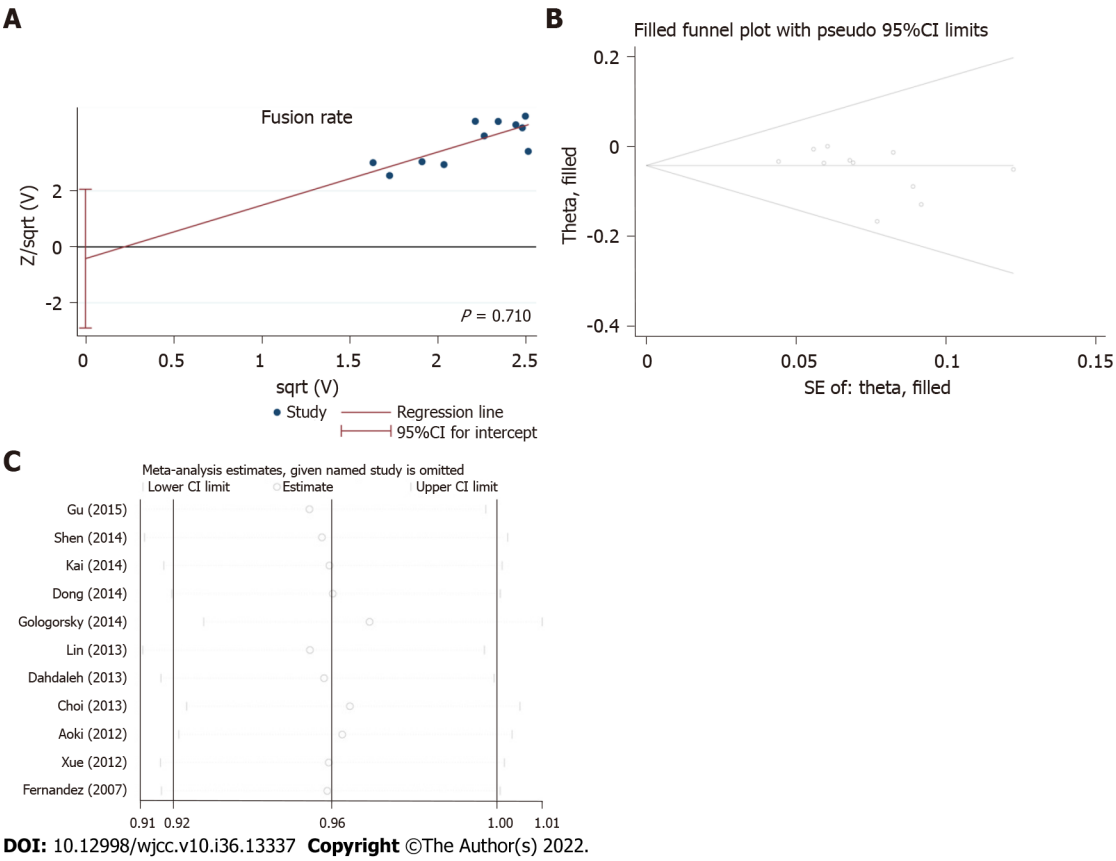

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Figure 8 Publication bias, metatrim, and metaninf of fusion rate. A: Publication bias; B: Metatrim; C: Metaninf.

is much preferred, assuming there isn't sufficient stability, such as during long segment fixation. However, current data only provide weak support, if any, favoring BPS over UPS for clinical improvement in fusion rates.

Within aging populations, there is a significant increase in lumbar degenerative diseases (LDD), resulting in great pain and reduced quality of life for patients[42]. Early increase of fusion rate and relief of pain, so that patients can move early, can effectively reduce venous thrombosis, pulmonary infection, pressure sores, and other complications[7,43]. Shortening hospital stay and reducing nosocomial infections are particularly important for the recovery of elderly patients[44]. Thus, it is urgently demanded to explore feasible, secure, and effective treatments for LDD.

Our study also has some limitations. First, all studies were single-center studies with small sizes of samples, which could possibly bring about selection bias. Second, none of the RCTs included in this study used blinding methods. Because of the type of intervention, blinding could not be performed to prevent the placebo effect or observer bias, resulting in low quality of the methodology. Third, different studies had different follow-up times, and the follow-up time of some studies was short. Finally, differences in diagnostic criteria, inclusion and exclusion criteria and details of treatment resulted in heterogeneity in the meta-analysis. Although subgroup and sensitivity analyses have been conducted, confounding statistical outcomes resulted from heterogeneity cannot be excluded to a complete extent.

CONCLUSION

According to our meta-analysis, UPS had a slightly poorer fusion rate but significantly improved prognosis regarding many important clinical outcomes, possibly associated with minimal invasion. To clarify whether UPS has the same reliability and effectiveness as BPS, longer follow-up and more clinical trials, especially RCTs, are required to provide stronger evidence regarding this observation. Further multicenter studies with more patients are required to obtain more reliable results.

ARTICLE HIGHLIGHTS

Research background

The use of unilateral pedicle screw (UPS) or bilateral pedicle screw (BPS) fixation for lumbar degenerative diseases remains controversial.

Research motivation

To provide objective evidence for the selection of UPS or BPS fixation for lumbar degenerative diseases.

Research objectives

To compare the efficacy and safety of UPS and BPS fixation in patients with lumbar degenerative diseases.

Research methods

We used meta-analysis to systematically review the current evidence.

Research results

UPS had slightly lower effects on fusion rate, which was the main contribution of this meta-analysis, and similar complication rates, Δ visual analog scale, and Δ Oswestry disability index. In contrast, there was a significant difference in Δ Japanese Orthopedic Association (JOA) score, total blood loss, operation time, and length of hospital stay.

Research conclusions

Unilateral fixation is less effective than bilateral fixation regarding fusion rate after lumbar interbody fusion. However, JOA, total blood loss, operation time, and length of stay were improved for unilateral fixation.

Research perspectives

To clarify whether UPS has the same reliability and effectiveness as BPS, longer follow-up and more clinical trials, especially RCTs, are required to provide stronger evidence regarding this observation. Further multicenter studies with more patients are required to obtain more reliable results.

FOOTNOTES

Author contributions: Sun L, Tian AX and Ma JX designed research, performed research, and wrote the paper; Ma XL was a major contributor in writing the manuscript and analyzed data, and all authors read and approved the final manuscript.

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CASE REPORT

Pregnancy-induced leukocytosis: A case report

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Abstract

BACKGROUND

Pregnancy is a complex physiological process. Physiological leukocytosis occurs often and is mainly associated with increased neutrophil counts, especially in the third trimester of pregnancy. Non-congenital leukocytosis with white blood cell counts above 20 × 10^9/L lasting 13 wk during pregnancy is rare and has been reported occasionally. Herein, we present a case of pregnancy-induced leukocytosis.

CASE SUMMARY

We present the case of a 33-year-old Chinese woman at 27 wk of gestation who had a leukocytosis complication. No abnormalities were detected in the examinations before pregnancy or in the first trimester. From the third trimester of pregnancy, the patient began to suffer from asymptomatic leukocytosis. We administered antibiotics to treat the patient; however, the complication persisted until the patient underwent a cesarean section after 40^{+3} wk of gestation. One day after the cesarean section, the patient's neutrophil count returned to normal. After 2 years of follow-up, we found that the patient and baby were healthy.

CONCLUSION

Pregnancy-induced leukocytosis seems to be associated with immunoregulation and pregnancy termination may be the most effective treatment approach for pregnancies complicated with malignant leukocytosis.

Key Words: Leukocytosis; Pregnancy; *In vitro* fertilization; Malignancy; Case report

Core Tip: Physiological leukocytosis often occurs and is mainly associated with increased neutrophil levels. We present the case of a Chinese woman in her 27th wk of gestation who had the complication of leukocytosis with a white blood cell count above 20 × 10^9/L for 13 wk. One day after a cesarean section, the patient's neutrophil levels returned to normal. After 2 years of follow-up, the patient and baby were found to be healthy. During pregnancy, asymptomatic leukocytosis appears to be related to immunoregulation and termination of pregnancy may be an effective treatment approach in pregnancies with malignant leukocytosis.

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INTRODUCTION

Pregnancy is a complex physiological process[1]. The normal range of white blood cell (WBC) counts changes with age and pregnancy[2,3]. In pregnant women, local adaptation of the maternal immune system enables the successful coexistence of the mother and fetus/placenta[4]. Physiological leukocytosis (3.5-9.5 × 10^9/L) has a high incidence and is mainly associated with the increased circulation of neutrophils (1.8-6.3 × 10^9/L), especially during the last trimester of pregnancy[5]. It is important for clinicians to distinguish between malignant and non-malignant causes and to identify the most common causes of non-malignant leukocytosis. During pregnancy, the normal WBC count increases gradually (third trimester 95% upper limit = 13.2 × 10^9/L; 99% upper limit = 15.9 × 10^9/L)[6]. Leukocytosis is similar in several non-obstetrical cases, such as infections, allergic reactions, malignancies, surgery[7], traumas[8], and strenuous physical activities[9]. For pregnant and parturient women, an increased WBC count may also be related to gestational and puerperal infections such as endometritis[10] and chorioamnionitis[11]. Other factors that affect WBC count include smoking[12], race[13,14], and body mass index[14]. Leukocytosis is a common symptom of infections, especially bacterial infections, and physicians should be encouraged to recognize other signs and symptoms of infections. Chorioamnionitis, defined as the inflammation of fetal membranes after 20 wk of gestation is one of the main causes of perinatal morbidity and mortality[15]. The traditional diagnostic criteria for clinical chorioamnionitis are fever and at least two of the following: Maternal tachycardia, maternal leukocytosis (maternal WBC > 15000 in the absence of corticosteroids), uterine tenderness, fetal tachycardia (> 160 bpm for 10 min or longer), and foul-smelling amniotic fluid[16,17].

Non-congenital leukocytosis with WBC counts above 20 × 10^9/L for 13 wk during pregnancy is rare and has been reported occasionally. Herein, we present the case of gestation-induced leukocytosis.

CASE PRESENTATION

Chief complaints

A 33-year-old woman presented to the emergency department with a complaint of high blood pressure for 6 wk and leukocytosis for 13 wk.

History of present illness

The patient had experienced leukocytosis for 13 wk at the time she presented to the emergency department. To prevent implantation failure after IVF, she took aspirin enteric-coated tablets 75 mg a day, 5 mg acetate orally once a day, and one vitamin complex tablet a day until 12 wk of gestation. During her pregnancy, repeated routine blood tests before 20 wk of gestation showed that the WBC and neutrophil counts were within the normal range. Ultrasonography suggested a post-placental hematoma with a diameter of approximately 20-30 mm before 20 wk of gestation, which disappeared thereafter. At 27 wk of gestation, the WBC rose to 23.73 × 10^9/L and the neutrophil count rose to 20.74 × 10^9/L (Figure 1).

History of past illness

The patient was diagnosed with polycystic ovarian syndrome and her partner was diagnosed with male factor infertility. The patient had no known allergies to food or medication. In addition, she denied any family history or history of sexually transmitted infections. The patient was an employee of an Internet company, did not smoke and was not exposed to second-hand smoking during pregnancy.

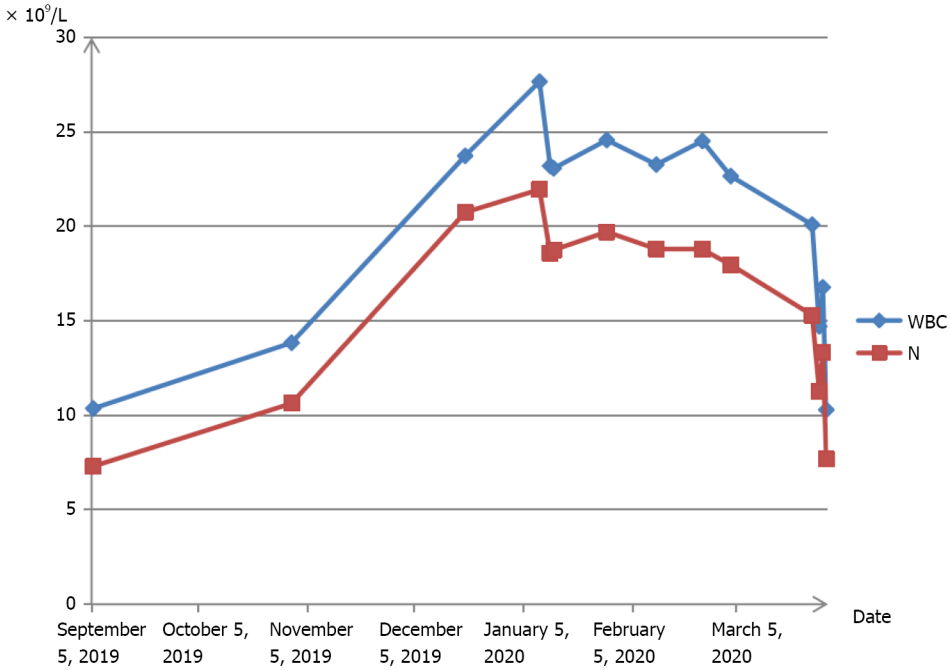

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Figure 1 Variation tendency of leukocyte and neutrophil. Line chart is shown depicting changes in white blood cell and neutrophil count over time. N: Neutrophil count; WBC: White blood cell count.

Personal and family history

The patient had no specific personal and family history.

Physical examination

At the initial inspection, the patient had a blood pressure of 126/87 mmHg and a pulse rate of 68 beats *per* minute. The patient's lungs were clear and she had normal heart sounds with no murmurs on auscultation.

Laboratory examinations

At 27 wk of gestation, blood analysis revealed leukocytosis of 23.73 × 10^9/L, with predominantly neutrophils (87.4%) with normal hematocrit and platelet count, and the neutrophil count rose to 20.74 × 10^9/L (Figure 1). C-reactive protein count was 0.52 (< 0.8) mg/dL, erythrocyte sedimentation rate was 30 (0-20) mm/h, and procalcitonin (PCT) count was < 0.05 (< 0.5) ng/mL, which showed no sign of infection.

Methods

The manuscript is a case report and meets the requirements of biostatistics.

FINAL DIAGNOSIS

The final diagnosis of the case is asymptomatic leukocytosis.

TREATMENT

The patient had no fever, and had a normal temperature. In addition, there was no presence of other symptoms, including no cough, expectoration, oral ulcers, or shivering. She was administered antibiotic treatment for 2 wk, which did not work. Afterward, the patient visited several other hospitals; during this time, routine blood tests showed a sustained high level of WBC and neutrophil counts. The patient visited the outpatient department of our institution because of leukocytosis. The C-reactive protein count was 0.52 mg/dL, the erythrocyte sedimentation rate was 30 mm/h, and the PCT count was < 0.05 ng/mL, which showed no sign of infection. Thereafter, the patient visited the outpatient hematology department. The patient refused a bone marrow biopsy. Peripheral blood smear showed that mature neutrophils accounted for 73.2%, and the count of immature granulocytes was 0.95 × 10^9/L, accounting

for 3.7%. Tests at another hospital showed leukocytosis, but normal levels of red blood cells and megakaryocytes. The patient was hospitalized with an elevated blood pressure at 40^{+3} wk of gestation. On admission, the WBC count was 20.09 × 10^9/L, the neutrophil granulocyte count was 15.3 × 10^9/L, the blood platelet count was 343 × 10^9/L, and the hemoglobin concentration was 140 g/L. The next day, she underwent a cesarean section because of fetal distress. The surgery was successful.

On the first postoperative day, the WBC count was 14.71 × 10^9/L, the neutrophil granulocyte count was 11.26 × 10^9/L, the hemoglobin concentration was 124 g/L, and the platelet count was 304 × 10^9/L. The thyroid function tests were within the normal range; free thyroxine was 16.27 pmol/L and thyrotropin was 1.16 uIU/mL. Ultrasonography of the fetus, abdomen, lower limb arteries, and deep veins showed that all the tested areas were normal. Ultrasonography of the kidneys showed a right hydronephrosis with a renal pelvis approximately 1.1 cm wide. Tests for immunoglobulin M (IgM) against toxoplasma, IgM against rubella virus, and IgM against cytomegalovirus, herpes simplex type I virus, and herpes simplex type II virus were negative. Tests for hepatitis, human immunodeficiency virus, and *Treponema pallidum* were all negative. By 34 wk, blood pressure had risen to a range of 138/80 mmHg and 142/90 mmHg, and the patient was diagnosed with pregnancy-induced suspicious hypertension without medication. During 40^{+3} wk of gestation, she underwent a cesarean section because her blood pressure had increased to 143/90 mmHg. Six weeks postpartum, the patient's blood pressure gradually returned to normal.

OUTCOME AND FOLLOW-UP

Postoperatively, neutrophil granulocytes returned to normal levels. The patient delivered a live, healthy, full-term baby *via* a cesarean section. After 2 years of follow-up, the patient and baby were found to be healthy.

DISCUSSION

Hematological diseases in pregnancy should be meticulously managed with multidisciplinary cooperation, including obstetrics and hematology. Distinguishing between reactive and malignant lymphocytosis is challenging and may vary with age and other demographics. Table 1 lists the most common etiologies[18]. The patient did not suffer from allergic reactions, malignancy, surgery, trauma, strenuous physical activity, or smoking; in addition, the patient had no fever, had normal temperature, experienced no other symptoms such as cough, expectoration, oral ulcers, or shivering. The patient visited the outpatient department for the complaint of an infection. The C-reactive protein count was 0.52 mg/dL, the erythrocyte sedimentation rate was 30 mm/h, and the PCT count was < 0.05 ng/mL, which showed no sign of infection. A peripheral blood smear showed that mature neutrophils accounted for 73.2%, and immature granulocytes count was 0.95 × 10^9/L, accounting for 3.7%. Tests at another hospital showed leukocytosis, but normal levels of red blood cells and megakaryocytes. Six weeks postpartum, the patient's blood pressure gradually returned to normal, which illustrated that it was not malignant. Molberg *et al*[19] found that the average WBC count in a laboring patient was 12.45 × 10^9/L, with a range of 4.4 × 10^9/L to 29.1 × 10^9/L. WBC counts in patients with postpartum complications were similar to that in patients without complications (12.9 × 10^9/L *vs* 12.3 × 10^9/L, P = 0.449)[19]. We describe a case of asymptomatic leukocytosis with WBC counts > 20 × 10^9/L during pregnancy. The patient did not suffer from leukocytosis until 27 wk of gestation; after cesarean section, WBC and granulocyte counts dropped to normal levels. Levothyroxine sodium is safe for pregnant women, and there is no evidence that its side effects include leukocytosis[20]. At the same time, there was no obvious evidence that hypothyroidism caused leukocytosis, and the patient had no history of using cytotoxic drugs or other medications that explicitly cause leukocytosis. Therefore, we believe that drug-induced leukocytosis was less likely the case.

There are a few reports on leukocyte counts and differentials related to the severity of pregnancy-induced hypertension. Terrone *et al*[21] assessed the difference in leukocyte counts between normal pregnancies and pregnancies complicated by preeclampsia (PE). In a retrospective study of 240 women, women with severe PE had a significantly higher WBC count than those with mild PE and normal pregnancy controls [10.66 +/- 3.70 *vs* 9.47 +/- 2.59 and 8.55 +/- 1.93 (× 10^9/L) (P < 0.0001)]. The increase in the total WBC count was mainly due to an increase in the number of neutrophils [8.05 +/- 4.01 (severe) *vs* 6.69 +/- 2.23 (mild) and 5.90 +/- 1.79 (controls) (× 10^9/L) (P < 0.0001)]. Terrone *et al*[21] evaluated the total WBC count of 86 patients with severe PE with and without hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome of 91 patients. The WBC counts in patients with HELLP syndrome (12.5 +/- 0.442 × 10^9/L) were significantly higher than those in patients with severe PE (10.3 +/- 0.288 × 10^9/L). The patient was diagnosed with hypertension during pregnancy, without PE. Furthermore, the counts of WBCs were above 20 × 10^9/L. Leukocytosis may have had nothing to do with hypertension in this case.

Table 1 Causes of leukocytosis

Infections	Lymphoproliferative disorders	Other hematological systemic disease	Drugs and drug hypersensitivity reactions	Stress	Asplenia
Viral infections	Chronic Lymphocytic Leukemia	MBL	Allopurinol	Cardiac conditions	
Bacterial Infections	Non-Hodgkin Lymphoma	Congenital B cell Lympho-cytosis	Carbamazepine	Status epileptics	
Parasitic Infections	Adult T cell lymphoma/leukemia	Persistent B-cell polyclonal B-Lymphocytosis	Vancomycin	Epinephrine use	
Mycobacterial Tuberculosis	Large Granular Lymphocyte Leukemia		Sulfa drugs		
	Acute lymphoblastic lymphoma				

MBL: Monoclonal B lymphocytosis.

There have been few reports on the relationship between leukocytosis and *in vitro* fertilization and embryo transfer (IVF). Ludwig *et al*[22] observed the effects of a luteinizing hormone-releasing hormone antagonist protocol (Cetrorelix) and the administration of recombinant follicle-stimulating hormone (FSH) on the development of leukocytosis compared to the administration of urinary human menopausal gonadotropin. Thirty patients underwent IVF/intracytoplasmic sperm injection treatment after controlled ovarian stimulation using a multiple dose protocol and the luteinizing hormone releasing hormone (LHRH) antagonist Cetrorelix, and no significant leukocytosis was discovered after controlled ovarian stimulation using the LHRH antagonist Cetrorelix and recFSH.

During pregnancy, the integration and balance of these immune factors produce an environment that allows the fetus to escape rejection by the maternal immune system. Multiple mechanisms influence the maternal immune system in accepting semiallogeneic fetal tissues during pregnancy[23]. Female sex hormones affect many immune pathways more often during pregnancy.

Limitations

In summary, the etiology and mechanism of this phenomenon remain largely unknown. In addition, during pregnancy, asymptomatic leukocytosis seems to be related to immunosuppression induced by immunoregulation. The termination of pregnancy may be effective in pregnancies complicated with leukocytosis; however, further studies are needed to confirm this.

CONCLUSION

Thus, we conclude that leukocytosis seems to be associated with the pregnancy itself and is associated with immunoregulations. Although this study presents a case of leukocytosis without evidence of clinical infection, caution should be exercised when applying these data clinically. We suggest that pregnancy termination may be a therapeutic approach for pregnancies complicated with leukocytosis.

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FOOTNOTES

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CASE REPORT

Acute moderate to severe ulcerative colitis treated by traditional Chinese medicine: A case report

Bin Wu

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Abstract

BACKGROUND

Ulcerative colitis (UC), also known as chronic nonspecific UC, is an inflammatory bowel disease characterized by diffuse colonic mucosal inflammation. The incidence and prevalence of UC have risen markedly, and the disease seriously affects the quality of life of patients and imposes a great burden on the world health care infrastructure and economy.

CASE SUMMARY

Case I describes a 34-year-old female who came to see a doctor because of repeated abdominal pain, diarrhoea and purulent blood for 2 mo. This patient had UC with an initial onset, an active stage and a wide range of lesions. After the poor effect of sulfasalazine and mesalazine, the patient's condition gradually deteriorated, her abdominal pain and bloody stools continued, and anemia occurred. She began treatment with the Chinese medicine Guizhi Dahuang decoction, which was taken orally twice a day, 200 mL each time. After 6 mo of treatment, abdominal pain, diarrhoea, bloody stool and other symptoms disappeared. No abnormality was found by repeat electronic enteroscopye, and the anemia was corrected. The patient's condition did not recur after nearly 4 years of follow-up.

CONCLUSION

A series of symptoms in this UC patient significantly improved with the administration of traditional Chinese medicine.

Key Words: Traditional Chinese medicine; Ulcerative colitis; Complementary and alternative therapy; Gastroenterology; Clinical efficacy; Case report

Core Tip: We present a 34-year-old female with acute moderate to severe ulcerative colitis (UC) that lasted for 2 mo. Treatment with mesalazine failed. After treatment with Guizhi Dahuang decoction, her symptoms were relieved. At reexamination, there was no erosion, bleeding, ulcers or new organisms in the colonic mucosa. This result suggested that Guizhi Dahuang decoction might be an effective treatment method for patients with UC.

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INTRODUCTION

Ulcerative colitis (UC) is a continuous inflammatory intestinal disease characterized by abdominal pain, diarrhoea, mucinous bloody stool and other clinical manifestations, (often accompanied by extraintestinal manifestations at sites such as the bone, eye, skin, liver and gall bladder), mainly with damage to the mucosa and submucosa of the colon. It gradually spreads to the whole colon and may injure the ileocaecal portion. Genetic, immune, intestinal mucosal barrier function, environmental, psychological and other factors are considered to be involved in the pathogenesis of the disease. Which is difficult to cure, easily to recurring, clustered and regional. Studies have shown that more than 20% of patients with UC will develop inflammatory colon cancer, with a mortality rate of 50% within 30 years. The drugs used in the clinical treatment of UC mainly include aminosalicylic acid, sulfasalazine and corticosteroids, immunosuppressants and monoclonal antibodies. However, long-term or high-dose use of these drugs may lead to more serious adverse reactions, such as abdominal pain, kidney damage, hepatotoxicity and blood diseases[1,2].

The treatment of UC by traditional Chinese medicine (TCM) includes nondrug intervention and drug interventions. The nondrug intervention measures in the treatment of UC are mainly acupuncture intervention measures, including acupuncture, moxibustion, and acupuncture combined with moxibustion. The treatment of UC by TCM involves multiple signal transduction pathways, which show advantages in many aspects, such as reducing inflammation, regulating intestinal immune function, regulating intestinal flora, and repairing the intestinal mucosa, with few adverse reactions and good safety. This study provides a new method and option for the treatment of UC. The present patient had UC with an initial onset, an active stage and a wide range of lesions. Her medical history was not very long. The diagnosis by Western medicine was clear, and specialized treatment was carried out. However, the curative effect was not ideal. The patient's condition gradually deteriorated, abdominal pain and blood in the stool did not stop, anaemia gradually appeared, and she was transferred to Chinese medicine for treatment. It has been reported that Guizhi Dahuang decoction can be applied to treat various kinds of abdominal pain. Guizhi Dahuang decoction was applied to the patient as guided by the theory of TCM syndrome treatment. After 6 mo of treatment, the symptoms of abdominal pain, diarrhoea and bloody stool disappeared, and the anaemia was corrected. Importantly, the patient's condition did not recur after nearly 4 years of follow-up.

CASE PRESENTATION

Chief complaints

A 34-year-old female patient visited our hospital on March 13, 2018, with manifestations of abdominal pain and bloody mucopurulent diarrhoea for 2 mo.

History of present illness

Two months prior, the patient had experienced abdominal distension without obvious inducement; paroxysmal dull pain in the whole abdomen that was aggravated at night; bloody and, thin stool; approximately 3-4 times/day; reduced pain after defecation; chills; and fever, with a maximum temperature of 38 °C. On January 9, 2018, the patient attended the local hospital for a colonoscopy, which suggested UC (Figure 1). On January 22, 2018, the patient was hospitalized in the Department of Gastroenterology of the local hospital for paroxysmal abdominal pain, mainly on the left side, with bloody, sparse stool, approximately 5-6 times/day. She began to be treated with: Mesalazine sustained release granules combined with mesalazine (suppositories). After 1 wk, she improved and was discharged, thereafter continuing outpatient treatment for 5 wk. However, the patient's condition did not improve further. She produced sparse stool 1-2 times/day, and coffee-like stool, abdominal pain

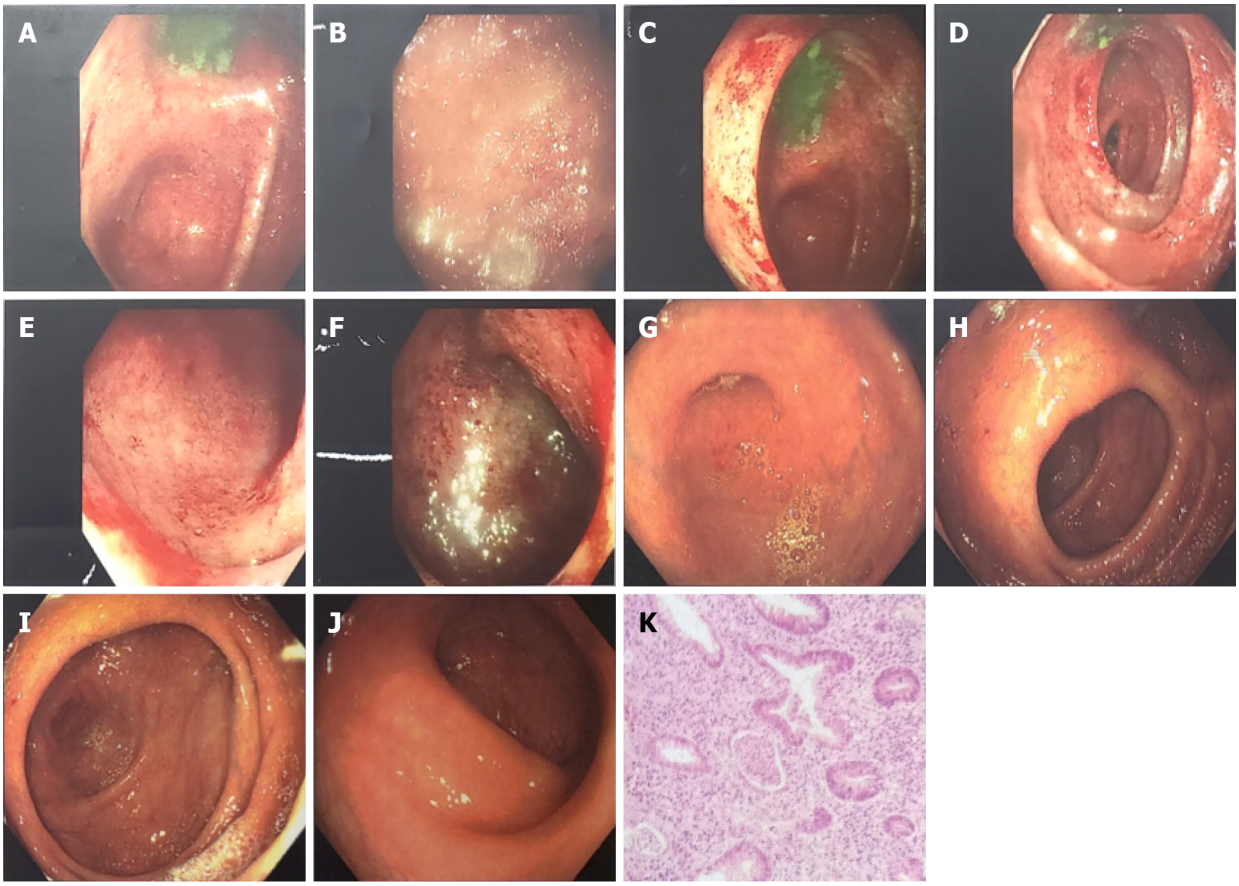

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Figure 1 Comparison of colonoscopy results before and after treatment. A-F: Before treatment (January 19, 2018): The mucosa of the whole colon and rectum was congested and edematous, showing patchy hemorrhagic foci, with purulent moss on the surface and partial erosion, of which the right colon and rectum were the most serious; G-J: After treatment (September 9, 2018): There was no hyperemia or swelling around the appendix, clear hyperemia or edema of the mucosa of the blind base and ascending colon, white mucus on the surface, erosion or bleeding, and no erosion or bleeding of the mucosa of the liver flexure, transverse colon, splenic flexure, descending colon and sigmoid colon, ulcers or new organisms were observed. The rectal mucosa was free of erosion, bleeding and new organisms; K: Pathological diagnosis: (Large intestine) mucosa acute and chronic inflammation with crypt abscess formation, consistent with ulcerative colorectal inflammation.

and abdominal distension were noted during defecation, accompanied by chills, night sweats, fatigue, poor appetite, and anaemia. Consequently, she came to the outpatient department of our hospital on March 13, 2018, to seek TCM treatment.

History of past illness

The patient had no previous medical history.

Physical examination

The patient's temperature was 37.0 °C, the heart rate was 78 beats/min, the respiratory rate was 18 breaths/min, and the blood pressure was 122/78 mmHg.

Laboratory examinations

Laboratory tests showed inflammation (73.4 mg/dL of C-reactive protein) and anaemia (9.7 g/dL of haemoglobin) at the time of visit. See Table 1 for further relevant results.

Imaging examinations

Colonoscopy results showed that the mucosa of the whole colon and rectum was congested and oedemtous, showing patchy haemorrhagic foci, with purulent moss on the surface and partial erosion; the right colon and rectum were the most seriously affected (Figure 1). Pathological diagnosis: Acute and chronic inflammation of the large intestinal mucosa with crypt abscess formation, consistent with ulcerative colorectal inflammation (Figure 1).

Table 1 Laboratory tests

Time	WBC (× 10^9/L)	RBC (× 10^{12}/L)	HGB (g/L)	PLT (10^9/L)	HCT (L/L)	ESR (mm/h)	CRP (mg/L)
January 23, 2018	4.6	3.53	107	237	0.496	24	7.8
March 8, 2018	5.6	3.23	97	334	0.300	/	73.4
November 4, 2018	6.9	4.55	139	258	0.310	/	21.1

Reference values: WBC: (3.5-9.5) × 10^9/L; RBC: (3.8-5.1) × 10^{12}/L; HGB: 115-150 g/L; PLT: (125-350) × 10^9/L; HCT: 0.114-0.282 L/L; ESR: 0.0-20.0 mm/h; CRP: 0-10 mg/L. WBC: White blood cell count; RBC: Red blood cell count; HGB: Hemoglobin; PLT: Platelets; HCT: Hematocrit; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

FINAL DIAGNOSIS

The final diagnosis was UC.

TREATMENT

Medical records are shown in Figure 2.

Guizhi Dahuang decoction was selected as the main prescription, which was administered through the whole treatment process. The main drug composition and dosage were Guizhi 9 g, fried white peony 18 g, liquorice 9 g, ginger 9 g, jujube 9 g, and rhubarb 3 g. The above prescription was a daily dosage, with approximately 600 mL of water added and approximately 300 mL of decoction taken orally twice. During the treatment period, appropriate flavouring was given according to different accompanying symptoms and signs of the patients. The dosage of medicine was prescribed for 7 d each time, and the total number of outpatient visits was 22. The whole treatment process lasted nearly 6 mo. During this period, some adjustments were made according to the specific situation of the patient at each follow-up visit. However, the drug composition of Guizhi Dahuang decoction was always maintained through the whole treatment.

During the treatment, the patient was encouraged to reduce the intake of spicy and stimulating food.

OUTCOME AND FOLLOW-UP

The patient was treated with TCM for approximately 6 mo. On September 7, 2018, reexamination of electronic colonoscopy showed that the mucosa of the colon liver flexure, transverse colon, splenic flexure, descending colon and sigmoid colon was free of erosion, bleeding, ulcers and new organisms. The rectal mucosa was also free of erosion, bleeding and new organisms.

Follow-up was carried out 2 mo after the treatment. The patient was generally in good condition, without abdominal pain, diarrhoea or purulent bloody stool. See Table 1 for laboratory inspection and Table 2 for clinical evaluation.

The patient was followed up again 4 years after the treatment. She was generally in good condition, without abdominal pain, diarrhoea, pus or bloody stool. See Table 2 for the clinical evaluation.

DISCUSSION

UC is a continuous inflammatory intestinal disease characterized by abdominal pain, diarrhoea, mucinous bloody stool and other clinical manifestations, often accompanied by extraintestinal manifestations at sites such as the bone, eye, skin, liver and gall bladder, mainly damaging the mucosa and submucosa of the colon. It gradually spreads to the whole colon and may injure the ileocaecal portion[3-5]. Genetic, immune, intestinal mucosal barrier function, environmental, psychological and other factors are considered to be involced in the pathogenesis of the disease[6-8]. UC is difficult to cure, easily to recurring, clustered and regional. Studies have shown that more than 20% of UC patients will develop inflammatory colon cancer, with a mortality rate of 50% within 30 years[9,10].

UC belongs to the category of "dysentery" and "intestinal bleeding" in TCM[11]. The treatment of UC by TCM includes nondrug intervention measures and drug intervention measures. Nondrug intervention measures in the treatment of UC mainly include acupuncture, moxibustion, and acupuncture combined with moxibustion. The drug intervention measures mainly include oral Chinese herbal medicine administration, enemas or oral Chinese herbal medicine combined with enemas. The mechanism of Chinese herbal medicine for the treatment of UC involves multiple signal transduction

Table 2 Disease condition assessment

Time	IBDQ (score)	Mayo (score)
Visit 1	83	11
Visit 2	159	/
Visit 3	177	/
Visit 4	191	/
Visit 5	207	0
Visit 6	208	/

Inflammatory Bowel Disease Questionnaire scores reflects the quality of life for nearly two weeks in patients with inflammatory bowel disease, including systemic symptoms, intestinal symptoms, social competence, and emotional competence. There are 32 questions, each with a different answer, 1 for the most severe and 7 for the least severe. Lower the total scores more severe disease. Mayo scores: The Mayo scoring system is used to assess ulcerative colitis activity. A total score less than 2 points indicates symptom relief, 3-5 points indicates mild relief, 6-10 points indicates moderate activity, and 11-12 points indicates severe activity. IBDQ: Inflammatory Bowel Disease Questionnaire.

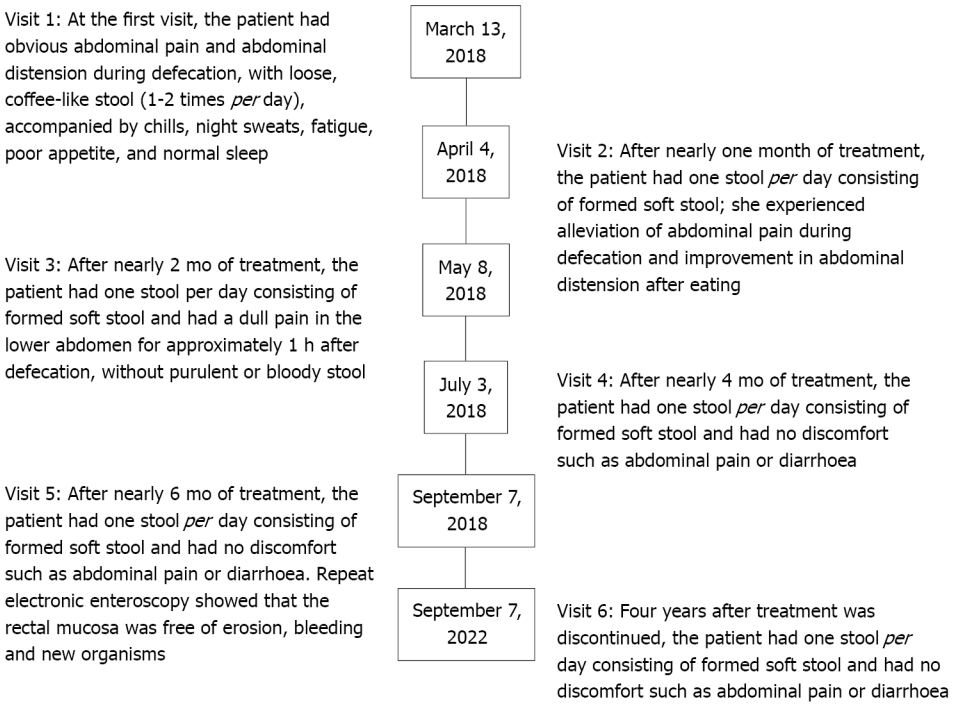

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Figure 2 Description of the medical records.

pathways, showing advantages in many aspects, such as reducing inflammation, regulating intestinal immune function, regulating intestinal flora, and repairing the intestinal mucosa, with few adverse reactions and good safety. It provides a new method and outlook for the treatment of UC[12-14]. Guizhi Dahuang decoction is derived from the treatise on febrile diseases written by Zhang Zhongjing in the Eastern Han Dynasty. According to the theoretical guidance of that book, Guizhi Dahuang decoction can be applied to patients with symptoms of weakness accompanied by abdominal fullness, abdominal pain and diarrhoea. Guizhi Dahuang decoction is composed of Guizhi decoction and rhubarb, and increases the amount of Paeonia in the prescription. There are many studies on Guizhi decoction. Modern pharmacological studies have shown that Guizhi decoction has regulating effects on body temperature, sweat gland secretion, blood pressure, immune function and gastrointestinal movement and has anti-inflammatory, antibacterial, antiviral, hypoglycaemic and cardiovascular protective effects [15]. Total glucosides of paeony (TGP) is the main component of the largest amount of paeony in the formula. More than 90% of the active substances in TGP are paeoniflorin[16]. It has been proposed that TGP and paeoniflorin may exert their immune effects in UC by reducing the accumulation of indole-3-lactic acid in the colon of mice with enteritis and restoring the imbalance of intestinal microbiota in mice with UC[17].The pharmacological effects of rhubarb include diarrhoea, antibacterial, anti-inflammatory,

and antitumor actions; improved renal function; cholagogic, liver-protecting, diuretic, and anticoagulant activities; scavenging of oxygen free radicals; immune regulation; and other functions[18]. As the main component of rhubarb, rhein can significantly alleviate dextran sulfate sodium induced chronic colitis by reducing the level of uric acid and regulating intestinal microbiota[19]. Guizhi Dahuang decoction is used to treat various kinds of abdominal pain, such as non ulcer dyspepsia and irritable bowel syndrome[20]. Although the components of Guizhi Dahuang decoction are complex, and its mechanism of action may involve multiple components and targets, so the pharmacology of a single TCM is not enough to explain the specific mechanism of Guizhi Dahuang decoction in the treatment of UC. However, the above findings combined with previous relevant literature reports lead the author to consider Guizhi Dahuang decoction as playing a role in UC treatment by reducing the inflammatory response, regulating intestinal flora imbalance, and other mechanisms.

This case involved a patient with UC exhibiting with an initial onset, an active stage and a wide range of lesions. After 2 mo of conventional Western medicine treatment, the effect was not ideal, and the condition showed a tendency toward gradual worsening. Abdominal pain and bloody stools were persistent, and there was also secondary aneamia. After 6 mo of the conventional treatment, the patient began to apply Guizhi Dahuang decoction. After 6 mo of further treatment, the abdominal pain, diarrhoea, bloody stools and other symptoms of the patient disappeared. Analysis by electronic colonoscopy showed that there were no obvious abnormalities, and the anaemia was also corrected.

UC has a long course and easily recurs. Therefore, long-term medication is needed to control the disease. The drugs used in the clinical treatment of UC mainly include aminosalicylic acid, sulfasalazine and corticosteroids, immunosuppressants and monoclonal antibodies. However, long-term or high-dose use of these drugs may lead to more serious adverse reactions, such as abdominal pain, kidney damage, hepatotoxicity and blood diseases. After 6 mo of TCM treatment, the patient did not have any adverse reactions. After 4 years of follow-up, it was confirmed that she did not have any symptoms of abdominal pain, diarrhoea or bloody stools and that her general condition was good. Compared with treatment by Western medicine, the advantages of TCM, such as safety and stable efficacy, were once again demonstrated[21-23].

The success of this patient's treatment suggests to us the following: (1) Although the theoretical system of TCM emphasizing personalized treatment is ancient, it can still solve clinical problems in the new era; and (2) Guizhi Dahuang decoction has the potential to treat UC. In addition, relevant studies in the early stage have shown that TCM treatment measures have positive effects in improving the antioxidation capacity of colon tissue, improving the intestinal flora of patients with UC, regulating the bodyily and intestinal immune function, inhibiting the infiltration of inflammatory cells, promoting the health of intestinal function, and alleviating the clinical symptoms of patients with UC; however, the long-term effects are still uncertain[24,25]. This case seems to suggest that the long-term efficacy of Chinese medicine in treating UC may be better than expected.

However, it is difficult to apply universal significance to a single case. The mechanism of Guizhi Dahuang decoction in treating acute UC is not clear. It is hoped that the mechanism of Guizhi Dahuang decoction in the treatment of UC can be explored in the future through randomized, double-blind, long-term, multicenter research and the application of new pharmacological technology to bring more effective, safer and more economical treatment options to patients with UC.

CONCLUSION

A series of symptoms in this UC patient significantly improved following Guizhi Dahuang decoction treatment.

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FOOTNOTES

Author contributions: Wu B is the only author.

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CASE REPORT

Solitary hyoid plasmacytoma with unicentric Castleman disease: A case report and review of literature

Yan-Hui Zhang, Yi-Feng He, Hao Yue, Yue-Ni Zhang, Lei Shi, Bin Jin, Pin Dong

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Abstract

BACKGROUND

Solitary plasmacytoma and unicentric Castleman disease (UCD) are rare lymphoproliferative disorders characterized by monoclonal plasma cells and a single set of locally enlarged lymph nodes, respectively.

CASE SUMMARY

A 48-year-old Han Chinese man presented to our department with a neck mass and progressive foreign body sensation in his throat. ^{18}F-FDG positron emission tomography revealed focally increased radioactivity centered around the hyoid, and computed tomography (CT) revealed osteolytic lesions. Histopathology revealed Castleman-like features and CD138/CD38-positive mature plasma cells. Systemic work-up ruled out the possibility of POEMS syndrome, lymphoma, and multiple myeloma, leading to a final diagnosis of solitary hyoid plasmacytoma with UCD. The patient underwent partial hyoid resection and selective neck dissection, followed by intensity-modulated radiotherapy. 99mTc-MDP single-photon emission computed tomography/CT reevaluation showed neither local recurrence nor distant bone metastasis at the 40-mo follow-up.

CONCLUSION

The diagnostic process and differential diagnosis of this rare case provided

valuable educational information to clinicians.

Key Words: ^{18}F-FDG; Positron emission tomography/computed tomography; Plasmacytoma; Hyoid bone; Castleman disease; Case report

Core Tip: In this study, we described the clinical presentations, diagnosis and differential diagnosis, management, outcome, and relative long-term follow-up for a man simultaneously affected with solitary plasmacytoma (SP) of the hyoid bone and unicentric Castleman disease. To our knowledge, this is the first reported case presented with these two rare clinical entities. Besides the comprehensive histopathological examination, ^{18}F-FDG positron emission tomography/computed tomography (CT) and 99mTc-MDP single-photon emission computed tomography (SPECT)/CT were broadly used in our clinical practice of differential diagnosis, disease staging, and follow-up monitoring, highlighting the advantages of nuclear medicine and other imaging techniques in the management of SP in the head and neck. Additionally, the diagnostic process and differential diagnosis of this patient provided valuable educational information to clinicians.

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INTRODUCTION

Solitary plasmacytoma (SP) is a rare disease characterized by abnormal proliferation of monoclonal plasma cells, with a cumulative incidence of 0.15/100000[1,2]. Solitary bone plasmacytoma (SBP) is a subtype of SP that occurs primarily in the red-marrow-containing axial skeleton and long bones[3] and accounts for 70% of all SP cases[1]. SBP with minimal (< 10%) bone marrow plasma cells progresses to multiple myeloma (MM) within 3 years in approximately 60% of patients[2,4]. All SP are radiation-sensitive; therefore, radiotherapy (RT) is recommended as the first-line treatment strategy for the long-term disease control in these patients[3,5].

Unicentric Castleman disease (UCD) is a rare lymphoproliferative disorder with unknown prevalence and belongs to a heterogeneous group of conditions characterized by similar histopathological features but has distinct pathological etiologies, clinical symptoms, management, and outcomes[6,7]. For patients with resectable UCD, complete surgical excision is the optimal first-line treatment, with a 5-year overall survival of up to 90%; even after a 10-year follow-up, disease relapse is rare[6,8].

Here, we report the case of a 48-year-old man with SBP of the hyoid and UCD along with the clinical diagnosis, management process, and follow-up. Moreover, we reviewed the literature of related SBP cases to provide a comparative experience in guiding the management of this rare disease.

CASE PRESENTATION

Chief complaints

A 48-year-old Han Chinese man presented with a neck mass and progressive foreign body sensation in his throat.

History of present illness

The patient reported no sore throat, dyspnea, or dysphagia during the course of the disease.

History of past illness

The patient had no history of past illness.

Personal and family history

The patient had no personal or family history.

Physical examination

Basic physical examination showed no obvious abnormalities.

Laboratory examinations

Laboratory tests showed that the routine blood and urine results as well as blood biochemical indices, including serum calcium-albumin-creatinine, blood urea nitrogen, lactate dehydrogenase, β2-microglobulin, and 24-hour urine for total protein, moreover, the results of serum immunoglobulin and complement assay (Supplementary Table 1), were all within normal limits.

Imaging examinations

Electronic laryngoscopy and plain computed tomography (CT) showed thickening of the left epiglottis (Figure 1A and C), arytenoid and aryepiglottic folds (Figure 1B and D), osteolytic lesions of the left hyoid (Figure 1E), and thyroid cartilage plate (Figure 1F). The left piriform fossa was occluded, and enlarged cervical and submandibular lymph nodes were observed bilaterally. The patient underwent selective neck dissection and partial hyoid resection to relieve neck compression, and a final diagnosis was made. ^{18}F-FDG positron emission tomography (PET)/CT revealed focally increased radioactivity centered around the hyoid body and its left greater horn (SUV_{max} = 8.8) and the left submandibular and submental soft tissue (SUV_{max} = 4.8) exhibited on PET (Figure 1G-I), CT (Figure 1J-L), and PET/CT fusion (Figure 1M-O). Osteolytic lesions were identified on the plain CT bone window. PET maximum-intensity projection image (Figure 1P) showed no other sites with abnormal ^{18}F-FDG uptake, except for the perihyoid region. These findings were suggestive of a malignancy.

Further diagnostic work-up

Histological results revealed angiofollicular lymph node hyperplasia of the hyaline-vascular type arranged in an onion-bulb appearance (Figure 2A and B, 200 × and 400 ×), and the presence of mature plasma cells characterized by an oval shape, abundant basophilic cytoplasm, perinuclear halo, round eccentric nuclei, and indiscernible nucleoli[6,7,9] (Figure 2C and D, 200 × and 400 ×). Histopathological results were positive for plasma cell markers [CD138 (Figure 2E), CD38 (Figure 2F), κ (Figure 2G) and λ (Figure 2H) light chains, CD79α (Figure 2I), IgG, IgM], and focal expression of T-cell markers [CD43 (Figure 2J), CD45], and CD56; however, deficiency of B-cell markers [CD20 (Figure 2K), CD19] was observed. The Ki-67 proliferation index was 3% (Figure 2L). No paraproteins and pathological elevation of κ and λ chains were detected by the serum protein electrophoresis and free light-chain assays[4,10]. Bone marrow biopsy indicated normal trilineage hematopoiesis with only 0.2% plasma cells in all leukocytes[4]. Additionally, polyneuropathy and other minor symptoms were absent.

FINAL DIAGNOSIS

Systemic work-up ruled out the possibility of POEMS syndrome, lymphoma, and MM[4,11,12], thus leading to the diagnosis of SP of the hyoid, with UCD. Inflammatory factors, such as TNFα, IL-6, IL1β, TGFβ1, and VEGFα (Supplementary Figure 1), were increased, confirming the multiple cytokine-producing property of SBP[13,14].

TREATMENT

The patient underwent intensity-modulated RT[5] for the hyoid bone and high-risk subclinical areas, with a total dose of 50.4 Gy, divided into 28 fractions[10].

OUTCOME AND FOLLOW-UP

No acute toxicity was observed during RT. After 3 mo, contrast-enhanced CT revealed a slightly shrunken tumor boundary. The patient underwent CT and ^{18}F-FDG PET/CT or 99mTc-MDP single-photon emission computed tomography (SPECT)/CT examinations at 6 and 12 mo, respectively. Recent 99mTc-MDP SPECT/CT reevaluation showed a slight increase in radioactivity around the hyoid, considering postoperative changes rather than local recurrence on SPECT (Figure 3A), CT (Figure 3B), and SPECT/CT fusion (Figure 3C). Focal bone destruction and secondary hyperosteogeny were also observed in the CT bone window (Figure 3D). Whole-body SPECT revealed no evidence of distant bone metastasis (Figure 3E and F). The patient was symptomatic and progression-free at the 40-mo follow-up visit.

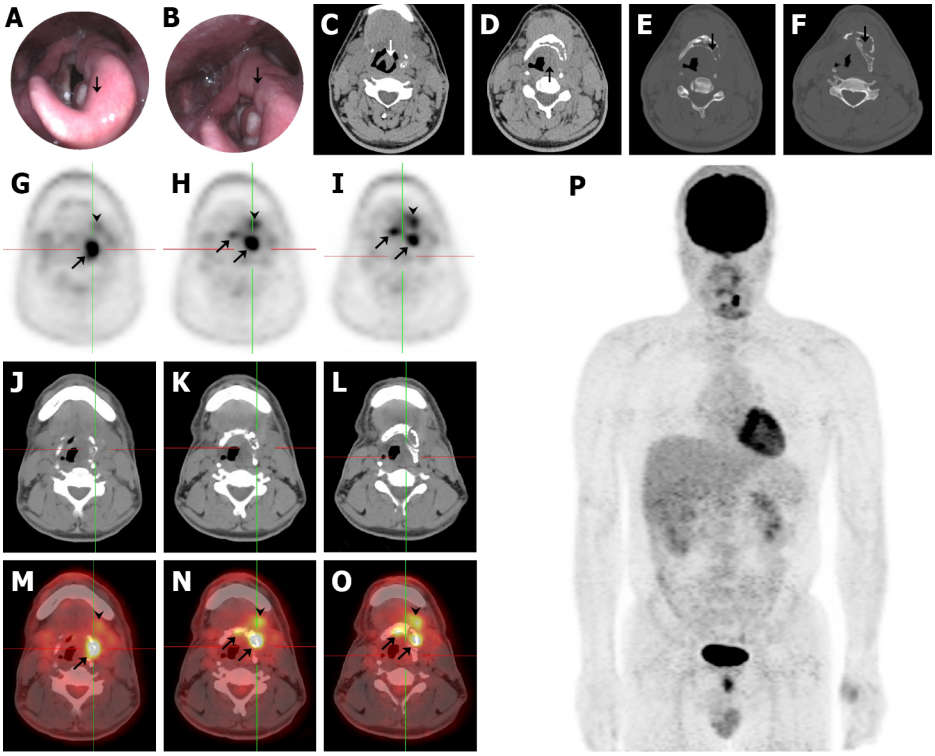

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Figure 1 Imaging findings during initial admission. A and C: Thickening of the left epiglottis; B and D: Arytenoid and aryepiglottic fold; E: Osteolytic lesions of the left hyoid; F: Thyroid cartilage plate; G-I: ^{18}F-FDG centered around the hyoid body and its left greater horn (SUV_{max} = 8.8), and left submandibular and submental soft tissue (SUV_{max} = 4.8) exhibited on positron emission tomography (PET); J-L: Computed tomography (CT); M-O: PET/CT fusion; and P: PET maximum-intensity projection image demonstrated no other sites with abnormal ^{18}F-FDG uptake.

DISCUSSION

Plasma cell disease comprises a heterogeneous group of disorders characterized by an increase in the number of monoclonal plasma cells[4]. Abnormally proliferative cells can secrete a large quantity of monoclonal immunoglobulin and invade and damage various tissues or organs, such as the bones, bone marrow, kidneys, hearts, lungs, and immune system. Precision clinical intervention is needed for the accurate diagnosis of these diseases. In the present study, the histology of the neck mass showed Castleman's lesion, such as vitreous degeneration with an "onion skin" appearance, and monoclonal proliferation of plasma cells, resembling the typical features of CD variant of POEMS syndrome. However, the patient did not meet the other major or minor criteria required for a definite diagnosis of POEMS syndrome or MM[4,11,12]; therefore, led to a final diagnosed with SBP of the hyoid and UCD. The National Comprehensive Cancer Network recommends using primary RT of a total dose of 40–50 Gy in 1.8–2.0 Gy per fraction over 4 wk, for patients with SP in whom the surgery is depended on clinical necessity[10]; in addition, for patients with UCD, excisional surgery is the optimal strategy with the benefit of long-term disease control[6,8]. The patient received intensity-modulated RT according to the guidelines after extended dissection of the neoplastic mass adjoining the primary lesion.

The hyoid bone is an atypical location and is extremely rare for the growth of SP; to the best of our knowledge, only three cases have been reported[15-17]. Goel *et al*[15] presented the first case treated with local RT followed by chemotherapy, and the hyoid swelling was significantly reduced in size during the 18-mo follow-up. Danaci *et al*[16] described the second case of a 60-year-old man. This patient underwent total excision of the hyoid mass but was not subsequently treated with RT or chemotherapy, and was alive and progression-free during the 24-mo follow-up period[16]. The third patient was diagnosed with non-secretory MM stage IIIA and presented with plasma cell infiltration into the hyoid bone. This patient received chemotherapy and anti-hypercalcemic therapy; however, the prognosis was not referred to in the report[17].

SP can be divided into SBP and solitary extramedullary plasmacytoma based on its origin from the bone marrow or soft tissue organs[4]. Abnormal monoclonal plasma cells and bone marrow stromal cells (BMSCs) in SBP strongly express multiple cytokines and their corresponding receptors that promote the growth and survival of tumor cells or angiogenesis through autocrine and paracrine mechanisms[13,14]. Plasma cell-derived matrix metalloproteinases participate in the degradation of the extracellular matrix and basement membrane, leading to chronic inflammation and bone-destructive lesions[18]. Abnormal plasma cells also induce local angiogenesis and stimulate neovascularization

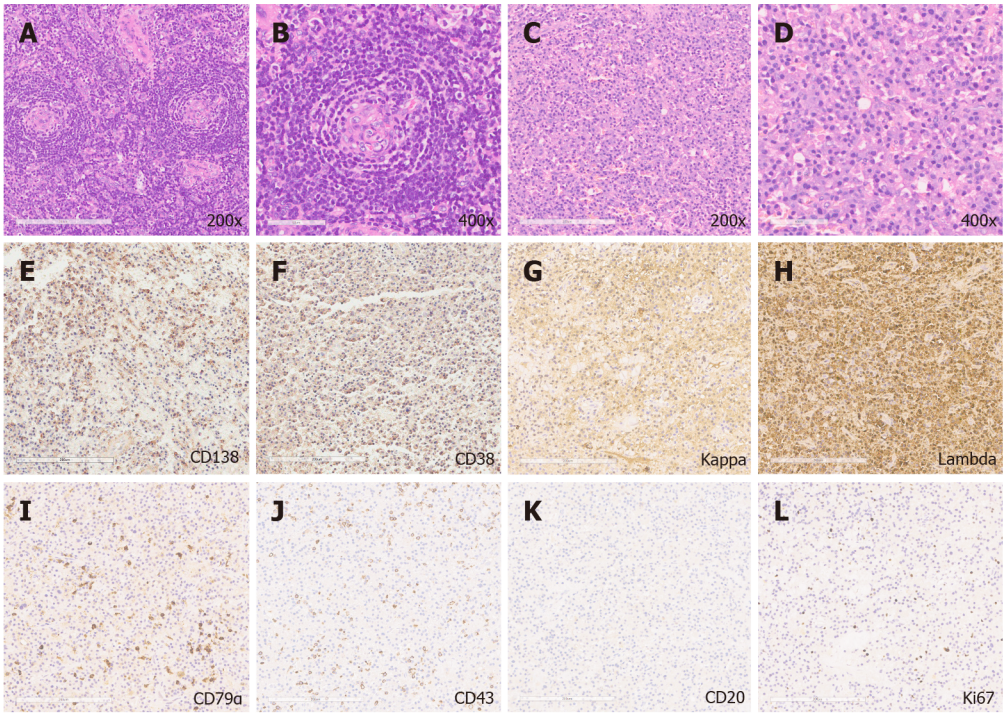

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Figure 2 Histopathological and immunohistochemical analysis. A and B: Hematoxylin and eosin staining revealed angiofollicular lymph node hyperplasia (200 × and 400 ×); C and D: The presence of mature plasma cells (200 × and 400 ×); E-J: Positive immunohistochemical staining for plasma cell markers: CD138, CD38, κ light chains, λ light chains, CD79α, T-cell marker CD43; K: Negative staining for B-cell marker CD20; and L: The Ki-67 positive staining.

depending on secreted cytokines, such as ANG-1, CXCL12, and VEGFα, which supply nutrition for tumor cell growth[19-21]. Cytokine homeostasis, particularly that secreted by BMSCs, acts as a regulatory mechanism for tumor growth[22]. Some reports indicate that aberrant activation of gp130-dependent and Notch signaling may provide strong advantages for the growth of plasmacytomas[19,23-25]. CD and POEMS syndrome are also associated with the elevation of several classical cytokines in serum, such as IL-6, VEGFα, TNFα, IL1β, and TGFβ1 secreted by proinflammatory cells, as found in SBP. CD and SP can present independently, concurrently, or sequentially with POEMS[26-28]. Patients with CD and/or POEMS syndrome usually have an upregulation of serum VEGFα and IL-6 mediated cytokine storm, which might impair cerebral vessels, resulting in vasculopathy of the central nervous system and an increased risk of cerebral infarction[26,29,30].

Recently, with the development of high-throughput sequencing technology, genetic analyses have been broadly applied to reveal the molecular mechanisms of UCD and idiopathic multicentric Castleman disease (iMCD)[31-35]. Overall, two recurrent hotspot somatic mutations, *PDGFRB* (NM_002609.4, c.1997A > G, p.N666S) and *NCOA4* (NM_005437.4, c.781 > T, p.L261F), were identified in 17% and 18% of the tested UCD and iMCD cases, respectively[33,34]. In a patient with iMCD accompanied by severe peripheral neuropathy, somatic alterations were identified in genes related to neuronal development, such as *PDLIM5*, *SEC24B*, *ZFHX3*, and *PACRG*[36]. Another patient harbored a somatic *JAK1* missense mutation, but normal serum IL-6 had a complete response rate to the IL-6 antibody siltuximab, implicating the essential roles of the IL-6/IL-6R/JAK1/STAT pathway and its mutations in the pathogenesis of iMCD[37]. Somatic mutations were prone to enrichment in the mitogen-activated protein kinase and interleukin pathways in UCD and iMCD; however, genes affecting chromatin remodeling were solely enriched in iMCD[38]. Moreover, patients with iMCD have a high prevalence of germline *MEFV* variants that modify their clinical phenotypes and treatment responses[39,40]. Transcriptome profiling also revealed that UCD and MCD are involved in unique genes, pathways, and cell types[35].

^{18}F-FDG PET/CT exhibits superior sensitivity and specificity for SBP lesions. It can detect minimal residual disease inside and outside the bone marrow at the same time in one examination, which cannot be identified by χ-ray and magnetic resonance imaging[41,42]. In the early stages of patients with SBP after RT, ^{18}F-FDG PET/CT performs poorly in disease staging; however, a high SUV_{max} value is a regular prognostic indicator for progression[43]. 99mTc-MDP scintigraphy shows a relatively low sensitivity to detect bone lesions of SBP due to the suppressed differentiation of osteoblasts[44] and can be more applicable for evaluating the complications of SBP[45]. 99mTc-MIBI scintigraphy shows the same sensitivity and specificity as ^{18}F-FDG PET/CT in the detection of SBP lesions[46] and even better performance in the detection of diffuse bone marrow involvement, but it is inefficient in the detection of focal lesions[47]. ^{18}F-FDG PET/CT has the ability to simultaneously collect anatomical structure and

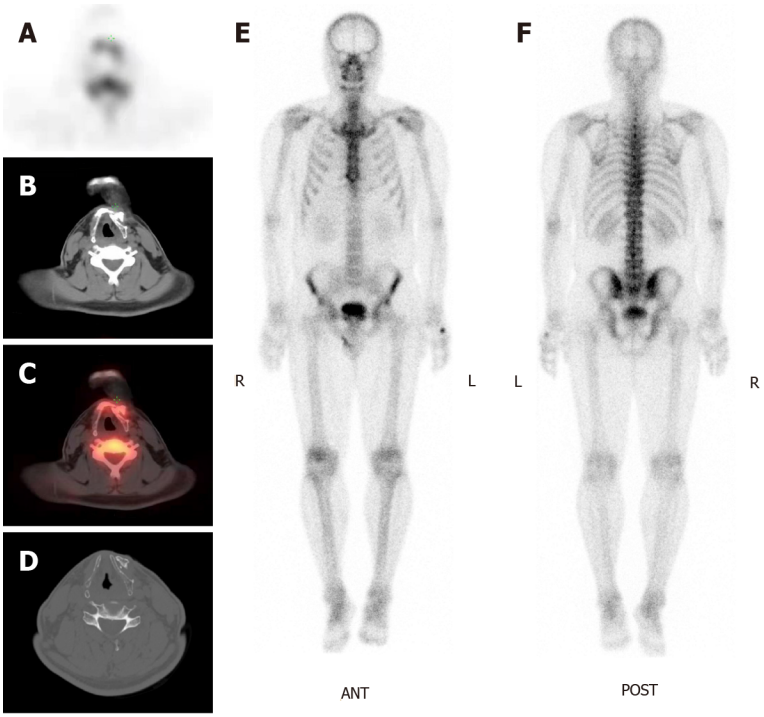

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Figure 3 Molecular imaging in the evaluation of local recurrence and ectopic metastasis during follow-up. A-C: 99mTc-MDP radioactivity around the hyoid exhibited on single-photon emission computed tomography (SPECT), computed tomography (CT), and SPECT/CT fusion; D: Focal bone destruction and secondary hyperosteogeny exhibited on CT bone window; E and F: No evidence of distant bone metastasis on whole-body SPECT.

metabolic information and can be used for the initial staging and response monitoring of CD[48]. It has high specificity and sensitivity for the identification of lymph node lesions in patients with CD[49] and is an important imaging marker for judging the severity and prognosis of the disease. A variety of metabolic parameters in ^{18}F-FDG PET/CT, including SUV_{max}, SUV_{mean}, SUV_{peak}, metabolic tumor volume, and total lesion glycolysis, can be used for the differential diagnosis of UCD and other diseases[50].

CONCLUSION

To our knowledge, this is the first reported case presented with these two rare clinical entities (SP of the hyoid bone and UCD). In addition to comprehensive histopathological analysis, ^{18}F-FDG PET/CT and 99mTc-MDP SPECT/CT are routinely used in the clinical practice of differential diagnosis, disease staging, and follow-up monitoring, highlighting the advantages of nuclear medical and other imaging techniques in the management of SP in the head and neck. In addition, the diagnostic and management processes provided valuable educational information to clinicians.

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FOOTNOTES

Author contributions: Shi L, Zhang YH and Zhang YN wrote this report; Jin B and Dong P reviewed and revised the manuscript; Zhang YH and Jin B involved in the clinical treatment and follow-up of the patient; Yue H, He YF, Zhang YN and Shi L interpreted the histopathology and radiology; and all authors had made a substantial contribution to this work and approved it for publication.

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CASE REPORT

Recurrence of intratendinous ganglion due to incomplete excision of satellite lesion in the extensor digitorum brevis tendon: A case report

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Abstract

BACKGROUND

Intratendious ganglions are rare lesions, especially on the foot and ankle. Although several studies have presented the intratendinous ganglion of the foot and ankle, there are only few reported cases, and no cases of recurrence or secondary surgery have been reported.

CASE SUMMARY

We present the case of a 32-year-old man with an intratendinous ganglion of the second extensor digitorum brevis (EDB) tendon that recurred after ganglion excision. Magnetic resonance imaging (MRI) performed before the first surgery was reviewed to analyze the causes of the recurrence. We confirmed that there was a lack of satellite detection. After recurrence, MRI revealed an extra-tendinous lesion, tenosynovitis, and intratendinous ganglion of the second EDB tendon. Since the second EDB tendon can compensate for the extrinsic muscle, *en bloc* resection was performed alone. In addition, meticulous excision and synovectomy were performed for extra-tendinous lesions and tenosynovitis, respectively. The patient returned to daily life without any functional problems or recurrence.

CONCLUSION

If removal of the affected tendon is not fatal, *en bloc* resection should first be considered to prevent incomplete excision and intraoperative leakage. When planning surgical excision, it is necessary to evaluate the presence of satellite lesions along the course of the affected tendon.

Key Words: Intratendinous ganglion; Recurrence; Surgical excision; *En bloc* resection; Case report

Core Tip: Intratendinous ganglion is rare, especially foot and ankle lesions. Surgical treatment should be considered for patients with persistent pain, nerve compression, tendon dysfunction, or recurrence after conservative treatments. Surgical methods include excision of the ganglion and *en bloc* resection. Surgical excision of the ganglion has the advantage of preserving tendon function, but the risk of recurrence due to incomplete excision is high. In addition, failure of complete excision can lead to more severe clinical features with extra-tendinous lesions and tenosynovitis. Therefore, if loss of function of the affected tendon does not cause significant functional impairment, *en bloc* resection may be considered first.

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INTRODUCTION

Ganglions are common benign tumor-like lesions caused by mucoid degeneration of connective tissues, including the joint capsule, tendon sheath, and tendon[1-4]. They were classified according to their sites of origin. Among these, the intratendinous ganglion, which occurs in the tendon substance, is the rarest [2,4,5]. Most intratendinous ganglions reported so far have been found in the extensor tendons of the wrist or hand[2,6-8]. An intratendinous ganglion on the foot or ankle is an even rarer disease, with few reported cases[9,10]. The etiology of intratendinous ganglions remains unclear. One possibility, based on the fact that tenosynovitis or associated tendon tears are commonly found around ganglion cysts, is the recurrent injury to the tendon with subsequent cystic degeneration[1]. Congenital anomalies may be present in patients with no history of trauma or sprains in the affected areas[3]. Intratendinous ganglions cause soft tissue swelling as well as symptoms such as pain and neuropathy[11-14].

An intratendinous ganglion can be treated using one of several methods, including aspiration, surgical excision, and *en bloc* resection of the entire affected tendon. Aspiration is a straightforward method; however, it has a high recurrence rate of approximately 50%-70%, which makes it less preferred as a treatment option[12,14]. Surgical treatment should be considered for patients with persistent pain, nerve compression, tendon dysfunction, or recurrence after more conservative treatments[11,15]. Surgical methods include excision of the ganglion and *en bloc* resection, with or without an additional procedure[8-10]. Although surgical excision can preserve tendon function, a risk of recurrence remains due to intraoperative leakage and incomplete resection of the ganglion[3]. However, *en bloc* resection of the affected tendon exerts a low risk of recurrence and can result in functional restrictions and deformities[10]. Therefore, additional procedures such as tenodesis and tendon transfer may be required[2,9,10]. The distinct advantages and disadvantages of each method make it clinically vital to decide which approach should be used for the primary treatment. In addition, for cases of recurrence, it is important to identify the cause and plan for secondary surgery.

To the best of our knowledge, there have been no reports on assessing the recurrence of intratendinous ganglions of the foot and ankle after excision and the results of secondary surgeries. We report a case of an intratendinous ganglion in the second extensor digitorum brevis (EDB) tendon that recurred after excision of the ganglion alone, with successful secondary treatment by *en bloc* resection of the entire tendon.

CASE PRESENTATION

Chief complaints

A 32-year-old Korean man presented to the orthopaedic clinic with a complaint of a painful mass on the dorsum of the right foot for 3 wk.

History of present illness

Symptoms started 3 wk prior to presentation and gradually worsened.

History of past illness

The patient with a painful mass on the dorsum of the right foot was diagnosed with intratendinous ganglion in the second EDB tendon at a local hospital. Open excision of the ganglion with tendon repair was subsequently performed. Histological examination of the tissue confirmed the diagnosis of intratendinous ganglion. Approximately 3 mo after surgery, the mass lesion recurred, and the patient was admitted to our hospital.

Personal and family history

The patient had no relevant family medical history.

Physical examination

The patient had no history of trauma to the affected area. Physical examination revealed a surgical scar on the dorsum of the right forefoot between the second and third rays. A palpable mass approximately 5 cm × 4 cm in size was found around the scar and was accompanied by slight tenderness. The range of motion of his toes was unrestricted.

Laboratory examinations

The results of the routine blood and urine tests, blood biochemistry, and immune and infection indices were normal.

Imaging examinations

Plain radiographs showed a slight enlargement of the soft tissue and no bony abnormalities. Magnetic resonance imaging (MRI) revealed multiple lobulated cystic lesions within and above the second EDB tendon, identified by regions of high signal intensity on a fat-saturated T2-weighted image (Figure 1A) and low signal intensity on a T1-weighted image (Figure 1B). Extensive tenosynovitis was observed around the ganglion cyst (Figure 2).

FURTHER DIAGNOSTIC WORK-UP

We diagnosed this as recurrence after open excision of the intratendinous ganglion. MRI scans taken before the first surgery were reviewed to understand the cause of recurrence. A previous MRI scan showed no lesions, except for a cystic lesion inside the second EDB tendon, with no indications of tenosynovitis in fat-saturated T2-weighted sagittal (Figure 3A) and axial (Figure 3B) images. However, a lesion with high signal intensity was observed at the proximal portion of the second EDB tendon before attachment to the calcaneus (Figure 4).

FINAL DIAGNOSIS

We concluded that incomplete resection was performed, mainly because of the failure to detect the satellite lesion located in the proximal portion of the second EDB tendon. In addition, contamination was thought to have occurred following intraoperative leakage during open excision, which in turn caused extra-tendinous lesions and tenosynovitis.

TREATMENT

Considering the presence of multiple ganglion cysts in the entire tendon from the proximal to the distal end, *en bloc* resection was planned to prevent a recurrence. As the EDB tendon can be compensated for by an extrinsic muscle, tendon transfer was not planned. Additionally, meticulous excision of the extra-tendinous ganglion and synovectomy were planned.

Under epidural anesthesia, the patient was placed in the prone position with a tourniquet applied to the ipsilateral thigh. The procedure was performed by extending a previous longitudinal incision. Extratendinous ganglions and tenosynovitis were observed in the extensor tendons (Figure 5). After the excision of the extra-tendinous ganglions, the second EDB tendon was found to have an enlarged spindle shape (Figure 6). Bulbous satellite lesions were observed in the proximal portion of the tendon (Figure 7A), and a colorless jelly-like content was found inside the cysts when incised (Figure 7B). Following the extension of the incision to the anterior process of the calcaneus, remnant tendon removal and electrocauterization were performed. (Figure 8). The second metatarsophalangeal joint capsule was then removed to prevent a recurrence.

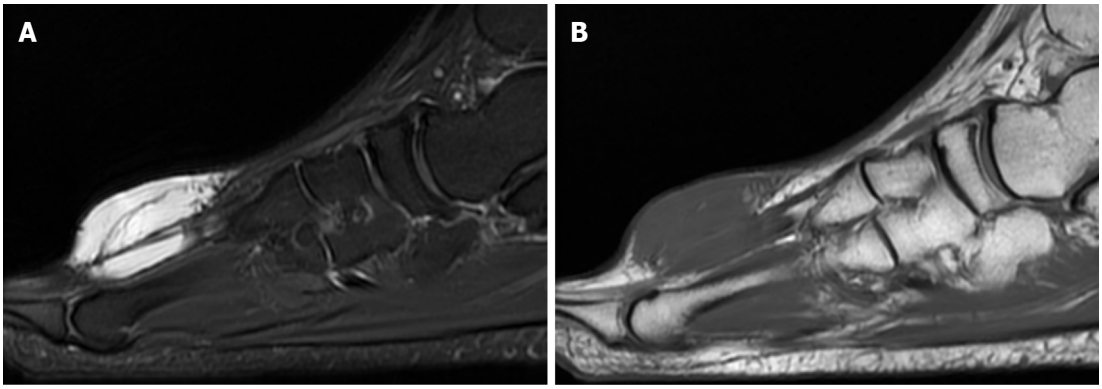

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Figure 1 Multiple lobulated cystic lesions within and above the second extensor digitorum brevis tendon. A: Fat-saturation T2-weighted image; B: Fat-saturation T1-weighted image.

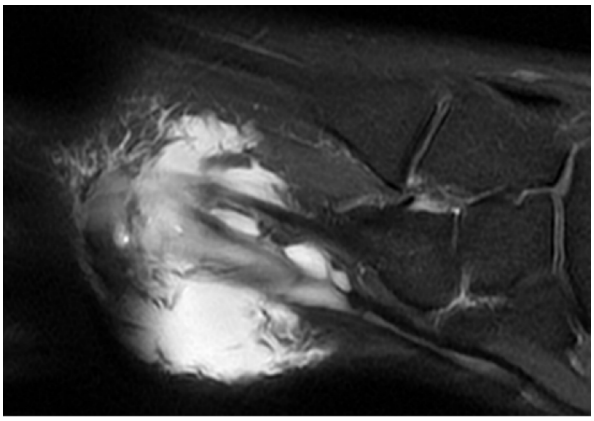

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Figure 2 Extensive tenosynovitis around the ganglion cysts.

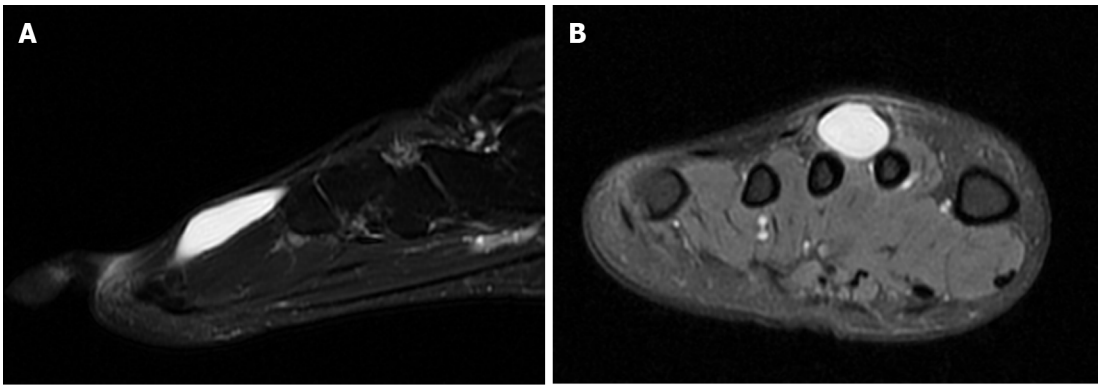

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Figure 3 Intratendinous ganglion of the second extensor digitorum brevis tendon without extra-tendinous lesion and tenosynovitis on a fat-saturation T2-weighted image. A: Sagittal image; B: Axial image.

OUTCOME AND FOLLOW-UP

Histological examination confirmed the diagnosis of intratendinous ganglion. The patient returned to his daily life without functional problems after surgery, and no recurrence of the lesions was found 18 mo after surgery.

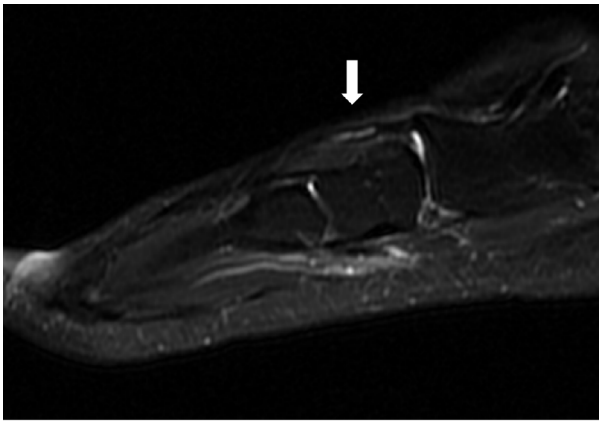

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Figure 4 Satellite lesion at the proximal end of the second extensor digitorum brevis tendon before attaching to the calcaneus.

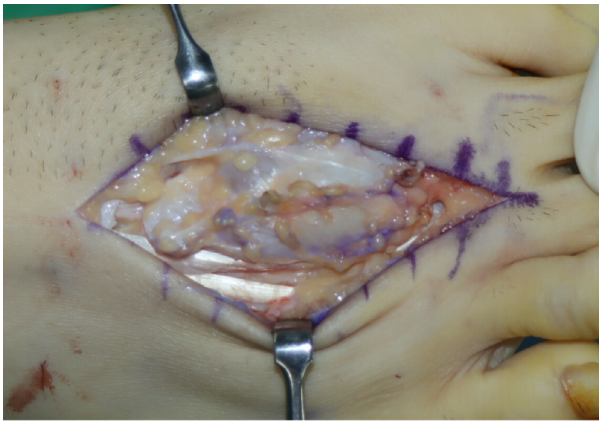

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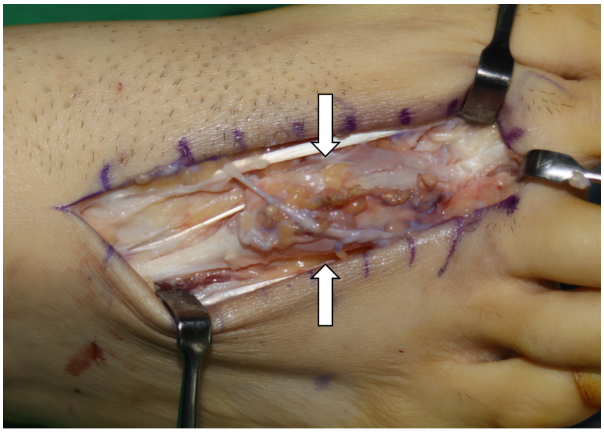
Figure 5 Extra-tendinous ganglion cysts and tenosynovitis over the extensor tendons.



DOI: 10.12998/wjcc.v10.i36.13373

Figure 6 The second extensor digitorum brevis tendon with enlarged spindle shape.

DISCUSSION

An intratendinous ganglion is a rare lesion that originates within the tendon substance and causes soft tissue swelling[13,16]. It can cause persistent pain, functional restriction, and neurovascular compression[12,14]. Spontaneous tendon rupture is reportedly a high-risk factor[4,9,16]. Surgical treatment is considered only in patients with these symptoms[11,15]. Surgical treatments for intratendinous ganglions may involve only excision of the ganglion or *en bloc* resection. *En bloc* resection

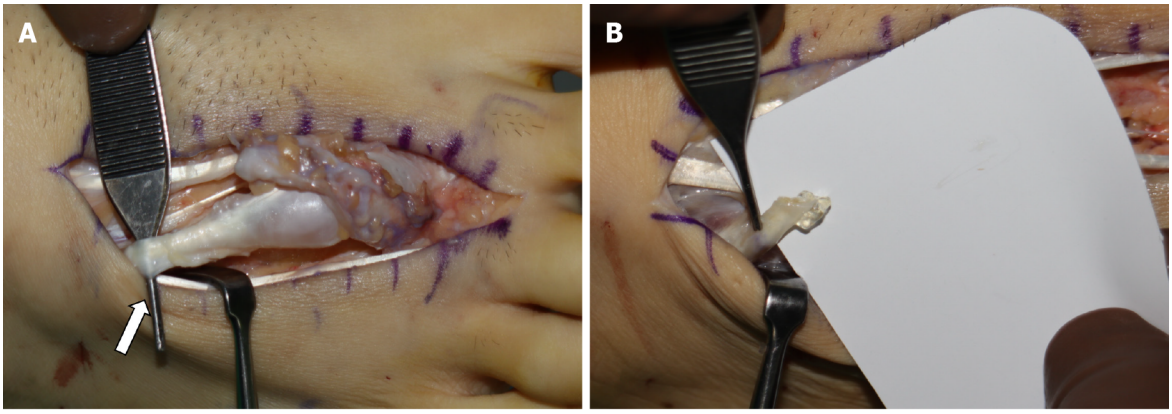


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Figure 7 Satellite lesion of the second extensor digitorum brevis tendon. A: Bulbous satellite lesions in the proximal portion of the tendon; B: Colorless jelly-like content from the inside of the incised tendon.

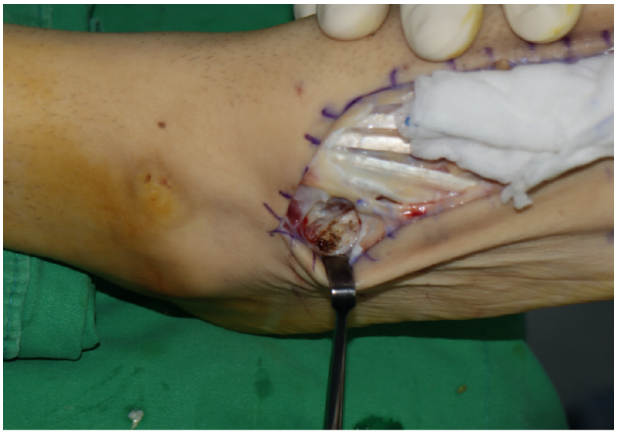

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Figure 8 Remnant tendon removal and electrocauterization were performed at the anterior process of the calcaneus.

is superior in preventing recurrence[10]; however, removal of the whole tendon results in functional loss of the affected tendon and may require additional procedures[10,15]. Therefore, when deciding on the optimal surgical approach, it is important to assess whether functional loss of the affected tendon may be fatal.

We reviewed previous cases of intratendinous ganglions that occurred in the lower extremities. Shimozono *et al*[15] and Endo *et al*[17] only performed excisions of the ganglions because none of the cases had any soft tissue to compensate for the muscle strength of the FHL tendon; good clinical results were obtained without recurrence. Kim *et al*[3] also performed an excision of the ganglion to preserve semimembranosus tendon function; however, they noted a recurrence that was thought to be due to incomplete excision. Kono *et al*[10] performed *en bloc* resection without additional procedures on the intratendinous ganglion of the second EDB tendon because the extrinsic muscle compensates for functional loss. The patient showed good progress, without functional loss or ganglion recurrence.

In our case, the patient underwent ganglion excision as the first surgery in a local hospital. The medical professionals treating him seemed to have thought that complete excision of the ganglion was possible because of the absence of a satellite lesion. However, when the previous MRI scan was reviewed, small cystic lesions with a high signal intensity on fat-saturated T2-weighted images were observed near the proximal end of the second EDB tendon. We believe that inability to detect satellite lesions is an important cause of recurrence. When clinical examination was conducted at our hospital after recurrence, the symptoms and lump size were more aggravated than those before, and MRI confirmed that these were accompanied by extra-tendinous ganglion cysts and tenosynovitis.

The recurrence rate after excision of the ganglion of the lower extremities has been reported to be approximately 10%[18,19]. Studies have not been conducted on the recurrence rate following surgical excision of intratendinous ganglions; however, it is expected to be much higher than 10% owing to the difficulty of complete removal of the ganglion[7,20,21]. In addition, considering the current case of extra-tendinous lesions and severe tenosynovitis after recurrence, repeated surgery requires not only expansion of the skin incision range but also removal of the massive soft tissue, which can lead to poor

clinical results. If the removal of the affected tendon does not cause a functional deficit, *en bloc* resection could be an ideal treatment method to avoid intraoperative leakage and incomplete resections that lead to recurrence. However, excision of only the ganglion should be considered first in cases of fatal functional deficiency and difficulty in performing additional procedures. To prevent incomplete excision, careful evaluation of MRI scans is essential to detect the presence of satellite lesions along the course of the affected tendon. Removal of all satellite lesions should be carefully planned to avoid the risk of another surgery. When complete removal is difficult, surgical treatment should be planned after evaluating the advantages and disadvantages of each approach.

CONCLUSION

To the best of our knowledge, no other case of an intratendinous ganglion recurrence despite open excision of the foot and ankle has been reported in the literature. Complete excision failure was accompanied by the recurrence of the intratendinous ganglion, extra-tendinous lesions, and tenosynovitis. If removal of the affected tendon is not accompanied by fatal functional restrictions, *en bloc* resection should first be considered to prevent incomplete excision and intraoperative leakage. Finally, when planning a surgical excision, it is necessary to carefully evaluate the presence of satellite lesions along the course of the tendon.

FOOTNOTES

Author contributions: Park JJ and Park CH contributed to manuscript writing and editing, and data collection; Park JJ, Seok HG, and Yan HF contributed to data analysis; Park CH contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

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CASE REPORT

Two methods of lung biopsy for histological confirmation of acute fibrinous and organizing pneumonia: A case report

Wen-Juan Liu, Shuang Zhou, Yan-Xia Li

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Abstract

BACKGROUND

Acute fibrinous and organizing pneumonia (AFOP) is a rare, noninfective lung disease, histologically characterized by a patchy distribution of intra-alveolar fibrin "balls" and organizing pneumonia. The clinical manifestations of AFOP are nonspecific. Diagnosis depends on pathology. Surgical lung biopsy is optimal for tissue sampling to diagnose AFOP. However, many patients have no tolerance to the operation, including mentally and physically. There is still no standard therapy for AFOP and the methods remain controversial. Therefore, further clinical attention and discussion are warranted.

CASE SUMMARY

A 53-year-old woman presented with fever, cough and dyspnea for 15 d. Anti-infective therapy was ineffective. Chest computed tomography showed bilateral patchy consolidation, especially in the lower lobes. We performed both ultrasound-guided transbronchial lung biopsy and ultrasound-guided percutaneous fine needle puncture at different lung lesion locations. Both samples supported the diagnosis of AFOP. The patient had a good clinical course after treatment with methylprednisolone, and no side effects of steroids.

CONCLUSION

Percutaneous needle biopsy combined with transbronchial lung biopsies may be a good choice in the absence of surgical biopsy. Methylprednisolone alone is effective in the treatment of idiopathic AFOP.

Key Words: Acute fibrinous and organizing pneumonia; Fibrin balls; Percutaneous needle

biopsy; Transbronchial lung biopsies; Methylprednisolone; Case report

Core Tip: We describe the case of a 53-year-old woman with fever, cough and dyspnea for 15 d. Chest computed tomography showed rapidly progressive bilateral patchy consolidation especially in the lower lobes. Anti-infective therapy was ineffective. We performed ultrasound-guided transbronchial lung biopsy of the posterior basal segment of the left lung and ultrasound-guided percutaneous fine needle puncture of the right lung nodule. Both samples supported the diagnosis of acute fibrinous and organizing pneumonia (AFOP). Methylprednisolone alone is effective and safe in the treatment of idiopathic AFOP.

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INTRODUCTION

Acute fibrinous and organizing pneumonia (AFOP), first described by Beasley *et al*[1] in 2002, is a rare histological form of interstitial pneumonia by the American Thoracic Society and the European Respiratory Society[2]. AFOP has been receiving increasing clinical attention in recent years. AFOP is typically characterized histologically by the presence of intra-alveolar fibrin "balls" and organizing pneumonia in a patchy distribution[1]. The most common symptoms are dyspnea, cough and fever, which often lead to misdiagnosis and delayed diagnosis. According to the literature, most cases were initially misdiagnosed as pneumonia and lung tumors[3,4]. Beasley *et al*[1] described a mean time from onset of symptoms to diagnosis of 19 d, and Gomes *et al*[4] reported a mean time of 43.9 d. A definitive diagnosis of AFOP requires histopathological evaluation[1,2]. Chen *et al*[3] suggested that surgical biopsy is optimal for tissue sampling to make an AFOP diagnosis. However, many patients showed no tolerance to the operation.

We report a case of a 53-year-old female patient with AFOP, who was diagnosed by pathology of percutaneous and transbronchial lung biopsies and successfully treated with steroid monotherapy. The patient was diagnosed 5 d after hospitalization, and discharged after 11 d of hospitalization.

CASE PRESENTATION

Chief complaints

A 53-year-old woman was referred to the First Affiliated Hospital of Dalian Medical University in April 2022 due to fever with cough and dyspnea for 15 d.

History of present illness

The patient had a fever without obvious precipitating causes for 15 d, and her body temperature was 38.5 °C, with cough, sputum and dyspnea. There was no chest pain, hemoptysis, or night sweats. Chest computed tomography (CT) at the local hospital suggested multiple exudative opacities in both lungs (Figure 1A–C). She received penicillin and macrolide antibiotics as treatment for 9 d. However, she had persistent fever, and her symptoms of dyspnea worsened.

History of past illness

She denied a history of previous illnesses or autoimmune system diseases such as joint swelling and pain, dry mouth and eyes, mouth sores, and rashes.

Personal and family history

She was a nonsmoker. She denied a history of exposure to occupational dust or keeping pets. She had no special drug history. She also denied a family history of lung disease.

Physical examination

On examination the patient was alert, with a temperature of 38.2 °C, pulse rate 94/min, respiratory rate 18/min, blood pressure 120/70 mmHg, and oxygen saturation with room air 92%. Chest auscultation

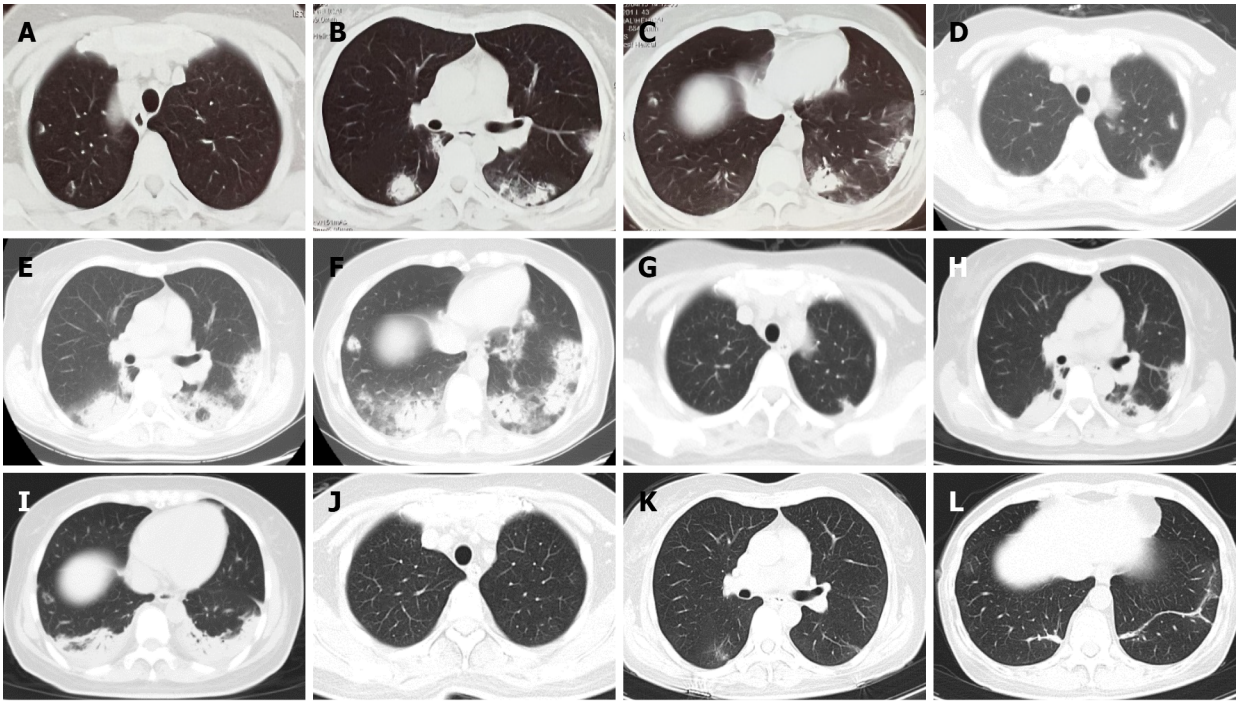

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Figure 1 Chest imaging changes. A–C: Chest computed tomography (CT) at the local hospital suggesting multiple exudative opacities in both lungs; D–F: Chest CT on admission revealed patchy, diffuse alveolar opacities and consolidation with bilateral and peripheral distributions after 9 d of anti-infective treatment in the local hospital; G–I: Chest CT shows that the lung opacities have decreased significantly after 3 d of steroid treatment; J–L: Chest CT shows that the lung opacities have almost been entirely absorbed after 1 mo of steroid treatment.

revealed increased breath sounds with no crackles. The rest of the physical examination was unremarkable.

Laboratory examinations

The patient's laboratory test results are shown in Table 1.

Imaging examinations

High-resolution CT (HRCT) of the thorax on admission revealed patchy, diffuse alveolar opacities and consolidation with bilateral and peripheral distributions, which was significantly more extensive than before (Figure 1D–F).

Further diagnostic work-up

Twodimensional echocardiography and electrocardiography were normal. Blood and alveolar lavage fluid were both examined by next-generation sequencing (NGS), and no bacteria, fungi or viruses were found.

Ultrasound-guided right lung puncture biopsy revealed intra-alveolar fibrin in the form of "fibrin balls" without the formation of hyaline membranes (Figure 2A and B).

Bronchoscopy followed by bronchoalveolar lavage (BAL) was performed. The molecular diagnostic test for tuberculosis was negative; BAL galactomannan was unremarkable. BAL cultures were negative. Transbronchial lung biopsy was performed from the left lower lobe, and the corresponding report revealed AFOP (Figure 2C and D).

FINAL DIAGNOSIS

AFOP.

TREATMENT

Based on the results of the lung biopsy, intravenous methylprednisolone 40 mg twice daily was initiated. The patient's body temperature returned to normal on the first day of corticosteroid therapy.

Table 1 Laboratory examinations

Laboratory examinations	Result
Blood gas	pH: 7.477, PO_2: 71 mmHg, PCO_2: 34.1 mmHg
Routine blood	WBC: 10.70 × 10^9, N%: 80.6%, HGB: 106 g/L, PLT: 583 × 10^9
CEA, Cyfra21-1, NSE	Negative
Coagulation	PT: 12.4 s, APTT: 28.2 s, Fib: 8.77 g/L
Liver biochemistry	ALT: 18 U/L, AST: 12 U/L, Prealbumin: 78 mg/L, ALB: 29.4 g/L
BNP	Normal
Nucleic acid testing for COVID-19	Negative
ESR	96 mm/h (0-20 mm/h)
PCT	Normal
CRP	143 mg/L (< 8.0 mg/L)
Serum HIV antibody	Negative
Tuberculosis-SPOT	Negative
(1,3)-beta-D-glucan assay	Negative
Galactomannan	Negative
CrAg	Negative
Bronchoalveolar lavage fluid	No bacteria, No aspergillus, No Tuberculosis, No Cryptococcus
Blood culture	Sterile
Respiratory pathogen profile detection	Negative
Lymphocyte subsets	CD4: 337 cells/μL, CD3: 590 cells/μL
Immunological test	
Antinuclear antibodies	Positive, titer 1:100
nRNP/Sm	Weakly positive
Sm	Weakly positive
Ds-DNA	Negative
ENA	Negative
ANCA	Negative
ACA	Negative
Anti-CCP	Negative
Rheumatoid factor	Normal
IgE	257 IU/mL (< 100)
Immunoglobulins and complement	Normal

PO_2: Partial pressure of oxygen in the blood; PCO_2: Partial pressure of carbon dioxide in the blood; ESR: Erythrocyte sedimentation rate; PCT: Procalcitonin; CRP: C-reactive protein; CrAg: Cryptococcal capsular antigen; ANA: Anti-nuclear antibodies; RF: Rheumatoid arthritis factor; ENA: Extractable nuclear antigen profile; CCP: Cyclide polypeptide; HIV: Human immunodeficiency virus; CEA: Carcinoembryonic antigen; NSE: Neuron specific enolase; BNP: Human brain natriuretic peptide; ANCA: Anti-neutrophil cytoplasmic antibody; IgE: Anti-immunoglobulin E; Sm: Anti-Smith antibody; nRNP: Nuclear ribonucleoprotein.

Her cough and shortness of breath improved significantly. The lung opacities decreased significantly after 3 d of corticosteroid treatment (Figure 1G–I). Then, methylprednisolone was decreased to 40 mg once daily. She was discharged home 3 d later, and continued oral methylprednisolone 40 mg/d for 10 d followed by 20 mg/d for 14 d, 16 mg/d for 14 d, 12 mg/d for 14 d, and 8 mg/d for 1 mo.

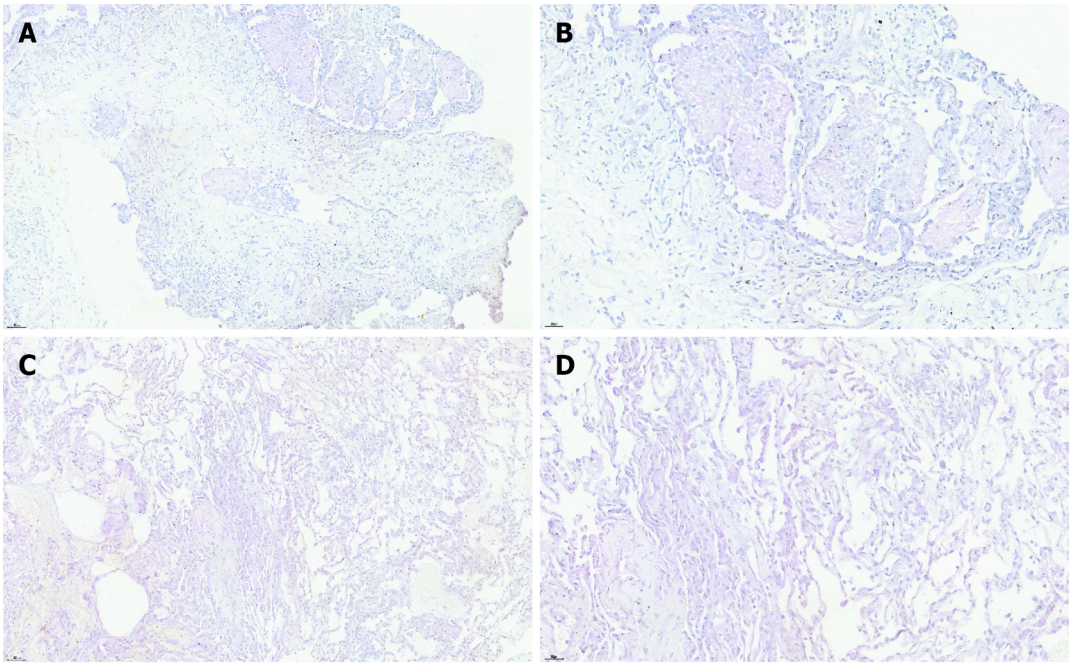

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Figure 2 Histological findings in the lung. A and B: Ultrasound-guided right lung puncture biopsy reveals intra-alveolar fibrin in the form of "fibrin balls" without the formation of hyaline membranes [Hematoxylin and eosin (HE): 20 ×, HE: 40 ×, respectively]; C and D: Transbronchial lung biopsy of the left lower lobe: fibrin balls are present in the alveolar cavities (HE: 20 ×, HE: 40 ×, respectively).

OUTCOME AND FOLLOW-UP

At follow-up of 1 mo after discharge, chest HRCT showed that most of the lesions had improved in absorption (Figure 1J–L). She is currently being treated with 4 mg methylprednisolone for 2 mo and on regular follow-up. She has no symptoms such as dyspnea, fever or cough, and no side effects of steroids such as obesity, hypertension, hyperglycemia or osteoporosis.

DISCUSSION

In 2002, Beasley *et al*[1] described a new histological pattern of lung injury named AFOP. The dominant histological pattern of AFOP is intra-alveolar fibrin deposition and OP without the presence of classical hyaline membranes and eosinophilia, differentiating the disease from diffuse alveolar damage (DAD), OP, and eosinophilic pneumonia[1,2]. Two forms of the disease are described: An acute form with a fulminant course and rapid progression to respiratory failure, and a subacute form with a better outcome[1,3]. AFOP can be idiopathic or associated with a variety of disease conditions, including infections, collagen vascular diseases, adverse drug or chemical reactions, hematological malignancy, altered immune status, inhalation disease, and occupational or environmental exposures[4-10]. Our patient was weakly positive for anti-Smith (Sm) antibody and nuclear ribonucleoprotein/Sm without any symptoms. Possibility of systemic lupus erythematosus should be considered. Therefore, it is necessary to monitor abnormal immune indicators and corresponding symptoms.

The clinical manifestations of AFOP are nonspecific. The most common symptoms are dyspnea, cough and fever. The most common radiological findings are diffuse, patchy opacities with both peripheral and bilateral distributions, and the lesions may be limited to the lung bases[1]. Chen *et al*[3] suggested that consolidation is manifested more frequently in patients with idiopathic AFOP, while converse ground-glass opacity is seen more frequently in patients with secondary AFOP.

As clinical characteristics associated with this disease are nonspecific, a definitive diagnosis of AFOP requires histopathological evaluation. The methods of lung biopsy often include percutaneous needle biopsy, endobronchial ultrasound-guided transbronchial lung biopsy, and surgical lung biopsy.

Chen *et al*[3] suggested that surgical biopsy is the best choice for tissue sampling for AFOP diagnosis, as it can minimize the missing areas of the hyaline membrane in DAD. However, our patient showed no tolerance to the operation. To increase the reliability of the biopsy, we performed both ultrasound-guided transbronchial lung biopsy of the posterior basal segment of the left lung and ultrasound-guided percutaneous fine needle puncture of the right lung nodule. Both samples supported the diagnosis of AFOP.

Most patients begin with respiratory symptoms such as fever and cough and often have elevated nonspecific inflammatory indicators such as C-reactive protein and erythrocyte sediment rate, and chest CT suggests a patch in both lungs, hence many AFOP patients are first diagnosed with community-acquired pneumonia (CAP)[4]. This leads to high use of antibiotics. AFOP needs to be differentiated from CAP because the treatment modalities are markedly different. The patient's blood and BAL fluid were examined with NGS, and no definitive etiological evidence was found, confirming the final diagnosis of AFOP. It is important to exclude infection. Lu *et al*[11] suggested that NGS technology plays an important role in the diagnosis of infectious diseases, and has potential for exclusion of non-infectious diseases.

The most common therapy for AFOP is corticosteroids. Other options include immunosuppressants and antibiotics, depending on the cause of AFOP. Usually 0.5–1 mg/kg/d prednisone (or equivalent) is prescribed initially[12,13]. A maximal dose of methylprednisolone was reported to be up to 1 g/d[8]. Corticosteroids should be reduced after remission, and the total course of treatment should be maintained in small doses for 6–12 mo[12,13]. Relapse is possible during corticosteroid tapering, and symptoms may be reduced when higher corticosteroids doses are resumed[3]. Considering that our patient weighed 75 kg, had no previous hypertension or diabetes, and had a wide range of imaging lesions with rapid progression, we chose 40 mg methylprednisolone twice daily as the initial treatment. After 3 d, due to the improvement of symptoms and imaging, and considering the side effects of steroids, we reduced the dose of methylprednisolone to 40 mg once daily. After 5 mo of gradual reduction, the dose of methylprednisolone was 4 mg/d. The patient has no symptoms such as cough, dyspnea or fever, or side effects of steroids such as obesity, hypertension, hyperglycemia or osteoporosis.

CONCLUSION

Percutaneous needle biopsy combined with transbronchial lung biopsies may be a good choice in the absence of surgical biopsy. Methylprednisolone alone is effective and relatively safe in the treatment of idiopathic AFOP.

FOOTNOTES

Author contributions: Liu WJ contributed to data analysis and wrote the paper; Zhou S contributed to data collection; Li YX contributed to the conception and design of the study; all authors revised the paper and approved the submitted version.

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CASE REPORT

Application of 3D-printed prosthesis in revision surgery with large inflammatory pseudotumour and extensive bone defect: A case report

Hong-Ping Wang, Ming-You Wang, Yu-Ping Lan, Zhuo-Dong Tang, Qi-Feng Tao, Chun-Yu Chen

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Abstract

BACKGROUND

Hip revision surgery is the final treatment option for the failure of artificial hip joints, but it is more difficult than the initial operation. For patients with hip joint loosening around the prosthesis combined with large inflammatory pseudotumours and large segment bone defects, hip revision is even more difficult, and clinical reports are rare.

CASE SUMMARY

Male, 59 years old. The patient underwent left hip replacement 35 years ago and was now admitted to hospital due to massive masses in the left thigh, shortening of the left lower extremity, and pain and lameness of the left hip joint. X-ray, computed tomography and magnetic resonance imaging revealed prosthesis loosening, left acetabular bone defect (Parprosky IIIB type), and a bone defect of the left proximal femur (Parprosky IIIA type). Inflammatory pseudotumours were seen in the left hip and left thigh. Hip revision surgery was performed using a 3D-printed custom acetabular prosthesis was used for hip revision surgery, which was produced by Arcam Electron Beam Melting system with Electron Beam Melting technology. The operation was successful, and the patient was followed up regularly after the operation. The custom-made acetabular prosthesis was well matched, the inflammatory pseudotumour was completely removed, the postoperative hip prosthesis was stable, and the old greater trochanter fracture was well reduced and fixed. The patient was partially weight-bearing with crutches 3 mo after the operation and walked with full weight-bearing after 6 mo. The hip prosthesis was stable, and there was no recurrence of inflammatory

pseudotumours at the last follow-up. The Visual Analogue Scale was 3, and the Harris hip score was 90.

CONCLUSION
The use of 3D-printed personalized custom prostheses for complex hip revision surgery has satisfactory surgical results and has great clinical application value.

Key Words: 3D printing; Inflammatory pseudotumour; Electron Beam Melting technology; Hip revision; Bone defect; Case report

Core Tip: We report a case of complex hip joint loosening around a prosthesis combined with a large inflammatory pseudotumor, extensive bone defect and an old fracture of the greater trochanter. A 3D-printed personalized prosthesis for artificial hip revision can be effectively installed. Preoperative planning and successful completion of complex hip revision surgery yielded good results.

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INTRODUCTION

Prosthesis loosening is one of the main reasons for revision surgery, and the appearance of an inflammatory pseudotumor, especially one with accompanying symptoms, is another[1]. Inflammatory pseudotumor parenchyma is a granulomatous or destructive cystic lesion, also known as a pseudotumor, metal metaplasia or sterile lymphocyte-dominated vasculitis[2], which has adverse reactions to metal fragments[3,4]. It is neither an infection nor a tumor and is prone to occur around total prostheses of the hip, with a tumor-like shape and varying sizes[5]. It can cause progressive pain, swelling, joint subluxation, compression, periprosthetic fractures and soft tissue destruction in the affected extremity[2,6]. Hip revision surgery is the final treatment option for prosthesis failure and for patients with periprosthetic loosening of the hip joint combined with a large inflammatory pseudotumor, extensive bone defects and nonunion of the greater trochanter. However, such surgery is rare in clinical practice and extremely difficult to perform. At present, with the continuous progress of science and technology and the continuous improvement of medicine, the application of 3D printing technology in orthopedics has gradually expanded from initial bone tumor patients to other patients with complex bone diseases, especially those with large bone defects. Due to the continuously improving cooperation between medicine and industry, the accurate 3D printing of materials is gradually being applied. The individualized materials for repair and reconstruction are prepared according to the characteristics of patients' bone defects and combined with 3D printing technology, which can meet the complex needs of patients for bone defect repair and achieve personalized and precise treatment of diseases. Therefore, the treatment of complex diseases is simplified. The successful application of 3D printing technology in the case study presented here fully demonstrates the advantages of this technology and may serve as a reference for its future clinical application. Here, we implanted a 3D-printed personalized acetabular prosthesis, and the long-term follow-up results were satisfactory.

This case report was approved by the Ethics Committee of Panzhihua Central Hospital, and written informed consent was obtained from the patient and his family.

CASE PRESENTATION

Chief complaints

Eight months ago, the patient developed left thigh swelling without obvious reasons, and the swelling gradually extended from the back to the front, accompanied by pain when moving the leg.

History of present illness

Underwent herniorrhaphy 40+ years ago in the local hospital without other diseases or operations. Unfortunately, an intertrochanteric fracture of the left femur was caused by a fall 40 years ago and was treated conservatively, with the presence of ununited fractures later. The patient underwent left hip replacement 35 years ago due to a left intertrochanteric fracture combined with left femoral head necrosis. Eight months ago, the patient developed left thigh swelling without obvious reasons, and the swelling gradually extended from the back to the front, accompanied by pain when moving the leg. The claudication of the left lower limb was aggravated, so he was admitted to our department.

History of past illness

Underwent herniorrhaphy 40+ years ago in the local hospital without other diseases or operations. Unfortunately, an intertrochanteric fracture of the left femur was caused by a fall 40 years ago and was treated conservatively, with the presence of ununited fractures later. The patient underwent left hip replacement 35 years ago due to a left intertrochanteric fracture combined with left femoral head necrosis.

Personal and family history

The patient was born in the original place, without industrial poisons, radioactive substances, dust exposure history, no contact history with epidemic water in epidemic areas, smoking history of 40+years, with an average of 20 cigarettes/day, and denied drinking history. Divorce, having a child, healthy family. Deny the history of family hereditary diseases and infectious diseases.

Physical examination

The left lower limb was shortened by approximately 8 cm compared with the right side. A 15-cm-long surgical scar was seen on the left hip, where there was no redness, swelling or exudation. The middle and upper parts of the left thigh were obviously swollen, there were palpable fluctuations, the local skin temperature was normal, and there was no obvious tenderness (Figure 1).

Imaging examinations

X-ray: Left superior pubic branch - irregular pubic comb bone. Computed tomography (CT): Partial bone absorption of the upper part of the left femur; bone destruction of the left acetabulum; swelling and unclear layers of soft tissue shadows in the upper part of the left thigh and around the hip joint; multiple cystic lesions in the upper part of the left thigh, with multiple cystic necrosis areas in the lesions, of which the posterior subcutaneous necrosis area is a long strip from the subcutaneous buttock to the lower back. Magnetic resonance imaging (MRI): The left upper femur and left hip joint have abnormal bone, with multiple necrosis sites around the hip joint and soft tissue of the left thigh as the main cystic disease. Considering the inflammatory disease, the size of the larger cystic lesion is approximately 8.7 cm × 9.3 cm × 18 cm (Figure 2).

FINAL DIAGNOSIS

Prosthesis loosening after left hip replacement; Inflammatory pseudotumor of left thigh; Old fracture of left greater trochanter of femur; Shortening deformity of left lower limb.

TREATMENT

CT examination of the patient's hip joint was performed after admission. The 1:1-sized hip joint model was printed through 3D printing technology (supported by Akcome Medical Co., Ltd.), which we used for preoperative planning and disease communication. Revision surgery is routinely performed to reconstruct acetabular side bone defects, but it is extremely difficult and costly. After fully explaining the scenario to the patient and his family members, the personalized 3D-printed custom acetabular prosthesis was used for hip revision surgery, which was produced by the Arcam EBM system with electron beam melting technology (Figure 3).

Operation method

Under general anesthesia, the skin, subcutaneous tissue and scar were incised layer by layer through the posterolateral incision of the left hip, the hip joint was released, and the large inflammatory pseudotumor around the hip joint and thigh was removed. The artificial prosthesis was removed, rinsed with a large amount of normal saline and soaked with iodophor solution. Allograft cancellous bone was implanted into the bone defect of the posterior wall of the acetabulum and pressed tightly. The abduction angle was kept at 45° after the acetabulum was worn down, and the customized 3D-printed

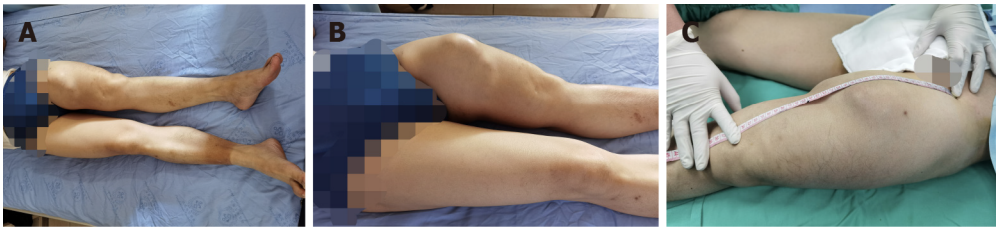

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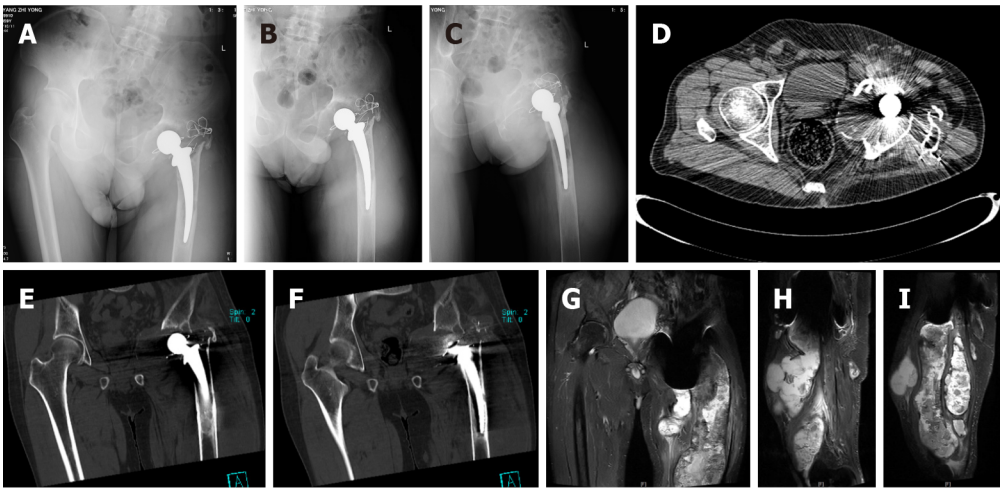
Figure 1 Preoperative swelling of both lower extremities and the left thigh. A: The unequal appearance of the lower limbs; B and C: The inflammatory pseudotumor of the left thigh.



DOI: 10.12998/wjcc.v10.i36.13388

Figure 2 Preoperative imaging examination. A: X-ray; A-C: Left superior pubic branch - irregular pubic comb bone; D: CT; D-F: Partial bone absorption of the upper part of the left femur; bone destruction of the left acetabulum; swelling and unclear layers of soft tissue shadows in the upper part of the left thigh and around the hip joint; multiple cystic lesions in the upper part of the left thigh, with multiple cystic necrosis areas in the lesions, of which the posterior subcutaneous necrosis area is a long strip from the subcutaneous buttock to the lower back; G: MRI; G-I: The left upper femur and left hip joint have abnormal bone, with multiple necrosis sites around the hip joint and soft tissue of the left thigh as the main cystic disease. Considering the inflammatory disease, the size of the larger cystic lesion is approximately 8.7cm × 9.3 cm × 18 cm.

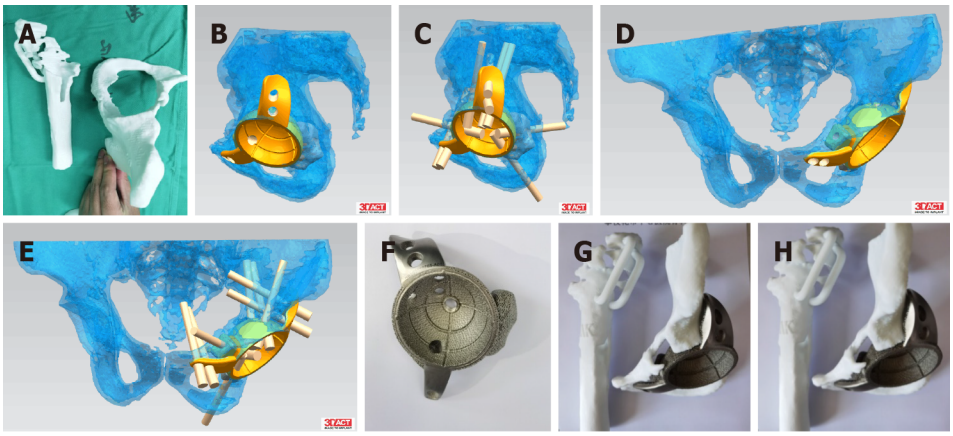


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Figure 3 Design process of personalized prosthesis. A: 1:1 printed model; B-E: Preoperative planning; F: Cup making; G-H: Preoperative surgery simulation.

Accurate Constructive Technology acetabular prosthesis was installed with an anterior tilt of 20°. The inner lining was installed, the appropriate femoral stem and femoral head were selected and implanted, and the hip joint was reset. The hip joint in all directions was relatively stable, and the tightness was appropriate. The fractured greater trochanter was reduced and fixed with a trochanteric plate after

satisfactory reduction. C-arm fluoroscopy showed that the prosthesis was in a good position (Figure 4). Complete hemostasis was performed, and an indwelling drainage tube was placed after repeated rinsing. A peripheral nerve block cocktail was given, tranexamic acid was perfused intraarticularly, and the incision was sutured.

OUTCOME AND FOLLOW-UP

We strove for a fast recovery in the perioperative period. Postoperatively, to prevent thrombosis, cefuroxime sodium was given for anti-inflammation and rivaroxaban was given for anticoagulation. Postoperative bacterial culture was negative, and the pathology showed a small amount of neutrophil and lymphocyte infiltration and no obvious tumor cells. X-ray imaging showed the following: The swelling of the thigh had subsided, the acetabular prosthesis was stable, the greater trochanter fracture was well reduced and fixed, the femoral stem and the greater trochanter were stably held in place, the fixation was effective, and the hip joint position was satisfactory. The patient was kept to strict bed rest after surgery, hip joint activities were performed on the 2nd day after surgery, and the drainage tube was removed on the 3rd day. The patient underwent debridement due to poor incision healing 3 wk after the operation. During the operation, it was found that the residual inflammatory pseudotumor recurred, but the wound recovered well after the residual inflammatory pseudotumor was completely removed. The patient regularly returned to the hospital for follow-up at 1.5 mo, 3 mo, and 6 mo. Partial weight-bearing with crutches was started 3 mo after the operation, and full weight-bearing was started at 6 mo. During the follow-up period, the wound healing was good, the greater trochanter plate and the hip prosthesis were well positioned, and no obvious osteolytic changes or inflammatory tumor recurrence were found around the prosthesis (Figure 5). There was no obvious pain or discomfort in the hip at the last follow-up, the Visual Analogue Scale was 3 points, and the Harris hip joint score was 90 points.

DISCUSSION

3D printing technology, which is a kind of additive manufacturing, emerged in 1984. It is based on the principle of discrete/accumulation of different 2D cross-sectional shapes. It is a new additive manufacturing technique that builds up materials layer by layer into 3D shapes based on digital models[7]. In recent years, with the development of 3D printing techniques in the medical industry and based on patient CT and MRI image data, reverse molding has been performed to achieve 3D model reconstruction of patient tissues and organs and medical implants, which helps optimize the surgical plan and procedure. Medical planning and surgical implementation methods have become very fast-growing innovations in clinical medicine[8,9]. At present, the application of 3D printing technology in the hip joint can be divided into four categories: (1) Establishment of an anatomical model based on patient images to promote a better understanding of the corresponding anatomy, and at the same time, to facilitate the simulations of surgery and improve the controllability of surgery in each sex; (2) Establishment of patient-specific instruments to improve surgical accuracy[10]; (3) Customizing and producing artificial joint replacement implants; and (4) Customizing the specific implanted prosthesis according to the patient's condition to increase the degree of matching with the specific anatomy of the patient[11,12,15]. How to preserve more bone mass in hip revision surgery is the key to the success of the surgery, especially for revision surgery with large bone defects. Preserving bone mass helps to achieve early full weight-bearing postoperatively, to retain as much range of joint movement as possible, and to maintain long-term prosthesis stabilization[13].

This patient had previously undergone left hip arthroplasty due to intertrochanteric fracture combined with left femoral head necrosis. During the operation, a cement prosthesis (stem and acetabulum) was used, and the intertrochanteric fracture was fixed with wire bundles after reduction. At the time of admission, the patient's left upper thigh was swollen, a local large mass bulged, and the left hip joint was painful when moving, but there were no chills, fever, skin sinus formation or exudation at the local site. White blood cells and inflammatory indicators were normal. No bacteria were found with arthrocentesis. X-ray, CT and MRI examinations showed osteolysis around the prosthesis, bone defects of the left acetabulum and proximal femur, and multiple cystic lesions in the soft tissue of the middle and upper left thigh. It was also found that the femoral trochanteric fixation wire was broken and the fracture was displaced again. The clinical manifestations of this patient are consistent with the diagnosis of an inflammatory pseudotumor, so it is highly likely that it was an inflammatory pseudotumor. According to related reports, the incidence of inflammatory pseudotumor is 40%-60% at the metal-metal interface and 20% at the metal-polyethylene interface. They are less common at ceramic-polyethylene and ceramic-ceramic interfaces[14,15], which is related to the low wear rate and the biological inertness of ceramics. Due to the long medical history of this patient, the friction between the metal femoral head and polyethylene, the micromovement of the bone cement and the bone surface, and the loosened wire continued to produce grinding. Metal ions in the synovial fluid produced by corrosion lead to the formation of inflammatory pseudotumor[14,16-18] and progressively

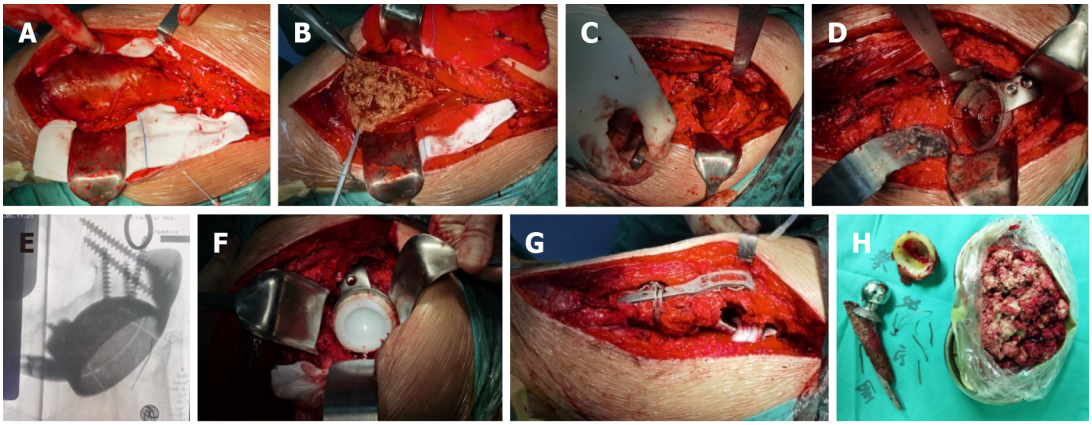

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Figure 4 Surgical steps. A: The inflammatory pseudotumor was freed; B: The pseudotumor was excised; C. Acetabular defect; D. Implanted acetabular cup; E. Intraoperative fluoroscopy; F. Uchimura implant; G. Steel plate-fixed rotor; H. Removal of prosthesis and inflammatory pseudotumor.

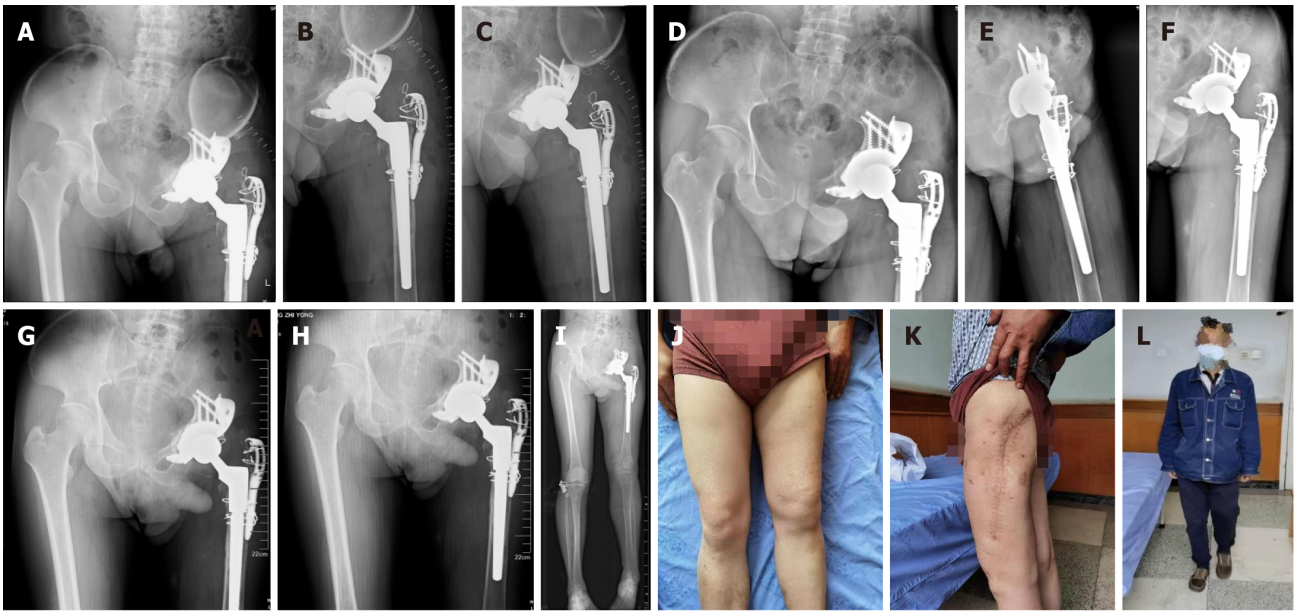

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Figure 5 Postoperative follow-up. A: X-ray in two days after surgery; B and C: Different view; D-F: Ninety days after surgery; G-L: Six months after surgery (a 30-cm surgical scar on the outside of the left thigh, without redness, swelling or exudation).

create large defects in the femur and acetabulum.

For this patient, we made a 3D-printed 1:1-sized hip joint model. Along with the difficulty of the imaging examination, the difficulty of the operation was mainly due to the following: (1) The acetabular bone defect was very large, and it was difficult to reconstruct the acetabulum; (2) The inflammatory pseudotumor had spread far, so it was difficult to completely remove it; (3) The greater trochanter of the femur had an old fracture that had not healed, and it was difficult to effectively reduce and fix the greater trochanter; (4) The proximal femoral bone defect made it difficult to maintain the effective fixation of the greater trochanter; and (5) The patient's lower limbs were not equal in length, and it was difficult to restore their length. Based on the above difficulties, we used 3D printing to create a personalized prosthesis. The acetabular cup was fixed on the ilium and pubis by screws. It was stable and ensured effective bone ingrowth later on. A high-molecular-weight polyethylene inner village and ceramic femoral head were used to reduce the recurrence rate of inflammatory pseudotumor induced by metal ions and prolong the service life of the prosthesis. The advantages of this scheme are as follows: (1) It fully preserved the patient's acetabular bone mass and greatly increased the contact area of the acetabular prosthesis; (2) The 3D printing module was used to repeatedly perform surgical simulation and refine the surgical plan before surgery; and (3) The design of the integrated 3D-printed prosthesis was more conducive to performing the operation and saved operation time. The greater trochanter needs to be effectively fixed to ensure the normal function of the abductor muscles, and it is

also important to the future stability of the hip joint. The greater trochanter provides conditions for late healing. There is controversy over whether the inflammatory pseudotumor needs to be completely removed. According to a study, in the natural history of an inflammatory pseudotumor without intervention, 60% of the lesions will increase in volume but can be reduced or regressed in 80% of patients undergoing hip revision surgery. Sassoon *et al*[4] reported on 5 patients who underwent revision surgery; the inflammatory pseudotumor was partially removed in 2 patients and retained in 3 patients, and the pseudotumor was significantly reduced or regressed in all patients at the 17-mo follow-up. Therefore, in the initial operation, we focused mostly on pseudotumor with large cystic cavities that were associated with the joint and did not give special treatment to the relatively closed and hidden pseudotumor. However, the wound returned due to the recurrence of inflammatory pseudotumor in the early postoperative period. Second-stage surgery was performed for complete debridement. This shows that large inflammatory pseudotumor need to be completely removed during the operation to avoid the adverse effects of repeated inflammatory pseudotumor.

CONCLUSION

We report a case of complex hip joint loosening around a prosthesis combined with a large inflammatory pseudotumor, extensive bone defect and an old fracture of the greater trochanter. A 3D-printed personalized prosthesis for artificial hip revision can be effectively installed. Preoperative planning and successful completion of the complex hip revision surgery yielded good results. This case provides a reference for the surgical treatment of similar diseases.

FOOTNOTES

Author contributions: Wang HP and Wang MY participated in the perioperative management, surgical process, and postoperative follow-up and wrote the main manuscript; Lan YP was in charge of the whole preoperative planning, operation scheme design and operation process and helped draft the manuscript and revise the article; Tao QF, Tang ZD and Chen CY were in charge of the follow-up of the patients and the collection and collation of the patients' pictures; All authors read and approved the final draft.

Informed consent statement: Written informed consent was obtained from the patient for the publication of this case report.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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CASE REPORT

Undetected traumatic cardiac herniation like playing hide-and-seek-delayed incidental findings during surgical stabilization of flail chest: A case report

Su Young Yoon, Jin-Bong Ye, Junepill Seok

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Peer-review report's scientific quality classification

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Abstract

BACKGROUND

Post-traumatic blunt pericardial injury is a rare condition with only a few reported cases which were generally diagnosed during initial examinations upon admission. However, pericardial injuries not bad enough to dislocate the heart may only cause intermittent electrocardiogram (ECG) changes or be asymptomatic.

CASE SUMMARY

In this case, we report a blunt pericardial injury undetected on preoperative transthoracic echocardiography and chest computed tomography. We misjudged intermittent ECG changes and blood pressure fluctuations as minor symptoms resulting from cardiac contusion and did not provide intensive treatment. The pericardial injury was found incidentally during surgical stabilization of rib fractures and was successfully repaired.

CONCLUSION

Post-traumatic blunt pericardial ruptures should be considered in patients with blunt chest trauma showing abnormal vital signs and ECG changes.

Key Words: Cardiac herniation; Flail chest; Multiple rib fractures; Pericardial rupture; Surgical stabilization of rib fractures; Case report

Core Tip: Post-traumatic blunt pericardial rupture is a rare but fatal injury that is usually diagnosed with computed tomography upon admission, but the condition can be asymptomatic or misdiagnosed. If a patient with blunt chest trauma shows fluctuating vital signs and accompanying electrocardiogram abnormalities, pericardial rupture and cardiac herniation should be considered.

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INTRODUCTION

Post-traumatic blunt pericardial injury is rare but has occasionally been reported[1-4]. Once diagnosed, surgical repair is mandatory as this condition can trigger devastating complications[5,6]. However, in some cases, cardiac herniations may be misdiagnosed or masked by concomitant injury. In this case report, we share our experience with a blunt pericardial rupture with no specific symptoms apart from intermittent electrocardiogram (ECG) changes; the case was undiagnosed even after chest computed tomography (CT) and transthoracic echocardiography (TTE) in the preoperative period.

CASE PRESENTATION

Chief complaints

A 46-year-old male patient who was involved in a motor vehicle accident presented with a left abdominal wall injury and severe chest pain.

History of present illness

The patient had no specific history of present illness.

History of past illness

The patient had no specific history of past illness.

Personal and family history

The patient had no personal or familial disease.

Physical examination

Tenderness and rebound tenderness were observed in the lower left quadrant of the abdomen. Crepitus and tenderness were present in the left chest wall, accompanied by decreased breath sounds. Symmetrical chest wall expansion during breathing was observed with no initial flail motion.

Laboratory examinations

Initial arterial blood gas analysis showed a pH of 7.4, PO_2 of 80.3 mmHg, and PCO_2 of 34.0 mmHg on room air. Cardiac enzymes were elevated at troponin T 244 ng/L (normal range: < 14 ng/L), CK-MB 23.32 ng/L (normal range: < 4.94 ng/L), and CPK 4176 U/L (normal range: 58–348 U/L).

Imaging examinations

Chest CT revealed multiple rib fractures with hemopneumothorax in the left hemithorax. No abnormalities were observed in the mediastinum. Abdominal CT revealed a bowel herniation through an abdominal wall defect. The initial ECG showed an elevated ST segment in the anterior leads; however, it was deemed to be insignificant (Figure 1).

Diagnosis at initial presentation

The patient was initially diagnosed with multiple rib fractures and hemopneumothorax in the left chest. Panperitonitis due to bowel perforation was suspected, and blunt cardiac contusion was considered highly likely.

Initial treatment

A 24-French thoracic drainage catheter was placed, and the hemothorax was confirmed to be minor.

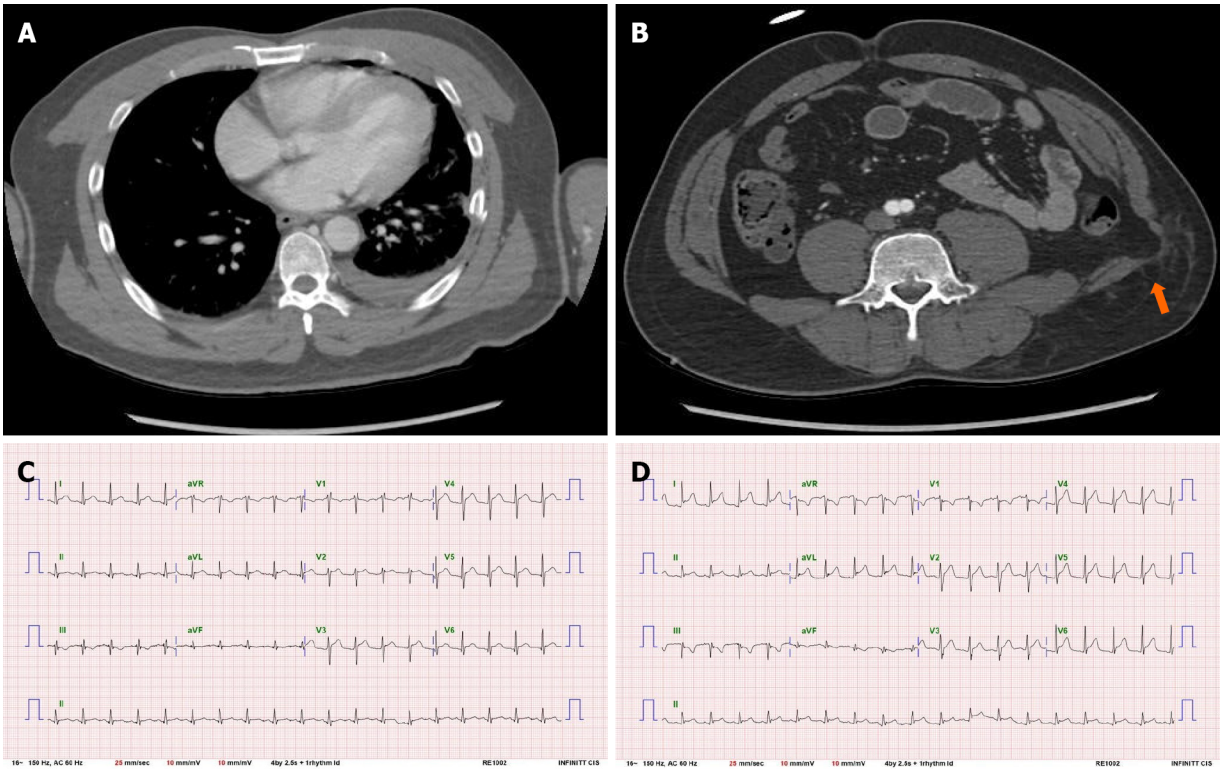

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Figure 1 Computed tomography scan. A: Initial chest contrast computed tomography (CT) showing traumatic hemothorax, with no evidence of heart injury; B: Initial abdominal contrast CT showing visceral herniation through an abdominal wall defect (orange arrow); C: The initial electrocardiogram (ECG) showed widespread abnormal findings, but did not meet the criteria for myocardial infarction (MI); D: ECG performed later when the patient showed fluctuating systolic blood pressure. The ECG showed prominent ST changes with depressions at the lead III, aVR, and V1, which are not the classical reciprocal ECG changes seen in MI.

Despite the perioperative risks associated with cardiac contusions, the patient underwent emergent surgery to rule out abdominal organ injuries. The peritoneum was intact, and no significant findings were observed except for several pelvic muscle tears.

Postoperative care in the surgical intensive care unit (SICU) was provided as usual. Blood tests for elevated cardiac enzymes were repeated every 4 h and showed gradual improvement. The patient did not complain of worsening chest pain, which was successfully controlled with analgesics. However, the patient's systolic blood pressure fluctuated intermittently with prominent ECG changes. Although the changes were not the classical reciprocal findings observed for the myocardial infarction (MI), we still found it necessary to confirm the patient's cardiac condition (Figure 1).

On Day 2 of hospitalization, TTE was performed to check for cardiac conditions. The patient was confirmed to have neither pericardial fluid collection nor abnormal cardiac movements. The patient's ECG remained variable, fluctuating from normal to prominent ST elevations, and we regarded these findings as non-meaningful and indicative of the usual transient changes after cardiac contusion.

On Day 3 of hospitalization, the patient complained of dyspnea and difficulty with expectoration. Paradoxical asymmetric chest wall motion was newly observed on the left anterior chest wall to the extent where the chest wall moved in rhythm with the patient's heartbeat. Despite proper support, including higher oxygen supplementation *via* a high-flow nasal cannula, the patient's condition gradually deteriorated. Follow-up chest CT revealed a worsening lung condition. However, the mediastinum was relatively clear (Figure 2). After thoroughly discussing the risks associated with cardiac contusions with anesthesiologists, we decided to perform surgical stabilization of rib fractures (SSRF).

Additional diagnosis during hospitalization and current problem list

A flail chest due to multiple rib fractures and blunt cardiac contusion were considered as additionally diagnosed conditions.

Additional treatment

The patient underwent SSRF on Day four of hospitalization. The surgery was performed routinely under general anesthesia with a single endotracheal intubation, with the patient placed in the 45-degree semi-lateral right decubitus position. An anterolateral thoracotomy was performed in the fifth intercostal space from the median border of the left pectoralis major muscle to the mid-axillary line.

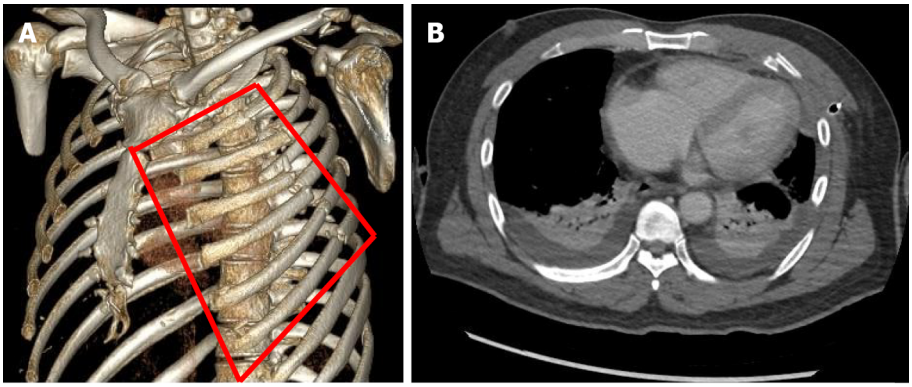

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Figure 2 3-dimensional contrast chest computed tomography. A: A 3-dimensional (3D) contrast chest computed tomography (CT) with rib rendering. The anterolateral flail segment (indicated by the red lines) was located on the left rib cage; B: An axial cut of the 3D chest CT showing bilateral pleural effusion with collapsed lungs, with no evidence of heart injury.

After opening the fifth intercostal space, a large hole was identified in the pericardium (Figure 3). The inferolateral left ventricular wall was visible through the hole and was covered by a thin whitish fibrin clot. We explored the pericardial space with an index finger and confirmed no apparent abnormalities.

FINAL DIAGNOSIS

Post-traumatic pericardial rupture with a flail chest by multiple rib fractures.

TREATMENT

The pericardium was subsequently repaired with 4-0 Prolene sutures. After stabilizing the fractured ribs with plates and screws and closing the wound, the patient was transferred to the SICU in stable condition.

OUTCOME AND FOLLOW-UP

The patient was successfully weaned off the mechanical ventilator two days following the operation (Day 5 of hospitalization). The postoperative ECG findings were still abnormal but had improved (Figure 3), and the patient was transferred to the general ward on Day 7 of hospitalization.

DISCUSSION

In most cases, pericardial ruptures are diagnosed or suspected on chest CT on admission. Pneumo- or hemopericardium strongly suggests heart damage; therefore, these are considered strong indicators that intensive treatment, such as surgery, will be required. However, in the classification of traumatic cardiac dislocations proposed by Graef *et al*[3], grade I pericardial rupture without dislocation of the heart can barely be detected on CT scans, and entirely secondary findings in patients with a diaphragm with intrathoracic herniation of abdominal organs can be diagnosed by chest radiography or CT[7]. Similarly, in our case, no preoperative examination suggested pericardial rupture. In cases of silent pericardial rupture accompanied by intermittent symptomatic cardiac herniation, as in our patient, it was almost impossible to suspect pericardial rupture until a thoracotomy was performed. If the patient had not worsened due to a flail chest, the probability of finding pericardial rupture would have been extremely low.

Motto *et al*[8] reported that cardiac herniation could be intermittent; therefore, sequential evaluation is recommended. We performed serial laboratory follow-ups for elevated cardiac enzyme levels, consecutive chest CTs, and preoperative TTE. In our case, however, the pericardial hole was only 4 cm × 4 cm and was too narrow to cause a severe symptomatic cardiac herniation. Instead, we hypothesized that it may have caused intermittent ECG changes and vital instability, resembling MI. In addition, pain from the patient's rib fractures may have masked chest discomfort due to cardiac herniation. Many

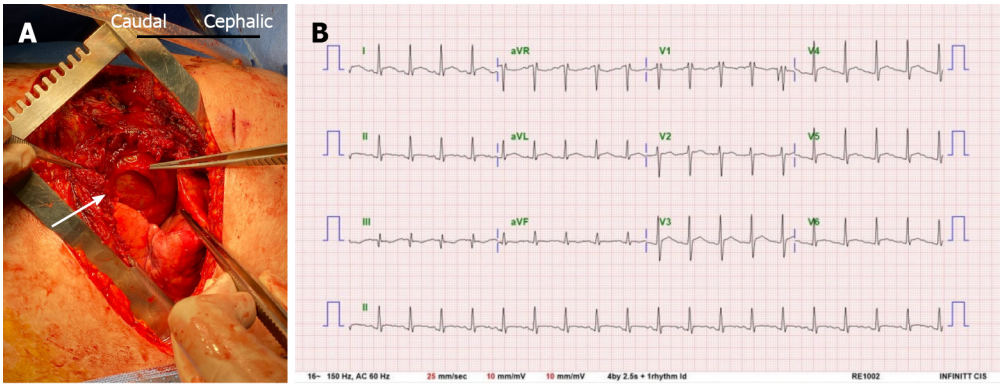

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Figure 3 Rib examination. A: The operation field during surgical stabilization of rib fractures. We routinely performed a thoracic cavity exploration before fixing the rib fractures. The white arrow indicates that the left ventricle was visible through the 4 cm × 4 cm pericardial rupture, which was an incidental finding; B: The postoperative electrocardiogram with the resolution of all ST depressions and lower ST elevations than that present in the preoperative period.

patients with cardiac contusions show elevated cardiac enzyme levels and abnormal ECG findings[9]. Finally, we deemed these findings to be typical of cardiac contusions, which do not require treatment. However, we believe that this case may not be unique, and such a mistake is common in practice.

CONCLUSION

Post-traumatic blunt pericardial rupture is a rare but fatal injury that is usually diagnosed by CT upon admission but may be asymptomatic and misdiagnosed. If a patient with blunt chest trauma shows fluctuating vital signs and accompanying ECG abnormalities, pericardial rupture and cardiac herniation should be considered.

FOOTNOTES

Author contributions: Seok J and Yoon SY wrote and revised the manuscript; Seok J, Yoon SY, and Ye JB contributed the patient care and management; Ye JB performed the initial emergency operation to rule out abdominal organ injuries; Seok J and Yoon SY performed thoracic surgery, including the pericardial repair and surgical rib fixations.

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CASE REPORT

Laparoscopic treatment of pyogenic liver abscess caused by fishbone puncture through the stomach wall and into the liver: A case report

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Abstract

BACKGROUND

Pyogenic liver abscess (PLA) due to foreign body penetration of the gastrointestinal tract is rare but can lead to serious consequences if not diagnosed and managed properly. We report a case of PLA caused by a fishbone puncture.

CASE SUMMARY

This report describes the clinical features, diagnosis and treatment of a 56-year-old male patient who presented with severe pneumonia, acute respiratory failure and septic shock. The main clinical manifestation was a nonspecific recurrent infection. Based on the findings of abdominal computed tomography examination and the detailed medical history, the diagnosis was made as PLA which was caused by fishbone puncture through the stomach wall and into the liver. After active anti-inflammatory treatment, the patient's general condition had improved. The laparoscopic drainage of the liver abscess and the foreign body removal was performed. There was no recurrence of abscess at discharge or during follow-up and the patient's general condition was satisfactory.

CONCLUSION

PLA caused by foreign bodies usually requires surgical treatment or percutaneous drainage combined with antibiotics. Our case confirms that a laparoscopic approach is safe and feasible for such cases.

Key Words: Liver abscess; Fish bone; Foreign body; Laparoscopic surgery; Case report

Core Tip: Pyogenic liver abscess (PLA) secondary to perforation of the gastrointestinal tract by a foreign body usually requires surgical treatment. This case report shows that the diagnosis of PLA caused by a foreign body is a medical challenge. Patients usually present with atypical symptoms. Clinicians should make a timely diagnosis and perform surgical intervention promptly.

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INTRODUCTION

Although ingestion of foreign bodies is common, complications are relatively rare in the clinical setting. Pyogenic liver abscess (PLA) due to gastrointestinal perforation by foreign bodies is even rarer, and the diagnosis is challenging due to the nonspecific symptoms and imaging difficulties. Timely diagnosis is very important for improving patient prognosis. If not timely diagnosed, surgical intervention for such cases may not be conducted in time, which may lead to serious consequences. This report presented a case with PLA caused by a fishbone puncture through the stomach wall and into the liver. The clinical features, diagnosis and treatment of this case were described. The report would contribute to the timely and accurate diagnosis and the treatment of PLA caused by foreign bodies.

CASE PRESENTATION

Chief complaints

A 56-year-old male patient presented with complaints of intermittent chest tightness and shortness of breath for 7 d, worsening for 1 d, and was admitted to the intensive care unit of the Emergency Department.

History of present illness

The patient presented with chest tightness and shortness of breath about 1 wk ago. One day prior, the aforementioned symptoms progressed and the patient further developed tremor of the hands, loss of appetite, general malaise and loss of consciousness without obvious cause.

History of past illness

The patient had no history of alcohol consumption, drug abuse or other high-risk behaviors causing PLA. He was in good health and denied any history of hypertension, diabetes and/or heart diseases.

Personal and family history

The patient denied any family history of hypertension, diabetes and heart diseases.

Physical examination

The patient's abdomen was soft with right upper quadrant tenderness but there was no rebound pain or muscle tension. The vital signs were as follows: Body temperature 39.2 °C; blood pressure 98/56 mmHg; heart rate 84 beats per min; respiratory rate 26 breaths per min. There was no obvious abnormalities in other physical examinations.

Laboratory examinations

Laboratory examinations showed that the white blood cell count was 22.22×10^9/L; neutrophil percentage was 91.7%; platelet count was 26×10^9/L; pH was 7.28; PCO_2 was 27 mmHg; PO_2 was 64 mmHg; HCO_3^- was 12.7 mmol/L; BE (Base Excess) was -12.5 mmol/L; C-reactive protein level was > 90 mg/L; interleukin 6 was > 5000 pg/mL; procalcitonin was > 100 ng/mL; and, myoglobin was > 2000 ug/L.

Imaging examinations

The cranial computed tomography (CT) showed that the soft tissue of the posterior top of the nasopharynx was slightly thicker. The thoracic CT observed that there were bilateral pneumonia, lung air sac in the right lung apex, multiple nodules in bilateral lungs and bilateral pleural effusion. On the abdominal and pelvic CT, there were foci with a slightly lower density in the right lobe of the liver and mixed density in segment IV of the liver near the first porta hepatis.

MULTIDISCIPLINARY EXPERT CONSULTATION

Multidisciplinary team (MDT) discussion results were as follows: On abdominal CT, there was a needle-like high-density shadow in the liver, however, this was missed in the initial report (Figure 1). The drainage from the indwelling gastric tube was brown, which suggests purulent infection. Based on these findings, we presumed that the cause of the PLA may be that the accidentally ingested fishbone may have pierced the pylorus and penetrated the liver, causing local inflammatory reaction, abscess, and the corresponding clinical manifestations. After reviewing the medical history again, it was found that the patient did have a history of eating fish a few days before the onset of disease

FINAL DIAGNOSIS

The final diagnosis was PLA caused by fishbone puncture complicated with severe pneumonia, acute respiratory failure, and septic shock.

TREATMENT

The patient received anti-inflammatory rescue therapy, electrolyte correction, and nutritional support for 8 d in the intensive care unit, and then was transferred back to the general ward. However, the patient had recurrent fever without significant decreases in the inflammatory index and was returned to the intensive care unit again. Repeat abdominal CT showed combined density, and PLA was considered based on the medical history. The diagnosis and cause of PLA were discussed by MDT. Subsequently, the patient was transferred to the Hepatobiliary Surgery Department for laparoscopic exploration. A multiport laparoscope was used. An inspection hole was made above the navel in order to introduce the laparoscope and the remaining three trocars. During the operation, it was found that there were dense adhesions between the pylorus and hepatic hilum and the liver was obviously swollen at the root of the ligamentum teres. After incision, a white foreign body about 2 cm long was found (Figure 2A), which was confirmed to be a fishbone after removal (Figure 2B). An abscess cavity was found by further in-deep exploration, which was incised and the white pus was drained. The abscess cavity was expanded and a drainage tube was placed for adequate drainage.

OUTCOME AND FOLLOW-UP

After the operation, the patient recovered smoothly. A small amount of reddish drainage fluid was observed. After 5 d of observation, the inflammatory indexes were decreased, and the above symptoms and discomfort disappeared. The drainage tube was therefore removed. The patient was discharged in stable condition. Follow-up at 2 wk and 2 mo after discharge was unremarkable.

DISCUSSION

Liver abscesses are purulent lesions of the liver caused by various pathogens such as bacteria, fungi or Entamoeba histolytica. Biliary route, portal vein route, hepatic artery route, cryptogenic route and direct route to the liver from an open wound are the common infection routes of bacterial liver abscess. Hepatic artery and open wound routes are relatively rare in clinical practice, but cannot be ignored[1]. PLA caused by foreign bodies are rare[2]. It has been reported that the incidence of foreign body penetration of the gastrointestinal tract is less than 1%, and the most common sites of gastrointestinal perforation include the stomach and duodenum. Accidental ingestion of foreign bodies is not uncommon, and the vast majority (80%-90%) of the ingested foreign bodies pass naturally through the gastrointestinal tract within 1 wk. In fact, less than 1% of the patients who ingest foreign bodies could experience symptoms, which are usually secondary to gastrointestinal obstruction or perforation[3]. PLA secondary to foreign body penetration of the gastrointestinal tract are even more rare. Lambert[4]

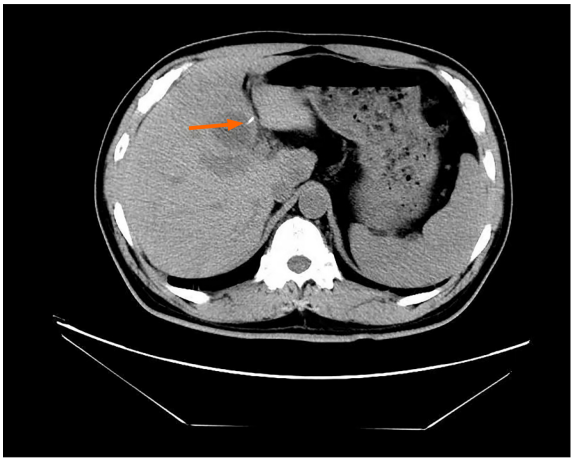

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Figure 1 Computed tomography scan showing a foreign body in the left lateral segment of the liver. The high-density foreign body is marked with an orange arrow.

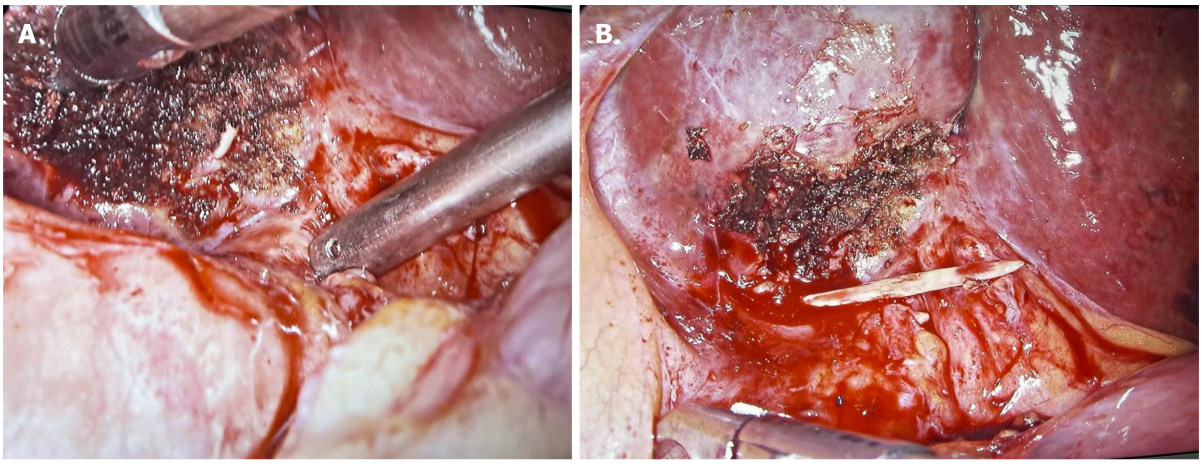

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Figure 2 Intraoperative findings. A: It was observed that a fishbone penetrated the liver and formed a purulent cavity; B: Removal of fishbone by laparoscopic surgery.

reported the first case in 1898. Since then, there has been an increasing number of studies on such cases, especially over the past 40 years. The duodenum and pylorus may be more prone to perforation[5]. PLA caused by perforation of fishbone through the stomach is relatively hidden and dangerous, which can often bring serious consequences. Theodoropoulou *et al*[6] reported a high fever in a 46-year-old man without comorbidities, who died of sepsis within 46 h of admission. In the autopsy, a fishbone was found in the liver. Their report points to the level of vigilance clinicians must be aware of in each particular case and this clinical presentation is very similar to our case reported herein. PLA is a disease well known to clinicians and its clinical manifestations are diverse. Some patients present with high fever, right upper quadrant pain, and jaundice. Most patients would be cured after anti-infective treatment, puncture, and drainage. More dangerous and systemic infection with PLA requires the identification of the cause, especially if the patient has no major infectious factors such as biliary tract infection, blood infection or diabetes. In this report, the thickening of the gastrointestinal tract adjacent to the abscess on the preoperative CT examination, as well as the presence of intraoperative adhesions, were clues of PLA secondary to foreign body penetration of the gastrointestinal tract. The clinical manifestations of PLA caused by foreign bodies are usually ambiguous and nonspecific, but abdominal pain (77.3%) and fever (58%) are the most common symptoms[7,8]. Occasionally, acute upper gastrointestinal bleeding may be present[9]. Chen *et al*[10] have summarized 86 cases of liver abscess caused by foreign bodies such as toothpicks, fishbones, chicken bones, needles, *etc.* They listed many groups at risk for foreign body perforations, including prison inmates, mentally ill, alcoholics, children, the elderly, carpenters, and tailors. Other conditions included fast food, hot or cold drinks, cognitive impairment, and people wearing dentures. Early identification and extraction of foreign bodies causing gastrointestinal perforation is critical to avoid morbidity and mortality[11,12]. However, early diagnosis

is challenging due to the lack of specific findings, the lack of patient awareness of foreign body ingestion, and the low index of suspicion by the medical team for the specific condition. Liver abscess due to foreign body ingestion is still rare and a difficult diagnosis because most patients do not recall foreign body ingestion events and usually present with nonspecific symptoms[13]. Moreover, the foreign bodies are not visible on X-rays and sometimes not even on CT scans.

It is worth noting that there can be a considerable time span of months or even years between the ingestion event and the onset of symptoms of an inflammatory lump or abscess. If foreign body perforation is not properly diagnosed in a timely manner, percutaneous interventional drainage can lead to recurrence or persistence of abscesses, and can even lead to a life-threatening sepsis. Therefore, in refractory abscess after interventional drainage and antibiotics, PLA caused by foreign bodies, although rare, should be considered as the underlying pathogenesis. Clinicians should also be aware that older adults wearing dental prosthetic devices may ingest foreign bodies. CT scans are currently the gold standard for diagnosing foreign body ingestion due to their high resolution and accuracy. Foreign bodies usually appear as high-density linear objects on CT, and CT scans of foreign body ingestion can also determine the presence of perforation, the degree of intra-abdominal inflammation with or without abscess formation, and adjacent organ damage[14]. Contrast-enhanced CT scan is the standard diagnostic modality that provides high resolution and accuracy, followed by abdominal ultrasound[15]. In this report, CT scan was also used for diagnosis. For patients with poor tolerance, unstable vital signs, or contraindications to resection, conservative treatment and supportive treatment can be accepted as the first step, and the situation will improve after re-evaluation. The removal of foreign bodies can be considered at the time of diagnosis. In the 86 cases summarized by Chen *et al*[10], the foreign bodies in the liver were successfully removed after exploratory laparotomy and 2 cases received laparoscopy for foreign body removal. Comparing the difference between traditional exploratory laparotomy and laparoscopy, it could be concluded that the postoperative hospital stay after laparoscopic surgery is significantly shorter than that of laparotomy. Burkholder and Samant[16] treated a case with fish bone-induced liver abscess with antibiotics and percutaneous drainage, avoiding the need for open surgical intervention. They concluded that percutaneous drainage was the appropriate first line treatment in most cases, even in cases of retained foreign body. When the percutaneous drainage and antibiotics are not effective, removal of foreign bodies causing the PLA is necessary, and laparoscopic surgery is an effective method for the treatment of PLA caused by foreign bodies[17].

CONCLUSION

Cases of PLA secondary to foreign body penetration of the gastrointestinal tract are extremely rare, the diagnosis of which requires comprehensive analysis and evaluation of the medical history, imaging data, disease progression and systemic condition. Surgery is an effective way to remove the cause, and laparoscopic removal of the foreign bodies is also an effective minimally invasive treatment. Meanwhile, clinicians should improve the understanding of this type of disease, and achieve early detection and early treatment, which is conducive to the prognosis of patients.

FOOTNOTES

Author contributions: Kadi A and Tuergan T are the co-first authors who organized the case content, collected all relevant data and drafted the manuscript; Shalayiadang P performed the surgical procedure; Tayier B and Tuohuti M participated in collecting the clinical data; Abulaiti Y and Abulizi A performed the literature research and contributed to manuscript revision; Ahan A conceived the study design, interpreted all data and revised the manuscript in depth; all authors have read and approved the final manuscript.

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CASE REPORT

Hepatic sinusoidal obstruction syndrome induced by tacrolimus following liver transplantation: Three case reports

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Abstract

BACKGROUND

Hepatic sinusoidal obstruction syndrome (HSOS) is a rare complication in solid organ transplant recipients, especially in liver transplantation recipients. However, the consequences of HSOS occurrence are pernicious, which could result in severe liver or renal failure, and even death. In addition to previously reported azathioprine and acute rejection, tacrolimus is also considered as one predisposing factor to induce HSOS after liver transplantation, although the underlying mechanism remains unclear.

CASE SUMMARY

In this study, we reported three cases of tacrolimus-related HSOS after liver transplantation. The diagnosis of HSOS was firstly based on the typical symptoms including ascites, painful hepatomegaly and jaundice. Furthermore, the features of patchy enhancement on portal vein and delayed phase of abdominal enhanced computed tomography were suspected of HSOS and ultimately confirmed by liver biopsy and histological examination in two patients. A significant decrease in ascites and remission of clinical symptoms of abdominal distention and pain were observed after withdrawal of tacrolimus.

CONCLUSION

Tacrolimus-induced HSOS is a scarce but severe complication after liver transplantation. It lacks specific symptoms and diagnostic criteria. Timely diagnosis of HSOS is based on clinical symptoms, radiological and histological examinations. Discontinuation of tacrolimus is the only effective treatment. Transplantation physicians should be aware of this rare complication potentially induced by tacrolimus.

Key Words: Hepatic sinusoidal obstruction syndrome; Tacrolimus; Refractory ascites; Orthotopic liver transplantation; Case report

Core Tip: Tacrolimus-induced hepatic sinusoidal obstruction syndrome (HSOS) is a scarce but severe complication after liver transplantation. It lacks specific symptoms and diagnostic criteria. Timely diagnosis of HSOS is based on clinical symptoms, radiological and histological examinations. Discontinuation of tacrolimus is the only effective treatment. Transplantation physicians should be aware of this rare complication potentially induced by tacrolimus.

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INTRODUCTION

Hepatic sinusoidal obstruction syndrome (HSOS), previously known as hepatic veno-occlusive disease (HVOD), is a rare disorder characterized by painful hepatomegaly, ascites, weight gain and jaundice[1]. The initial lesion of HSOS originated from the injury of hepatic sinusoidal endothelial cells, followed by the migration of damaged sinusoidal endothelial cells to the centrilobular veins, thus contributing to progressive fibrocystic occlusion of centrilobular veins and congestion of hepatic sinusoidal veins, and finally leads to intrahepatic post sinusoidal portal hypertension[2].

The diagnosis of HSOS is relatively difficult owing to the lack of specific symptoms. Although ascites, painful hepatomegaly and jaundice are identified as the most typical symptoms of HSOS, the clinical presentations are variable, from few symptoms to multi-organ failure and even death[3]. At present, the clinical suspicion of HSOS is based on the Baltimore and modified Seattle criteria which was actually formed for the diagnosis of HSOS in hematopoietic stem cell transplantation (HSCT) recipients[4]. In addition, no diagnostic criteria are available for HSOS after liver transplantation. Doppler ultrasound examination can present some non-specific signs of HSOS, including ascites, hepatomegaly and attenuated hepatic veins[5]. Moreover, enhanced computed tomography (CT) can further confirm the ultrasound findings. A flow obstruction is suspected if it shows patchy enhancement of the liver with unclear hepatic veins on the portal vein phase and delayed phase[6]. Additionally, magnetic resonance imaging (MRI) can monitor similar signs[7]. It also needs to exclude other diseases, such as Budd-Chiari syndrome, acute rejection, ischemic liver injury and biliary stricture. So, liver biopsy is recommended as the gold standard for the diagnosis of HSOS[8].

State of the art

In general, the frequencies of HSOS are associated with large amounts of toxins or drugs during chemotherapies, immuno-suppressive therapies and irradiation. It was reported that the main causes of HSOS were highly related with high-dose chemotherapy regimens and irradiation in HSCT recipients, as well as in liver, lung, renal and pancreatic transplantation recipients in Western countries[2]. In contrast, HSOS is most frequently associated with oral intake of Chinese herbal medicines that contain pyrrolidine alkaloids in China[8]. As reported, the morbidity of HSOS after liver transplantation was rare, only ranging from 1.9% to 2.3%[9]. However, although rare, the mortality rate of severe HSOS is more than 90%[4].

For liver transplantation recipients, azathioprine and acute rejection were thought to be two main causes of HSOS[10]. Recently, several studies have reported that tacrolimus could cause HSOS and discontinuation of the drug may be the only effective treatment[5,10,11]. In this study, we present 3 cases of HSOS related to tacrolimus after orthotopic liver transplantation. Among them, only one patient experienced acute rejection. All patients underwent orthotopic liver transplantation for hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC). Tacrolimus and mycophenolate mofetil were applied as the initial immunosuppressive therapy. Acute rejection occurred in one patient and was relieved after the application of corticosteroid. Also, the immunosuppressive treatments were converted to sirolimus after the diagnosis of HSOS. Eventually, two patients achieved clinical remission after the discontinuation of tacrolimus, while one patient died of gastrointestinal bleeding and acute renal failure. To the best of our knowledge, this is the first paper to present the dynamic course with clinical manifestation, radiological, pathological features and treatment for HSOS after liver transplantation.

CASE PRESENTATION

Chief complaints

Case 1: A 43-year-old man was hospitalized on POD (post-operative day) 14 after liver transplantation with chief complaints of abdominal pain and distension accompanied by poor appetite for 2 d.

Case 2: A 56-year-old man was readmitted on POD 50 after liver transplantation with chief complaints of fatigue and abdominal distension, accompanied by chest stuffiness for 10 d.

Case 3: A 57-year-old man went to the doctor with the chief complaints of abdominal pain and distention, accompanied by 850 mL of ascites and was hospitalized on POD 14 after liver transplantation.

History of present illness

Case 1: The patient described that abdominal pain and distension occurred 2 d ago. These symptoms were particularly severe in the upper abdomen. Although diuretics were administrated, abdominal distention was not relieved and renal function deteriorated. He also suffered from poor appetite and hypourocrinia.

Case 2: The patient suffered from abdominal distension and paroxysmal upper abdominal pain without any obvious inducement 10 d ago, accompanied by chest stuffiness and oliguria. Although diuretics were applied, the symptoms did not relieve significantly.

Case 3: The patient described that abdominal pain and distention occurred on postoperative day (POD) 14 after liver transplantation and this was accompanied by 850 mL of ascites. Diuretics were administrated but showed ineffective. The amount of ascites continued to increase, which peaked at 1050 mL on POD 16.

History of past illness

Case 1: The patient had a history of hepatitis B virus infection for more than 20 years and was diagnosed with HCC (BCLC stage A) at a local hospital about 8 mo ago. After the diagnosis of HCC, he received two radiofrequency ablations and one transcatheter arterial chemoembolization. However, the tumor was not completely necrotic and parts of it remained viable. At last, the patient underwent orthotopic liver transplantation. No specific pathology was observed in the graft liver at the time of transplantation. It took about 8 h for the operation, which was performed successfully with the satisfactory reconstruction of the vessels and biliary duct. The donated liver worked well after transplantation and the early recovery post-operative period was uneventful. The liver function and coagulation returned to normal 1 wk after transplantation. The portal venous phase of contrast-enhanced CT on POD 10 showed the blood flow of hepatic veins were fluent. No stenosis was observed at the vascular anastomosis of hepatic veins or the suprahepatic inferior vena cava (Figure 1). The patient was discharged 12 d after transplantation and administered a routine immunosuppressive treatment consisting of tacrolimus (1.5 mg, twice daily) and mycophenolate mofetil (MMF).

Case 2: The patient was a hepatitis B virus carrier for more than 20 years and took entecavir regularly. He received orthotopic liver transplantation for HBV-related HCC 1.5 mo ago. The operation was successful and early recovery after transplantation was smooth. The liver function and coagulation function returned to normal 10 d after liver transplantation. The patient was discharged on POD 14 following liver transplantation.

Case 3: The patient had a history of hepatitis B virus infection for 10 years. He was diagnosed with HCC 2 mo ago and received transcatheter arterial chemoembolization therapy. But the tumor was not completely necrotic. At last, he underwent orthotopic liver transplantation for small HCC. The operation was successfully performed and the early recovery after transplantation was stable. Liver function returned to normal 1 wk after transplantation while it showed a little fluctuation on POD 8. It was suspected that the patient suffered from acute rejection after liver transplantation. So, methylprednisolone was applied to enhance anti-immune rejection and the liver function soon returned to normal.

Personal and family history

Case 1: The patient had a history of hepatitis B virus infection for more than 20 years. There were no other special findings in his personal and family history.

Case 2: There were no other special findings in his personal and family history except for a history of hepatitis B virus.

Case 3: The patient had a history of hepatitis B virus infection for 10 years. There were no other special findings in his personal and family history.

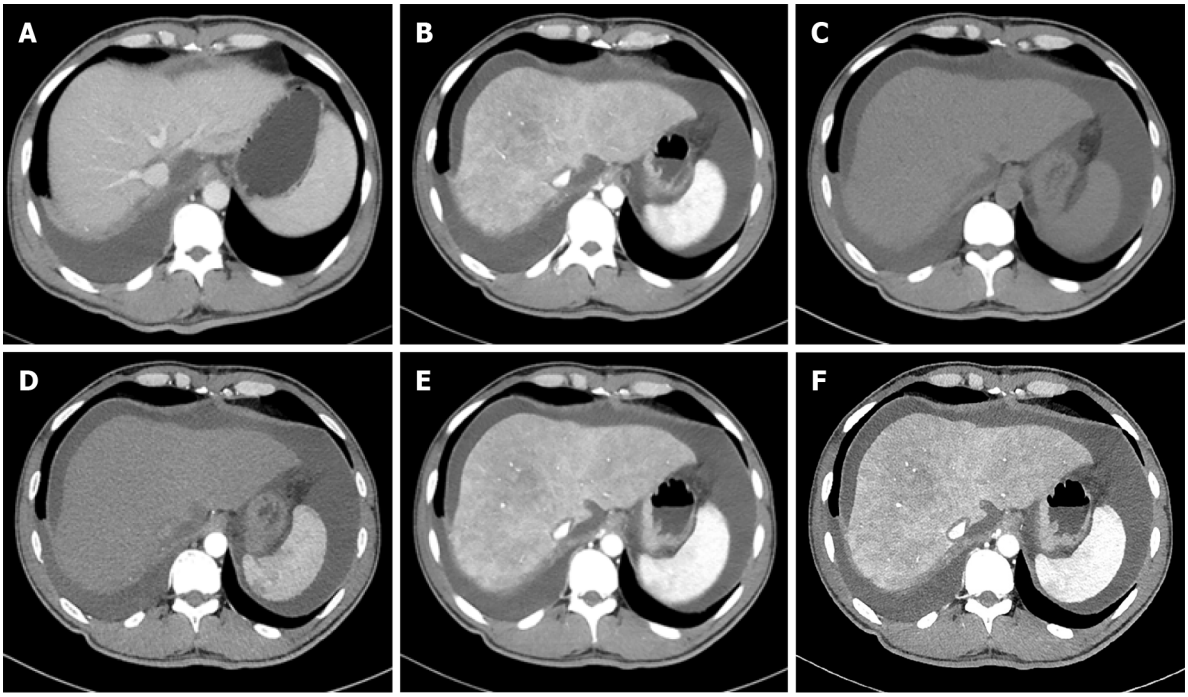

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Figure 1 Typical abdominal contrast-enhanced computed tomography features of hepatic sinusoidal obstruction syndrome after liver transplantation. A: Portal venous phase computed tomography (CT) on postoperative day (POD) 10 showed the blood flow of hepatic veins were fluent. No stenosis was observed at the vascular anastomosis of hepatic veins and suprahepatic inferior vena cava; B: Portal venous phase CT on POD 14 showed hepatic veins were obscured, while no stenosis was observed at the vascular anastomosis of suprahepatic inferior vena; C, D: Plain scan and arterial phases CT on POD 14 showed that liver parenchyma was heterogeneous low-density; E, F: Portal venous phase CT on POD 14 showed enlarged liver with patchy enhancement, massive ascites and unclear hepatic veins and these signs existed persistently to delayed phase.

Physical examination

Case 1: Physical examination revealed hepatomegaly and positive shifting dullness of the abdomen.

Case 2: Physical examination showed positive shifting dullness of the abdomen.

Case 3: Physical examination showed no positive signs.

Laboratory examinations

Case 1: Laboratory examinations showed a mildly abnormal liver function, severe renal insufficiency and hyperkalemia. Tests of viral infection of hepatitis A, B, C, D, E as well as cytomegalovirus and Epstein-Barr virus were all negative and the serum trough concentration of tacrolimus was 8.0 ng/mL. The clinical characteristics during the disease were shown in Table 1.

Case 2: Laboratory examinations showed liver function was a little increased, but renal function had continuously deteriorated. Blood routine examination was normal. Virus infections such as hepatitis A, B, C, D, E as well as cytomegalovirus and Epstein-Barr virus were all negative. The serum trough concentration of tacrolimus was higher than 30 ng/mL. The patient presented with 1200 mL of ascites drainage when admitted and it peaked at 2480 mL on POD 59. The clinical characteristics during the disease were shown in Table 1.

Case 3: Laboratory examinations revealed a mild elevation of total bilirubin, aminotransferase and the biliary enzyme spectrum. Virus infections such as hepatitis A, B, C, D, E as well as cytomegalovirus and Epstein-Barr virus were negative while renal function got worse and worse. The minimal serum concentration of tacrolimus was 6.9 ng/mL. The clinical characteristics during the disease were shown in Table 1.

Imaging examinations

Case 1: Ultrasonography demonstrated that more than 2000 mL of ascites and an enlarged liver were present. Abdominal enhanced CT showed an enlarged liver with patchy enhancement and unclear hepatic veins with massive ascites (Figure 1).

Case 2: Ultrasonography showed large amount of ascites and an enlarged liver. Enhanced CT on POD 57 showed the liver with patchy enhancement, indistinct hepatic veins, massive ascites and pleural

Table 1 Clinical characteristics of three presented cases during the disease course

No.	Age (yr)/sex	Clinical course	POD (d)	Ascites (mL/d)	TBIL (μmol/L)	ALT (U/mL)	AST (U/mL)	GGT (U/mL)	ALP (U/mL)	Scr (μmol/L)	BUN (mmol/L)	GFR (mL/min/L)
1	43/M	Diagnosis of HSOS	13	4600	28.2	97.6	173.2	244.6	240	231	25.61	26.92
		Tac → Siro	69	3250	48.4	273.6	210.7	113.1	153	379.9	40.11	15.16
		Discharged	74	2150	23.5	12.2	25.8	72.6	123	679.1	53.97	7.76
2	56/M	Diagnosis of HSOS	50	1200	28.2	48.7	54.3	89.2	122	227.7	13.15	25.94
		Tac → CsA + Siro	59	2480	20.4	39.2	38.3	50.7	94	702	18.33	7.08
		Resolution	87	30	12.7	22.3	27.6	79.2	121	72	3.56	97.96
3	57/M	Diagnosis of HSOS	15	850	22.5	143.6	47.3	129.9	159	111.5	12.28	58.93
		Tac → Siro	23	400	26.6	37.1	17.7	59.8	102	176.1	25.11	34.77
		Resolution	37	50	13.6	37.2	27.3	26.8	81	66.9	10	106.25

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; GFR: Glomerular filtration rate; GGT: Gamma-glutamyl transpeptidase; HSOS: Hepatic sinusoidal obstruction syndrome; POD: Postoperative day; Scr: Serum creatinine; Siro: Sirolimus; Tac: Tacrolimus; TBIL: Total bilirubin.

effusion at the phases of portal vein and a delayed period (Figure 2).

Case 3: Ultrasonography revealed an enlarged liver with moderate ascites and reflux of the left portal vein. Enhanced abdominal CT showed an enlarged liver with patchy enhancement and moderate ascites.

FINAL DIAGNOSIS

Case 1

All these findings supported the diagnosis of a tacrolimus-related HSOS by excluding the possibilities of viral infection, chylous fistula, tumor recurrence or acute rejection.

Case 2

The patient was suspected of HSOS as acute rejection and viral infections were excluded. Liver biopsy was performed on POD 59 and the results showed hepatocyte edema, dilatation and congestion of hepatic sinusoidal with the formation of a local thrombosis (Figure 3). These results were in favor of the diagnosis of tacrolimus-related HSOS.

Case 3

The patient was suspected of HSOS based on the clinical symptoms and radiological examinations. To confirm the diagnosis of HSOS, he received a liver biopsy. The liver biopsy demonstrated dilatation and congestion of the hepatic sinusoidal with focal moderate edema of hepatocytes, enlarged portal area, lymphocytic infiltration, and venous endocarditis (Figure 3). The patient was finally diagnosed with HSOS by excluding acute rejection, obstruction of outflow, viral infection and biliary complications.

TREATMENT

Case 1

Although diuretics were administrated on admission, abdominal distention was not relieved and the renal function deteriorated. Ascites and pleural effusion were drained to alleviate the symptoms. The serum trough concentration of tacrolimus was 9 ng/mL on POD 20. Upon the diagnosis of HSOS, tacrolimus was switched to sirolimus with MMF being continued and enoxaparin was applied to improve the congestion of small hepatic veins.

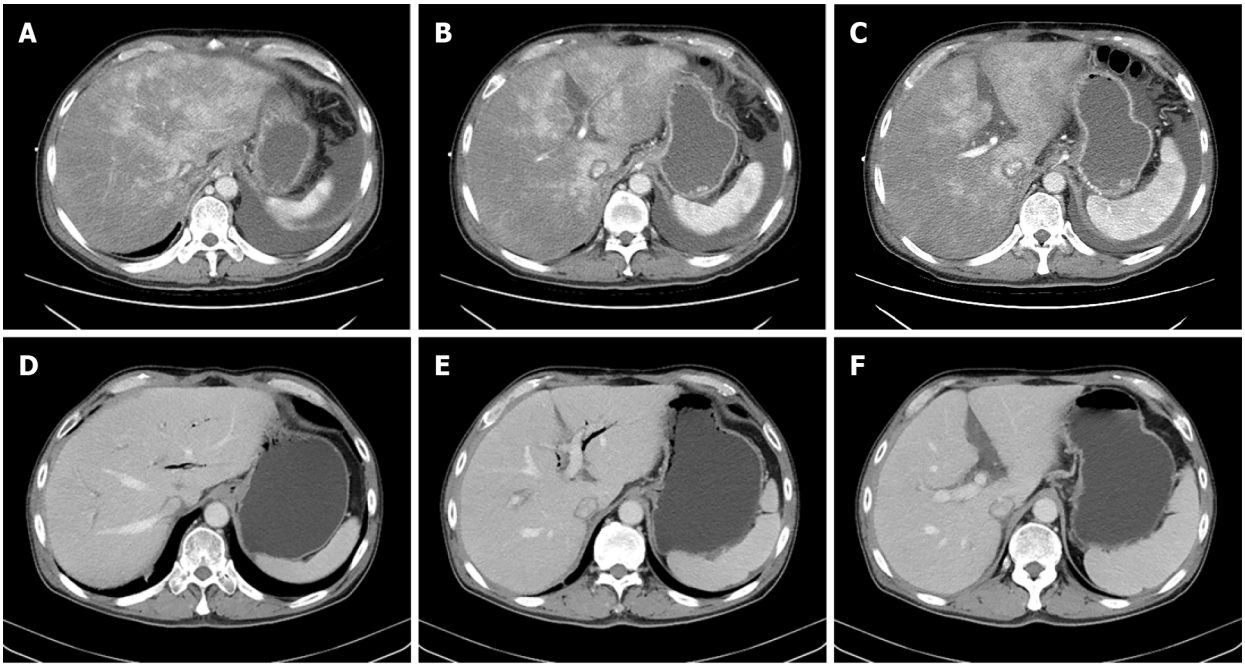

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Figure 2 Contrast-enhanced computed tomography images of Case 2 before and after switching tacrolimus to sirolimus. A, B, C: Before changing tacrolimus to sirolimus, portal venous phase computed tomography (CT) showed enlarged liver with patchy enhancement, moderate to massive ascites and obscured hepatic veins on postoperative day (POD) 59 after liver transplantation; D, E, F: After switching tacrolimus to sirolimus, portal venous phase CT showed normal liver with resolved patchy enhancement and disappeared ascites, and clear hepatic veins on POD 175.

Case 2

Diuretics were applied but proved to be ineffective. Ascites and pleural effusion were drained to relieve the symptoms of abdominal distention. The patient was finally diagnosed with HSOS, tacrolimus was replaced by sirolimus, and enoxaparin was used for antithrombotic therapy.

Case 3

At first, it was suspected that the patient suffered from acute rejection after liver transplantation. So, methylprednisolone was applied to enhance anti-immune rejection, and liver function soon returned to normal after that. Diuretics were also applied to relieve the clinical symptoms. But the amount of ascites continued to increase where diuretics were ineffective, which peaked at 1050 mL on POD 16. As tacrolimus was thought to be the most predisposing factor for HSOS. Upon the diagnosis of HSOS, tacrolimus was replaced by a sirolimus-based regimen and the MMF continued.

OUTCOME AND FOLLOW-UP

Case 1

After the adjustment of immunosuppressant, the amount of ascites reduced and the symptoms were alleviated but then deteriorated from an upper gastrointestinal hemorrhage. The patient ultimately died of upper gastrointestinal hemorrhage and acute renal failure.

Case 2

As tacrolimus was replaced by sirolimus, the amount of ascites and plural effusion was significantly reduced and the symptoms of abdominal distention were also relieved after these treatments. After liver and renal function returned to normal, the patient was discharged on POD 87. Two months later, the abdomen enhanced CT showed normal morphology of liver, homogenous enhancement and clear hepatic veins without ascites (Figure 2). And the patient remained asymptomatic during the last follow-up.

Case 3

The levels of liver enzymes and total bilirubin decreased continuously and returned to normal after discontinuation of tacrolimus. The ascites reduced to 50 mL on POD 34. The liver function and renal function recovered to normal. The patient was discharged on POD 36 and remained asymptomatic on immuno-suppressive treatment of sirolimus and MMF in the last follow-up.

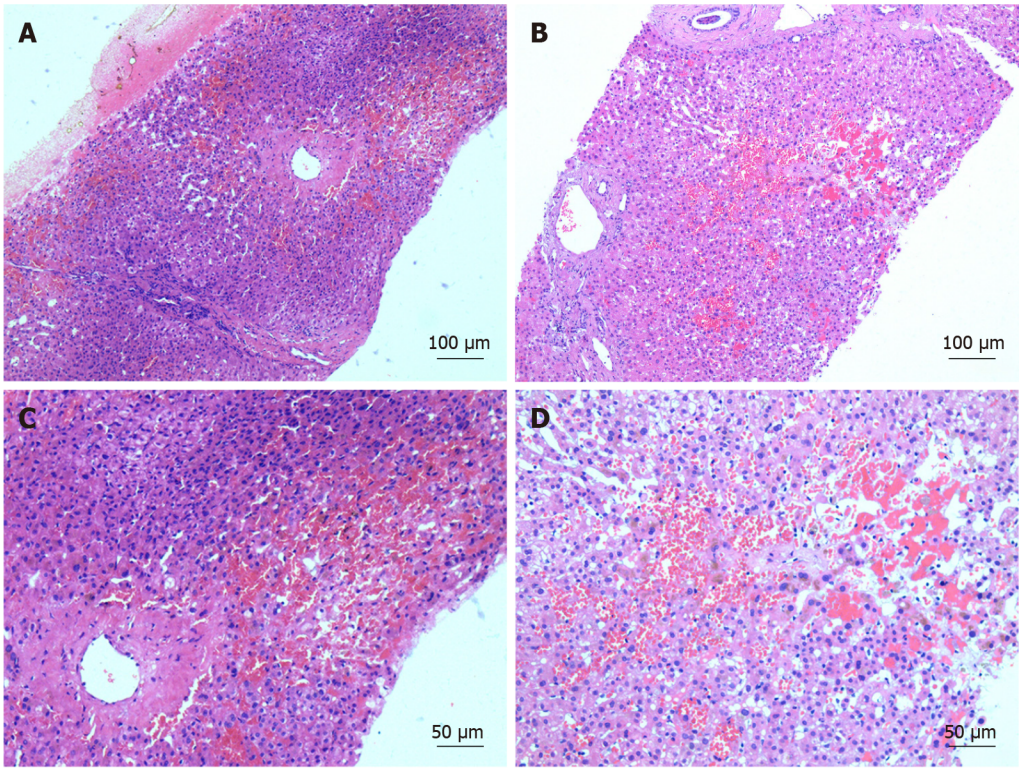

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Figure 3 Typical pathological features of hepatic sinusoidal obstruction syndrome after liver transplantation. A and C: Histopathologic examination of Case 2 showed congestion of hepatic sinusoids, fibrosis of centrilobular veins and edema in portal areas; B and D: Histopathologic examination of Case 3 showed significant dilation and congestion of sinusoids, regional hepatocytes necrosis, infiltration of red blood cells in the space of Disse, and fibroplasias in the portal areas (A, B magnification, × 100; C, D magnification, × 200).

DISCUSSION

HSOS is a rare complication after liver transplantation, which ranges from 1.9% to 2.3% according to the literature[9,10]. Although the incidences are quite low, HSOS can cause graft failure and even death in liver transplant recipients[2]. So, it's of great importance to recognize the clinical characteristics of HSOS in liver transplantation recipients. HSOS is associated with injury of hepatic sinusoidal endothelial cells, which might be induced by many toxic agents, such as chemotherapeutic drugs, immunosuppressants, and Chinese herbal medicines containing pyrrolizidine alkaloids[1,8]. Azathioprine and acute rejection are considered as two main predisposing factors to induce HSOS after liver transplantation. In fact, azathioprine is rarely used nowadays due to its vascular hepatotoxicity. Although the incidences of acute rejection decreased due to the applications of new immunosuppressants, the morbidity of HSOS after liver transplantation remained unimproved. Therefore, we reviewed the literature on HSOS after liver transplantation[5,9-14], and recent progress in the early diagnosis and treatment of HSOS after liver transplantation were presented in Table 2. Several recent studies showed that tacrolimus was the most possible predisposing factor to induce HSOS and withdrawal of the drug may be the only effective treatment. Recently, some research also reported tacrolimus-related HSOS in renal, pancreas and lung transplantations[5,15-17]. However, the mechanism of tacrolimus-related HSOS still remains unclear. One possible explanation is that the genetic polymorphisms of cytochrome P450 and glutathione-S-transferase influence the metabolism of tacrolimus, thus resulting in hepatoxicity[2,18]. In this study, we describe 3 patients suffering from HSOS after liver transplantation, among which one experienced acute rejection. Two patients were relieved of symptoms after switching from tacrolimus to sirolimus, indicating that tacrolimus might be the most relevant predisposing factor. However, this study was a single center retrospective case report and the sample size was small. The evidence may not be convincing. In the future, multicenter large sample retrospective case-control studies and randomized controlled studies are needed to verify these results.

Although the typical symptoms of HSOS are painful hepatomegaly, ascites and jaundice, the clinical manifestations of HSOS after liver transplantation are not specific. Thus, early diagnosis of HSOS is difficult, which may lead to a missed diagnosis or misdiagnosis. Besides, pathology is the gold standard for diagnosing HSOS and liver biopsy is difficult to achieve in most patients because of various reasons, such as severe coagulation disorders, massive ascites, patient refusal of an invasive examination and so on. It was reported that reversed blood flow in the branch of the portal vein may be the positive sign of HSOS[19]. In fact, we found reversed blood flow in the left branch of the portal vein and an ultimately

Table 2 Literature review of recent progresses in the diagnosis and treatment of hepatic sinusoidal obstruction syndrome after liver transplantations

Ref.	Number of patients	Etiology of HSOS	Time after OLT	Symptoms of HSOS	Screening method of HSOS	Final diagnosis method of HSOS	Treatments
Li *et al* [5], 2022	1	Tacrolimus	4 mo	Abdominal distention, enlarged graft, and ascites	Doppler ultrasound and Contrast-enhanced CT	Liver biopsy: sinusoidal congestion and fibrosis of centrilobular veins	Withdraw tacrolimus and switch to CsA and MMF
Zhou *et al*[14], 2021	1	Tacrolimus	36 d	Abdominal distension, weight gain, ascites and positive shifting dullness	Abdominal CT	Liver biopsy: sinusoidal dilation, congestion, and fibrosis of centrilobular veins	Switch from tacrolimus to CsA and MMF
Li *et al* [11], 2020	5	Tacrolimus, acute rejection	6 to 183 d	Hepatomegaly, jaundice and ascites	Ultrasonography and CT	Liver biopsy: sinusoidal dilation, congestion, fibroplasias in portal areas, acute rejection, fibrous obliteration and edema in portal area.	Withdraw tacrolimusand switch to CsA-based regimen
Hosseini *et al*[13], 2018	1	Tacrolimus	10 d	Massive ascites	Color doppler ultrasonography	Liver biopsy: no significant abnormality	Convert tacrolimus to sirolimus
Shen *et al* [10], 2015	1	Tacrolimus	80 d	Anorexia, abdominal pain, polypnea, hepato-megaly, ascites and positive shifting dullness	Ultrasonography and CT	Liver biopsy: sinusoidal congestion and fibrosis of centrilobular veins	Switch from tacrolimus to CsA and MMF
Sebagh *et al*[12], 2011	31 of 1364	Acute rejection, tacrolimus, CsA and oxaliplatin	9 to 7378 d (median, 230 d)	Hepatomegaly, ascites, pleural effusion, pruritus or jaundice	Doppler ultrasound	Liver biopsy: fibrous obliteration of centrilobular veins, centrilobular hemorrhagic necrosis, sinusoidal dilatation and congestion, peliosis, and nodular regenerative hyperplasia	Withdraw hepatic toxic drugs, change the immunosuppression regimen, anticoagulation therapy, TIPS and re-transplantation
Sebagh *et al*[9], 1999	19 of 1023	Azathioprine and acute rejection	8 to 3972 d (median, 15 d)	Jaundice, painful hepatomegaly, ascites	Doppler ultrasound	Liver biopsy: sinusoid-aldilatation, centrilobular congestion and acute rejection	Withdraw Azathioprine, convert to tacrolimus, TIPS and re-transplantation

CT: Computed tomography; CsA: Cyclosporine A; HSOS: Hepatic sinusoidal obstruction syndrome; MMF: Mycophenolate mofetil; OLT: Orthotopic liver transplantation; TIPS: Transjugular intrahepatic portosystemic shunt.

formed thrombus in Case 3. Some studies analyzed the radiologic characteristics of HSOS and they found that an enlarged liver with patchy enhancement, massive ascites and pleural effusion accompanied by slender hepatic veins due to congestion of sinusoidal were the common features of abdominal enhanced CT and MRI of HSOS. The patchy enhancement of liver on abdominal enhanced CT and MRI is rarely presented in other liver diseases[6,7]. Therefore, the radiologic features are of great value in the diagnosis of HSOS and the extent of liver patchy enhancement might be highly associated with the prognosis of HSOS.

In fact, it still lacks an evidence-based treatment for HSOS after liver transplantation at present. Though defibrotide was recommended for HSOS treatment after HSCT, it was proven ineffective on patients with HSOS after liver transplantation[8]. All three patients in our study were not exposed to azathioprine or other hepatoxicity drugs except tacrolimus and tacrolimus was recognized as the potentially offending drug, so it was discontinued thereafter .The immunosuppressant therapy was replaced by sirolimus, where mycophenolate mofetil was continued. A significant decrease in ascites and remission of clinical symptoms of abdominal distention and pain were achieved following the discontinuation of tacrolimus, which further verified the suspicion that HSOS was triggered by tacrolimus. Although we and other researchers speculated tacrolimus may be the most possible predisposing factor for inducing HSOS after liver transplantation, the mechanism remains unclear. Further basic studies are needed to clarify the underlying mechanism.

CONCLUSION

In conclusion, we present three cases of HSOS after liver transplantation. The diagnosis of HSOS was first based on the typical symptoms including ascites, painful hepatomegaly and jaundice. Furthermore, the features of patchy enhancement on portal vein and delayed phase of abdominal enhanced CT were suspected of HSOS and ultimately confirmed by liver biopsy in two patients. Clinical and radiologic remissions were observed after withdrawal of tacrolimus. Transplantation physicians should be aware of this rare complication that might be caused by tacrolimus.

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CASE REPORT

Staphylococcus aureus bacteremia and infective endocarditis in a patient with epidermolytic hyperkeratosis: A case report

Yu Chen, Dian Chen, Hao Liu, Chen-Guang Zhang, Lin-Lin Song

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Abstract

BACKGROUND

Staphylococcus aureus bacteraemia (SAB) is among the leading causes of bacteraemia and infectious endocarditis. The frequency of infectious endocarditis (IE) among SAB patients ranges from 5% to 10%-12%. In adults, the characteristics of epidermolytic hyperkeratosis (EHK) include hyperkeratosis, erosions, and blisters. Patients with inflammatory skin diseases and some diseases involving the epidermis tend to exhibit a disturbed skin barrier and tend to have poor cell-mediated immunity.

CASE SUMMARY

We describe a case of SAB and infective endocarditis in a 43-year-old male who presented with fever of unknown origin and skin diseases. After genetic tests, the skin disease was diagnosed as EHK.

CONCLUSION

A breached skin barrier secondary to EHK, coupled with inadequate sanitation, likely provided the opportunity for bacterial seeding, leading to IE and deep-seated abscess or organ abscess. EHK may be associated with skin infection and multiple risk factors for extracutaneous infections. Patients with EHK should be treated early to minimize their consequences. If patients with EHK present with prolonged fever of unknown origin, IE and organ abscesses should be ruled out, including metastatic spreads.

Key Words: *Staphylococcus aureus* bacteremia; Infective endocarditis; Epidermolytic

hyperkeratosis; Case report

Core Tip: Emergency physicians often encounter patients with fever of unknown origin, some of who present with skin diseases. We hope the case can heighten awareness that, in patients with epidermolytic hyperkeratosis or other skin diseases presented with prolonged pyrexia, infectious endocarditis, *Staphylococcus aureus* bacteraemia and organ abscess could be identified and treated early to minimize the consequences and avoid further life-threatening episodes.

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INTRODUCTION

Epidermolytic hyperkeratosis (EHK), originally termed bullous congenital ichthyosiform erythroderma, is a rare autosomal dominant disorder caused by mutations in keratins 1 and 10. It has characteristics of erythema, blistering, erosions and skin denudation present at birth and develop marked hyperkeratosis in adults[1,2]. EHK is easy to distinguish from other congenital ichthyoses through its pathological features[2]. These manifestations are due to mutations in genes mostly involved in skin barrier formation. When the skin barrier function is significantly impaired, it can lead to hypernatremic dehydration, impaired thermoregulation, increased risk for eletrolyte imbalances and infection. A breached skin barrier secondary to EHK is likely to provide the opportunity for bacterial seeding and invasion, leading to *Staphylococcus aureus* bacteraemia (SAB) and infectious endocarditis, as in our case. We discuss a case of SAB and infective endocarditis in a 43-year-old man with EHK and no history of drug addiction.

CASE PRESENTATION

Chief complaints

A 43-year-old male presented with a 10-d history of pyrexia, fatigue, diarrhoea, and weight loss.

History of present illness

Upon presentation, he was pyrexial at 39°C, accompanied by fatigue, confusion, and diarrhoea.

History of past illness

He regarded his skin disease as psoriasis since childhood, with recurrently diffuse palmoplantar hyperkeratosis, erythema and hypernatremia on the flexor surfaces of both arms. He was not on regular medications and had never sought medical advice about his hyperkeratosis. He had never smoked, did not drink alcohol, and had no history of drug addiction. The patient had never received professional dermatological treatment.

Personal and family history

The patient had no significant prior family history.

Physical examination

The patient was pyrexial at 39°C with a blood pressure of 132/78 mmHg on admission. His hyperkeratosis affected his upper and lower limbs as diffuse palmoplantar hyperkeratosis, erythema, and scales on the flexor surfaces of both arms (Figure 1). He had a systolic murmur over the mitral area but did not exhibit the meningeal irritation sign or cardiopulmonary or abdominal issues.

Laboratory examinations

White cell counts and C-reactive protein levels were elevated to 17.07 × 10^9 cells/L and above 250 mg/L, respectively. His procalcitonin levels were 3.38 ng/mL. His tests for human immunodeficiency virus

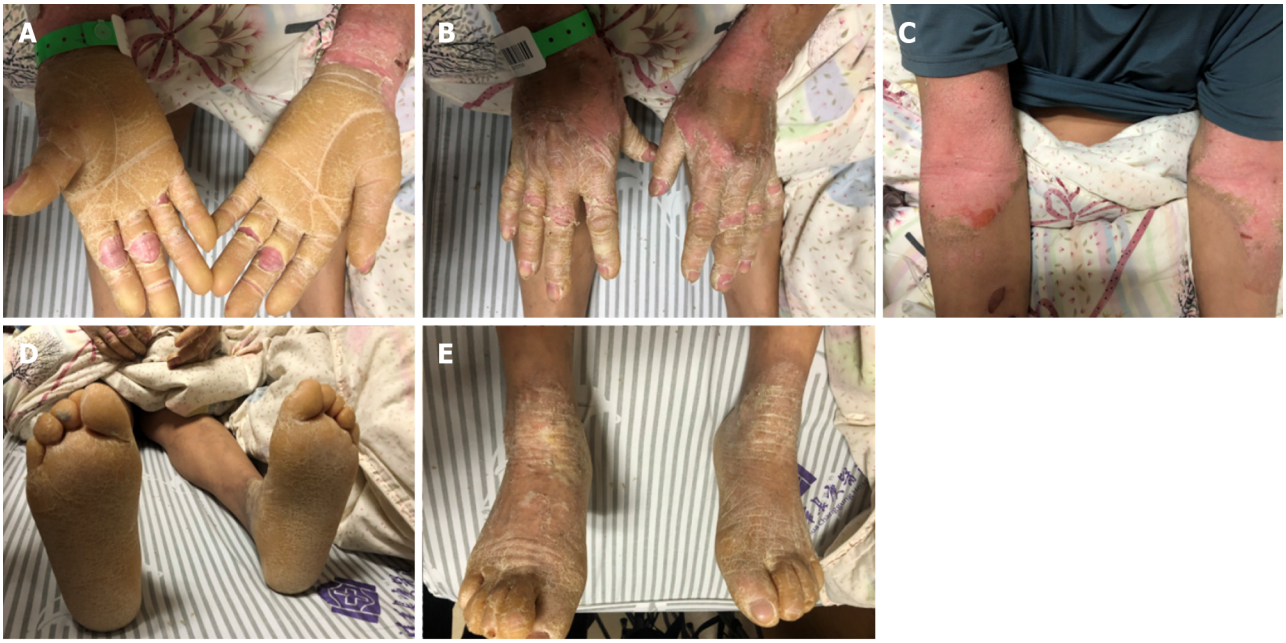

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Figure 1 Images of the skin lesions. Diffuse palmoplantar hyperkeratosis, erythema, and scales on the flexor surfaces of both arms and lower limbs. A: Palms; B: Opisthenar; C: Arms; D: Planta pedis; E: Dorsum of the foot.

(HIV) and syphilis antibodies were negative. His electrocardiogram showed sinus tachycardia. Blood cultures isolated methicillin-sensitive *Staphylococcus aureus* (MSSA) 2 and 4 d after admission to the hospital. Transthoracic echocardiography indicated mitral valve disease with severe insufficiency.

Imaging examinations

Cranial computed tomography revealed multiple low-density shadows in the brain (Figure 2). The computed tomography (CT) results of the chest were normal. Abdominal enhanced CT showed multiple low-density shadows in the spleen, which were considered to be splenic abscesses with subcapsular effusion (Figure 2). Given the persistent fever, bacteraemia, abscesses, and mitral valve insufficiency, we conducted transoesophageal echocardiography (Figure 3), which revealed a wart in the mitral valve with prolapse along with severe insufficiency. He was diagnosed with definitive infective endocarditis, clinically suspected to be attributable to his skin lesions. He was urgently referred to a dermatologist, who advised treatment with tretinoin, urea cream for external use, skin biopsy (Figure 4), and genetic tests. Later, a pathological examination was conducted on his skin, which showed epidermal hyperkeratosis, acantholysis, and lymphocytes infiltrating the superficial dermis around the blood vessels and adjuncts. Genetic tests revealed mutations in the keratin 1 (*KRT1*) gene (Figure 4).

FINAL DIAGNOSIS

The final diagnosis of the presented case was EHK combined with infectious endocarditis (IE).

TREATMENT

He was started on intravenous 0.5 g levofloxacin once a day (QD). Four days later, levofloxacin was escalated to vancomycin 500 mg Q12 h due to a positive blood culture for Gram-positive coccal bacteraemia and persistent fever. When infective endocarditis and brain abscesses are diagnosed, the selection of antibiotics depends on drug sensitivity experiments; based on the results, his treatment was changed to 2 g ceftriaxone QD.

OUTCOME AND FOLLOW-UP

Cardiac surgery was planned for approximately 6-8 wk after completion of the course of antibiotics. Because of the use of antibiotics, his white cell counts and C-reactive protein levels remained within the

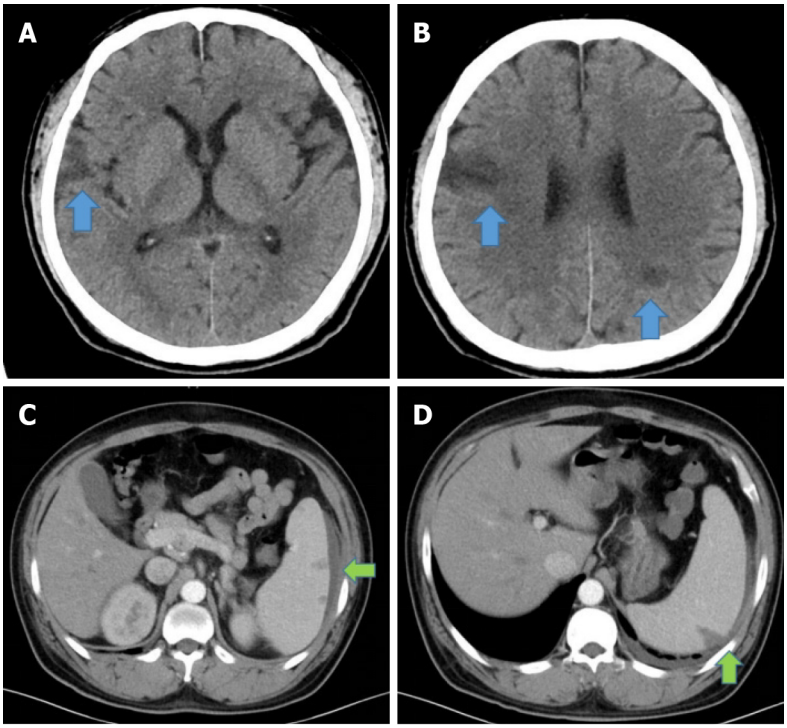

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Figure 2 Computed tomography. A and B: Cranial computed tomography showing multiple low-density shadows (blue arrow, A and B) in the brain; C and D: Abdominal enhanced CT scan showing multiple low-density shadows (green arrow, C and D) in the spleen, considered a splenic abscess with subcapsular effusion.

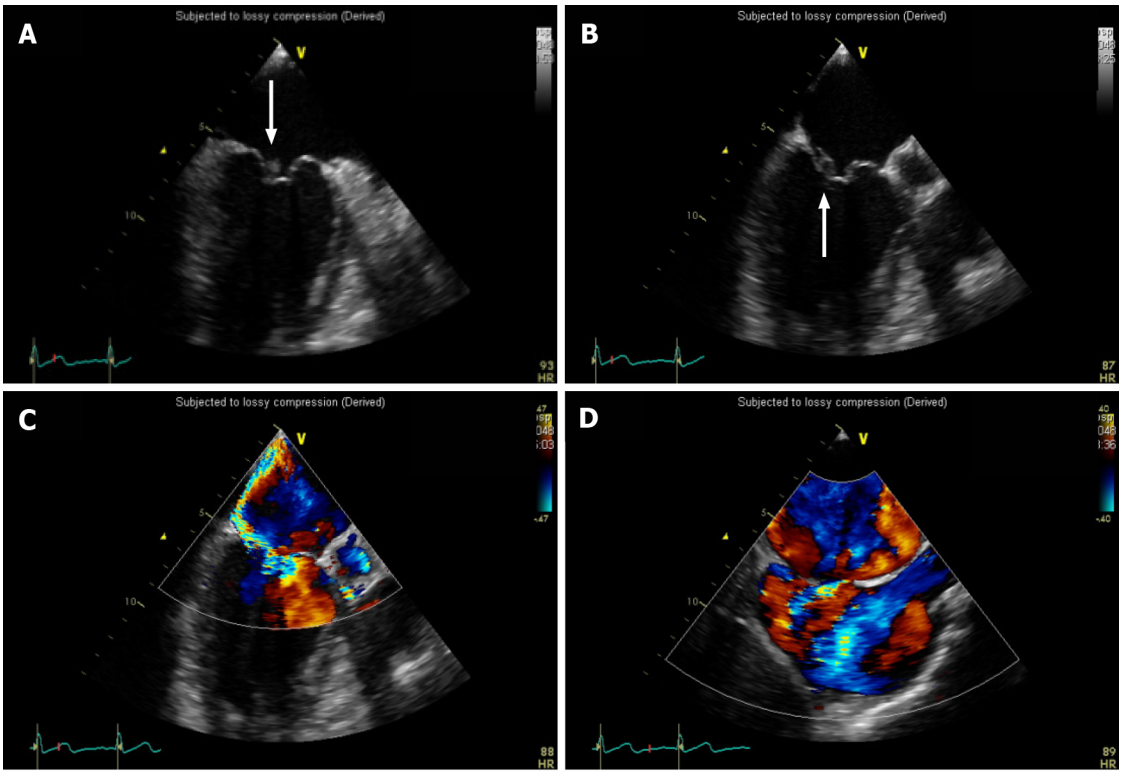

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Figure 3 Transesophageal echocardiography. A and B: The anterior leaflet of the mitral valve was detected with a wart (white arrow) of a cord-like medium echoic substance about 10mm and the posterior leaflet was detected with the wart (white arrow) of a medium echoic substance about 7 mm × 7 mm; C and D: There was severe mitral regurgitation and the regurgitation bundle was distributed along the posterior leaflet of the mitral valve. There was mild tricuspid valve and the aortic valve regurgitation.

A

Gene	mutation site	Gene subregion	HGVS	mutation type	heterozygosity	grading of variation	Diseases and genetic patterns
KRT1	Chr12:52679810-52679810	exon1	NM_006121.4:c.539A>G:p.E180G	nonsynonymous SNV	heterozygosis	Likely pathogenic	Heterozygosis, AD/AR; Curth-Macklin ichthyosis hystrix, AD; Periodic ichthyosis with epidermolytic hyperkeratosis, AD; Striate palmoplantar keratoderma; epidermolytic palmoplantar keratoderma, AD; nonepidermolytic palmoplantar keratoderma, AD .

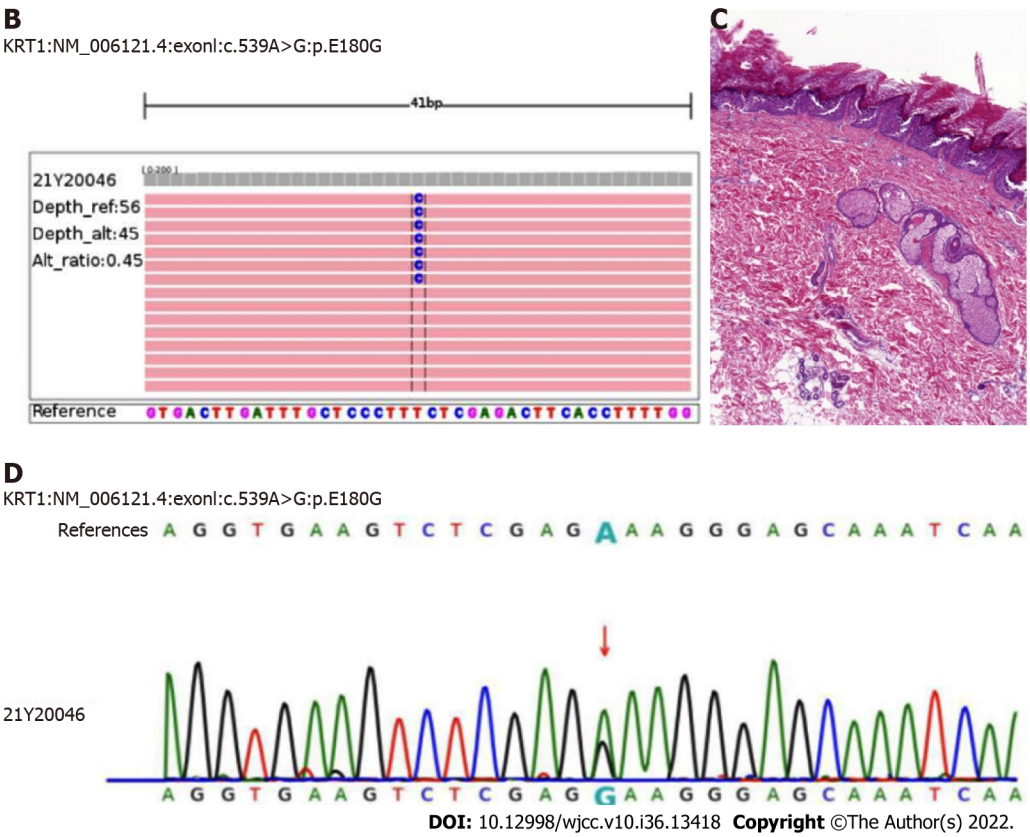

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Figure 4 Histopathological, and genetic features of the patient. A and B: The c.539A>G mutation was detected in KRT1; C: The pathological examination indicated epidermal hyperkeratosis, acantholysis and lymphocytes infiltrating the superficial dermis around blood vessels and adjuncts (H&E stain, original magnification 100×); D: c.539A>G detection using Next Generation Sequencing and Sanger sequencing.

normal range. Subsequent echocardiograms still showed a wart in the mitral valve with prolapse and severe insufficiency, but the valve excrescences appeared to be getting smaller. CT of the chest was repeated, which revealed a small pleural effusion. Cranial CT was also repeated, which indicated shrinking lesions. Blood cultures were repeated and were negative, and he remained apyrexial. Because of his medical insurance policy, the patient decided to return to his local hospital for further treatment.

DISCUSSION

The clinical manifestations, histopathological findings, and mutations in the KRT1 gene observed in this patient were consistent with the diagnostic criteria of EHK[3,4], a rare genodermatosis with autosomal-dominant inheritance[5]. EHK is associated with erythema, blistering, erosions and skin denudation present at birth, and develop marked hyperkeratosis in adult. The KRT1 mutation c.539A>G: p. E180G was found; this has been reported previously[6].

Patients with skin diseases often exhibit a disturbed skin barrier and tend to have poor cell-mediated immunity, such as atopic dermatitis, irritant contact dermatitis, ichthyosis, rosacea, and acne[7,8]. Patients with EHK, especially with subtypes of ichthyosis, are prone to repeated episodes of skin infections, including bacterial infection and fungal infection, but the mechanism is still elusive[4,9]. Several factors have been proposed, including disruption of skin barrier function, hyperkeratotic plaques and defective cell-mediated immunity[10-12]. *Staphylococcus aureus* is a leading cause of human bacterial infection, and the most common site of *Staphylococcus aureus* infection is the skin[13]. Skin and soft tissue infections with Staphylococcus remain a dominant cause of bacteraemia and IE[14,15].

The definition of SAB is as presence of ≥ 1 positive blood cultures for *Staphylococcus aureus*[16]. The most frequent site is the anterior nares, but the skin, axilla, oropharynx, perineum, and vagina may also be colonized. These colonized sites may serve as reservoirs for future infections. Colonization is relatively higher among patients with insulin-dependent diabetes, skin damage, HIV infection, and in patients undergoing maintenance haemodialysis[16]. SAB can lead to seeding and invasion of virtually any body site and associated complications[17]. The case fatality rates for SAB have only slightly improved in recent decades[18]. Patients with SAB can develop all kinds of complications, such as IE, epidural abscess, vertebral osteomyelitis, brain abscess, and discitis, which may be difficult to identify and can lead to high rates of disability and mortality[17,19].

SAB is a leading cause of bacteraemia and infective endocarditis. Only a minority of bacteraemic patients will show involvement of the heart valves. The frequency of endocarditis among SAB patients ranges from 5% to 10%-12%[20]. IE is a severe complication in patients with nosocomial SAB. It has a low incidence but high mortality. Therefore, prevention and early detection of IE are important. The incidence is highest in those with a previous history of IE or who have prosthetic, repaired valves, intravenous drug use or rheumatic heart disease[21,22]. Our patient had no history of these risk factors except EHK.

CONCLUSION

A case of atopic dermatitis, IE and multiple cerebral infarctions has been reported[23], but there are no previous reports of EHK and IE, such as in our case. Some factors have been speculated to increase the risk of infection, such as including disruption of skin barrier integrity, defective cell-mediated immunity, and delayed keratin scaling. In our case, a breached skin barrier secondary to EHK, coupled with inadequate skin sanitation, likely provided the opportunity for bacterial seeding by MSSA, triggering IE and abscesses. EHK may be associated with skin infection and multiple risk factors for extracutaneous infections. Patients with EHK should be treated early to minimize the consequences. If patients with EHK present with prolonged fever, IE and organ abscesses should be suspected or checked, including metastatic spreads. In conclusion, we highlight that in the absence of thorough treatment, clinicians should recognize that patients with EHK are susceptible to bacterial infections owing to disruption of the skin barrier.

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CASE REPORT

Compound heterozygous p.L483P and p.S310G mutations in GBA1 cause type 1 adult Gaucher disease: A case report

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Abstract

BACKGROUND

Gaucher disease (GD) is caused by a *GBA1* gene mutation that leads to decreased acid β-glucosidase activity [glucocerebrosidase (GCase)]. This study aimed to identify and characterise compound heterozygous mutations in *GBA1* in a patient with type 1 GD.

CASE SUMMARY

Here, we report a rare adult-onset type 1 GD in a 46-year-old female patient with clinical manifestations of giant spleen, thrombocytopenia, and bone pain, diagnosed by enzymatic and genetic testing. Enzymology and whole exome sequencing revealed heterozygous missense mutations in exon 10 c.1448T>C (p.L483P) and exon 7 c.928A>G (p.S310G) of *GBA1*. The latter was first reported in patients with GD. Structural modelling showed that p.S310G and p.L483P were distant from the GCase active site. The p.S310G mutation in domain 1 may decrease stability between the α2 and α3 helices of *GBA1*. The p.L483P mutation in domain 2 reduced the van der Waals force of the side chain and disrupted the C-

terminal β-sheet. The patient was treated with imiglucerase replacement therapy, and her condition was stable.

CONCLUSION

The p.L483P/p.S310G novel compound heterozygous mutation underlies type 1 GD and likely affects GCase protein function. This is the first description of p.S310G being associated with mild type 1 GD in the context of a coinherited p.L483P mutation.

Key Words: Gaucher disease; Parkinson's disease; Lipid metabolism; Molecular mechanism; Case report

Core Tip: We report a rare adult-onset type 1 GD patient in a 46-year-old female with clinical manifestations of giant spleen, thrombocytopenia, and bone pain, diagnosed by enzymatic and genetic testing. Using enzymology and whole exome sequencing, it is indicated that heterozygous missense mutations in exon 10 c.1448T>C (p.L483P) and exon 7 c.928A>G (p.S310G) of GBA1. The latter was first reported in GD. Structural modeling showed that p.S310G and p.L483P are far away from the glucocerebrosidase active site. The p.S310G mutation in domain 1 could cause decreased stability between the α2 and α3 helices of GBA1. The p.L483P mutation in domain 2 could reduce the van der Waals force of the side chain and disrupt the C-terminal-sheet. The patient was treated with imiglucerase replacement therapy, and her condition was basically stable.

Citation: Wen XL, Wang YZ, Zhang XL, Tu JQ, Zhang ZJ, Liu XX, Lu HY, Hao GP, Wang XH, Yang LH, Zhang RJ. Compound heterozygous p.L483P and p.S310G mutations in GBA1 cause type 1 adult Gaucher disease: A case report. *World J Clin Cases* 2022; 10(36): 13426-13434

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INTRODUCTION

Gaucher disease (GD) is a rare autosomal recessive hereditary lysosomal storage disease with a global incidence of approximately 0.4/100000-5.8/100000[1]. It arises from *GBA1* gene mutations, resulting in the accumulation of glucosylceramide in the reticuloendothelial system, leading to anaemia, low platelet counts, and damage to the liver and spleen. *GBA1* (RefSeq: NG_009783.1) located at chromosome 1q21, spans 7.6 kb with 11 exons. There are 459 reported *GBA1* mutations, including point mutations, splicing, insertions and deletions, frameshift mutations, and recombination alleles; however, not all are pathogenic[2]. GD is heterogeneous and is classified into three types based on neurological severity[3, 4]. In type 1, neuronal features are not observed, and patients can be asymptomatic and present at any age[5]. Both type 2 and 3 GD have neurological involvement and are present in infancy, but only type 2 GD results in early death.

Surprisingly, *in vitro* expression experiments have demonstrated that these *GBA1* mutations are relatively stable and active[6,7]. *In vivo*, glucocerebrosidase (GCase) is synthesised in the rough endoplasmic reticulum (ER) and then transported to the lysosome. *GBA1* mutations cause GCase to exit the ER and are destroyed by the ubiquitin-proteasome system[8]. Thus, GD patients have reduced amounts of acid β-glucosidase (GCase) in their lysosomes.

The current study examined the aetiology of type 1 GD in an adult female patient and found double heterozygosity for c.1448T>C (p.L483P) and c.928A>G (p.S310G) mutations in *GBA1*. The p.L483P mutation is common in Asian populations, and homozygous p.L483P mutations result in a severe GD phenotype with neurological manifestations and early death[9]. The patient with the heterozygous mutation p.L483P/p.S310G had a milder phenotype and did not have clinical GD symptoms until adulthood. The p.S310G mutation has only been reported in Parkinson's disease (PD)[10] However, its molecular pathogenesis remains unclear. In the current study, the effects of p.L483P/p.S310G on the clinical manifestations of GCase and GD were preliminarily explored through gene diagnosis and protein structure analysis.

CASE PRESENTATION

Chief complaints

A 46-year-old Chinese woman was admitted to the hospital in December 2019 because of progressive enlargement of the spleen for more than 3 years and a progressive decrease in platelet count for more than 9 mo.

History of present illness

The patient presented with asymptomatic splenomegaly (ultrasound: Spleen length, 154 mm; width, 41 mm) in December 2016. In December 2018, the patient complained of persistent right hip joint pain without mobility problems. Radiographic studies did not reveal significant hip joint or femoral abnormalities. In March 2019, a review ultrasound revealed an enlarged spleen (length, 153 mm; width, 57 mm) and thrombocytopenia (52 × 10^9/L). In November 2019, another ultrasound showed continuous spleen enlargement (length, 249 mm; width, approximately 66 mm) and further decreased platelet count (40 × 10^9/L).

History of past illness

She was hepatitis B surface antigen-positive in December 2016.

Personal and family history

Except for her mother's PD diagnosis, her family history was insignificant.

Physical examination

Megasplenomegaly was noted 18 cm below the ribs, the liver was not palpable under the ribs, and the nervous system examination was normal.

Laboratory examinations

Complete blood counts showed white blood cells 3.59 × 10^9/L [normal: (4-10) × 10^9/L], haemoglobin 102 g/L (normal: 110-160 g/L), and platelets 34 × 10^9/L [normal: (100-300) × 10^9/L]. Bone marrow cytomorphological examination revealed that Gaucher-like cells accounted for 4.4% (Figure 1). The GCase activity of the peripheral blood leukocytes was 3.8 nmol/(mg·h) (reference range: 10-25 nmol/mg · h). The *GBA1* gene test showed heterozygous mutations c.1448T>C (p.L483P)/c.928A>G (p.S310G) (Figures 2 and 3). The patient was diagnosed with GD (type 1). The father was a p.L483P heterozygous carrier, and the mother was a p.S310G heterozygous carrier. The younger sister did not harbor any mutations. Predictions made by PolyPhen-2, SIFT, and MutationTaster suggested that the p.L483P and p.S310G mutations might be pathogenic. According to the American College of Medical Genetics and Genomics guidelines[11], p.L483P was evaluated as a pathogenic variant, and p.S310G was probably a pathogenic variant.

Imaging examinations

Bone mineral density testing of the thoracolumbar and bilateral hip joints revealed decreased bone mineral density; computed tomography showed bilateral hip joint changes; and magnetic resonance imaging showed an abnormal signal in the medullary cavity of the lower segment of the right femur, bone infarction, and abnormal signal in the medullary cavity of the left lower femur.

Protein structure analysis

GCase belongs to the GH30 family of glycoside hydrolases. In contrast to the traditional three-domain classification method, domains I and II were reclassified as domain 2, and domain III was classified as domain 1[12,13]. The GCase protein contains two domains, in which the active sites, E274 and E379, are located in the β-folded plates β4 and β7 of domain 1. The mutation point p.S310G was located in α-helix α4. However, it appears to be closer to E274 in the secondary structure. In the three-dimensional structure, p.S310G was located at the bottom of α4 and E274 at the top of β4. The distance between the two was relatively large. The mutation point p.L483P was located at the β-pleated-sheet βs6 in domain 2, which was far away from the two active centres. Therefore, being far away from the GCase active centres, the mutation points p.S310G and p.L483P were predicted not to have a significant impact on the catalytic properties of the protein.

The p.S310G mutation is located in α-helix α4. In the wild type, the C-β atom of the side chain of the Ser residue formed a van der Waals force with the C-γ2 atom of the Val253 side chain and the C atom of the Leu307 main chain. In addition, the N atom of the Ser residue main chain formed a hydrogen bond with a length of 3.5 Å and 3.2 Å with the O atom of the Thr306 and Leu307 main chains, respectively; the O atom of the main chain formed a hydrogen bond with a length of 3.3 Å with the N atom of the His313 main chain. After Ser310 was mutated to Gly310, the hydrogen bond of the main chain remained, while the van der Waals force formed by the side chain and surrounding residues disappeared. The p.S310G mutation weakened the force between this point and Val253, which is located

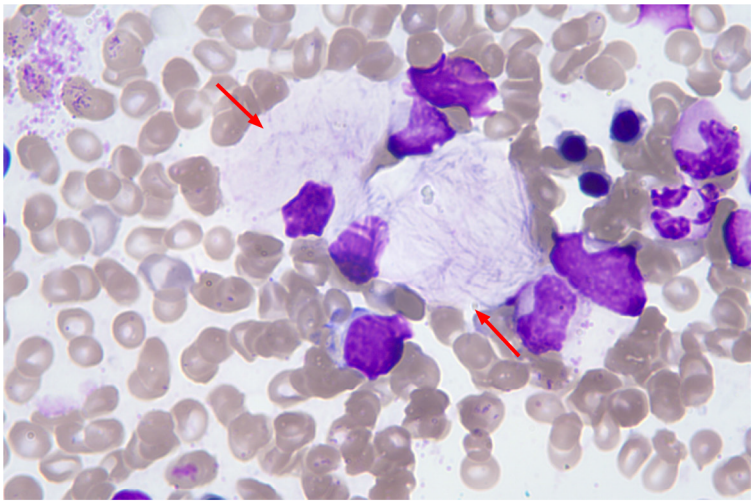

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Figure 1 Bone marrow cytomorphology. Haematoxylin-eosin stain (magnification: 100 ×).

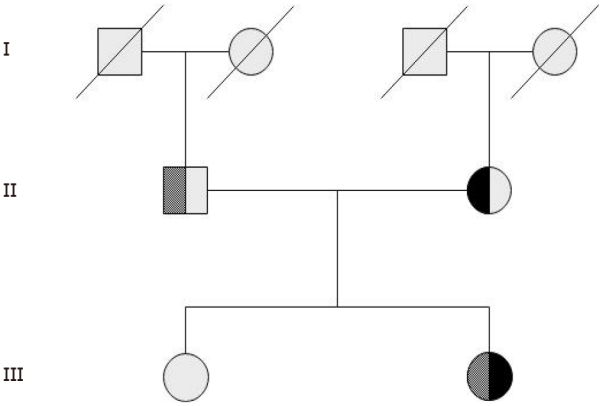

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Figure 2 Family pedigree of the proband. The first-generation members have no information. The second generation is the father of proband is heterozygous for exon 10 c.1448T>C (p.L483P) mutation, and the mother is heterozygous for exon 7 c.928A>G (p.S310G) mutation. The third generation is the proband who was compound heterozygous for p.L483P/p.S310G. Her sister was normal and did not carry either mutation.

above the α helix α3, therefore might affect the stability between α2 and α3 (Figure 4).

p.L483P was located in the loop region connecting βs5 and βs6 (near βs6). In the wild type, the side chain of Leu483 formed abundant van der Waals forces with the surrounding residues. The C-δ1 atom of its side chain could form van der Waals forces with the C-δ2 atom of Leu104, C-γ1 atom of Val499, C-γ1 atom of Val507, and C-δ2 atom of Leu509, and the C-δ2 atom could form van der Waals forces with C-γ atom of Asn501 and C-β atom of Ser523. Those van der Waals forces were formed because of the interactions between the side chains. When Leu483 mutated into Pro483, the N-Cα rotation of Pro was bound by the pyrrolidine ring in its structure, thereby having less conformational freedom. This structure limited the diversity of its spatial conformation, especially in the loop region. The existence of Proline could help stabilise the loop region, which was originally more flexible. Therefore, theoretically, the p.L483P mutation located in the loop region should have enhanced the stability of this region. However, owing to side chain changes, the original 6 van der Waals forces were reduced to 3, and the retained van der Waals forces were formed between C-γ of Pro483 and C-δ2 of Leu104 and C-γ1 of Val507 and one between C-β and C-γ1 of Val499. Thus, it can be seen that the introduction of Pro stabilised the conformation of the loop region, but the reduced van der Waals forces of the side chain might also affect the function of the protein structure (Figure 5).

FINAL DIAGNOSIS

GD (type 1).

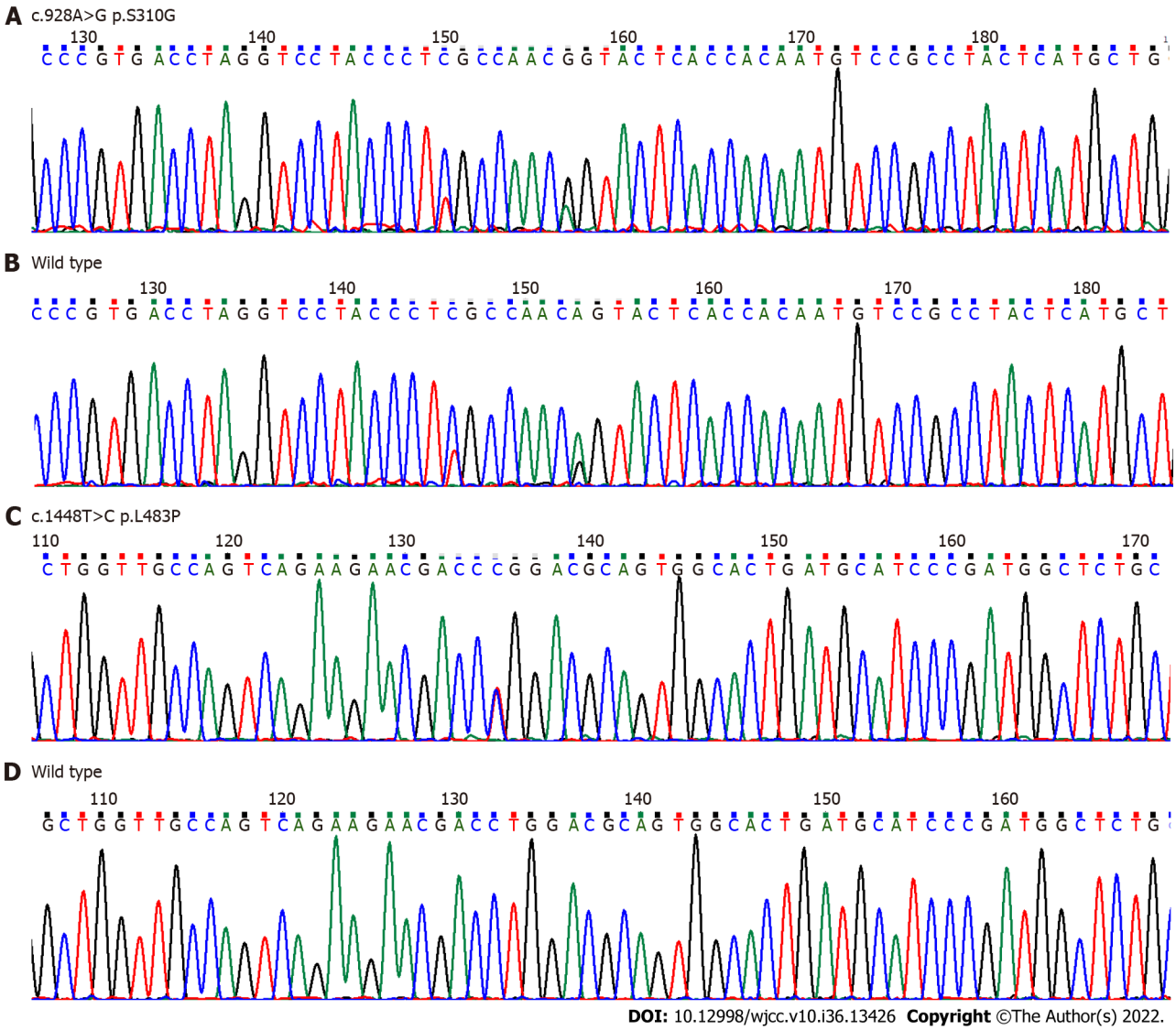

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Figure 3 DNA sequencing analysis of glucocerebrosidase gene. A and B: Exon 7 c.928A>G (p.S310G) novel heterozygous missense mutation compared to the corresponding wild-type sequence; C and D: Exon 10 c.1448T>C (p.L483P) heterozygous mutation compared to the corresponding wild-type sequence.

TREATMENT

In January 2020, imiglucerase was administered intravenously (45 U/Kg, once every 2 wk).

OUTCOME AND FOLLOW-UP

The bone pain was relieved, the blood routine was rechecked several times, and the platelet count was continuously lower than 30 × 10^9/L. No significant improvement was observed in the spleen size.

DISCUSSION

GD is a rare inborn metabolic error secondary to *GBA1* gene mutations that leads to reduced GCase activity. The substrate glucocerebroside (also known as glucose ceramide) accumulates in the macrophage lysosomes to form Gaucher cells. Gaucher cells accumulate widely in the liver, spleen, bones, lungs, brain, and other tissues and organs, resulting in the progressive worsening of dysfunction. Based on different clinical manifestations, GD can be divided into three types, of which type 1 (non-neuropathic) is the most common, accounting for approximately 95% of cases[4]. GD can occur at all ages with widely varying clinical manifestations. No primary central nervous system involvement is found in type 1 GD, and enzyme replacement therapy is the main treatment.

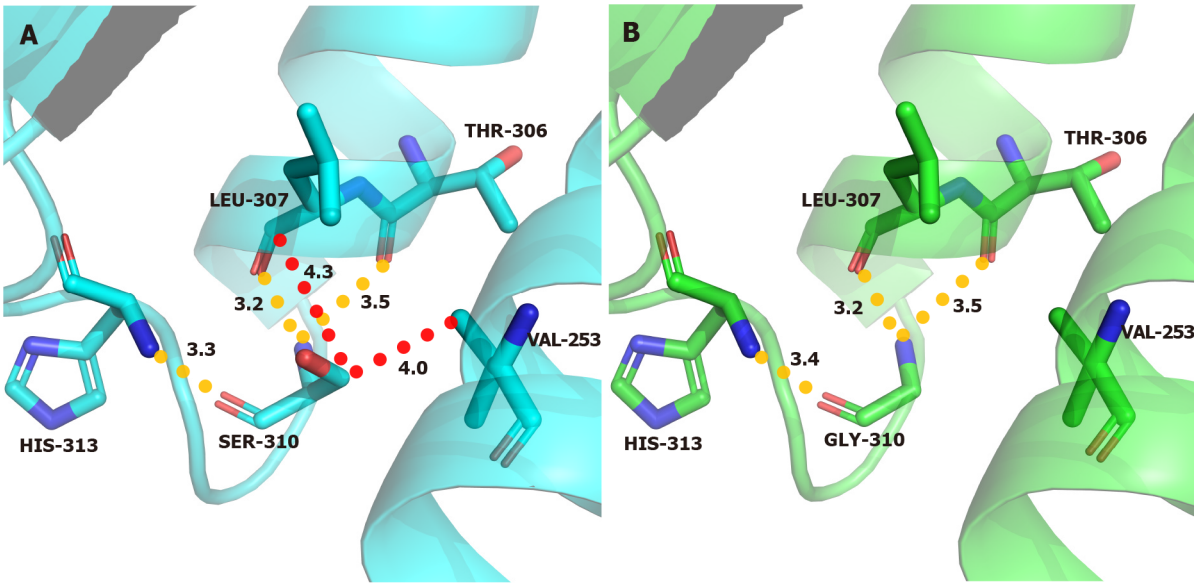

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Figure 4 Molecular contacts of residue 310. A: Wild-type acid β-glucosidase protein; B: Mutant type.

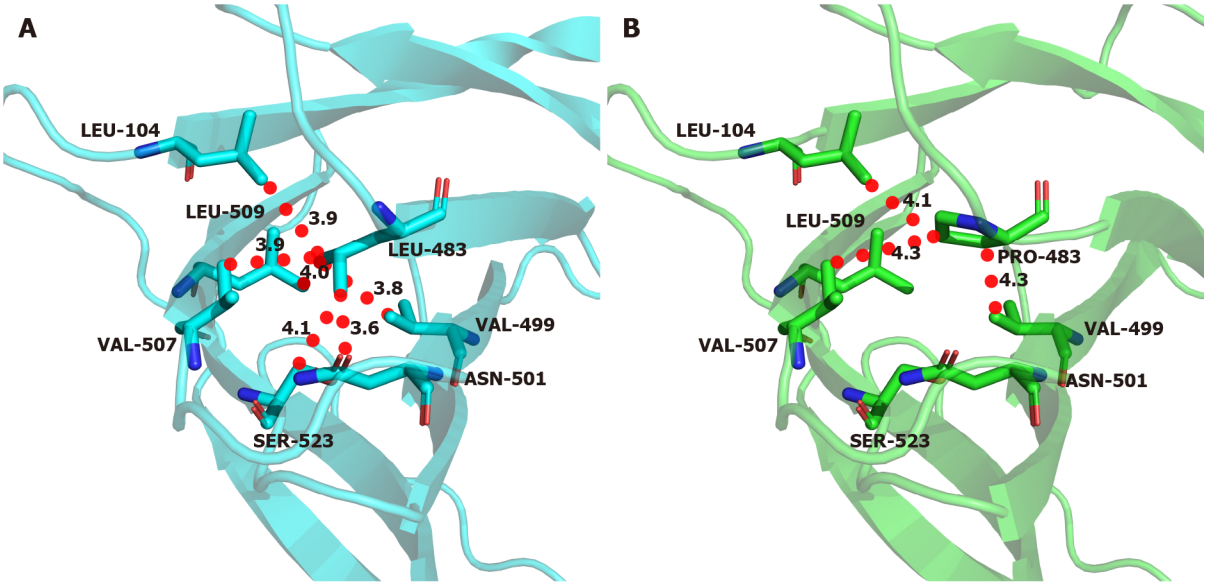

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Figure 5 Molecular contacts of residue 483. A: Wild-type acid β-glucosidase protein; B: Mutant type.

A previous study suggested that *GBA1* mutations are closely associated with PD[14]. Carriers of *GBA1* gene mutations, such as p.N370S and p.L483P, were found to increase the risk of PD disease by 2.16 times, with the characteristics of early-onset age and declined cognitive ability. A possible pathogenic mechanism is that these mutations increase α-synaptic nucleoprotein aggregation[15-18]. The coexistence of p.L483P with recombinant alleles, splice variants, or known severe missense alleles, such as p.D488H and p.R159W, has been reported to commonly lead to neuronopathic GD. When coexisting with mild mutations, such as p.N409S and p.P305A, it manifests as non-neuronopathic GD[9, 19]. p.L483P has long been considered a serious pathogenic mutation; however, p.L483P has been reported to be associated with delayed onset of neurological symptoms in type 3 patients with Japanese patients[20], which may be related to the possible genetic heterogeneity among different ethnic groups. Enzyme replacement therapy can significantly improve haematological and other systemic symptoms in patients with type I GD, but its efficacy in patients with type 3 GD remains controversial. It has been reported in the literature that some type 3 patients developed symptoms of nervous system involvement after a median treatment period of 7.6 years[21]. In this study, the patient was treated with imiglucerase for 2 years, the platelet count continued to fail to recover, and the splenomegaly did not improve significantly. The proband with type 3 GD is the most common pathogenic mutation, p.L483P, and her

mother carries the p.S310G mutation, which has been confirmed to be a patient with PD. Therefore, this proband is a high-risk patient for PD and should be aware of the combination of neurological symptoms. The p.S310G mutation has only been reported in PD, and to the best of our knowledge, this is the first report of this mutation in patients with GD. However, its molecular mechanism of action and significance in GD remain unclear. In our patient with type 1 GD, the p.L483P mutation alone was not sufficient to result in the GD phenotype, suggesting that the p.S310G mutation contributed to the manifestation of type 1 disease.

In this study, to further understand the significance of p.L483P/p.S310G compound heterozygous mutations in GD, GCase protein structure analysis was conducted to probe the pathogenic characteristics of p.L483P/p.S310G mutations at the protein level. GCase belongs to the glycoside hydrolases GH30 family. The GH30 protein structure was first defined in 2010[13]. Based on the overall characteristics of GH30 family proteins, this study divided the GCase protein into two domains. *GBA1* mutations can significantly influence the structure and function of the protein, including reducing the stability of domain III, premature termination of translation, and interference with catalytic activity[22-24]. Protein structure simulation revealed that p.L483P and p.S310G mutation points were far from the GCase active centre, suggesting that they should have little effect on the catalytic properties of the GCase protein. This also conformed to the patient's late-onset age with a mild clinical phenotype. Located in domain 2, the p.L483P mutation is believed to affect the structure and function of the protein by reducing van der Waals forces of the side chain. Earlier studies have suggested that the p.L483P mutation could lead to decreased enzymatic activity[25], affect the catalytic activity of GCase[26], disrupt the hydrophobic core and domain folding[17], or alter protein stability by reducing intramolecular hydrogen bonding[22]. Our study is different from the previous study, which further enriches the understanding of the impact of the p.L483P mutation on the protein structure. In this study, we demonstrated the first observed influence of the p.S310G mutation on the GCase protein. The p.S310G mutation in domain 1 could decrease the stability between α2 and α3 of the α-helix of the GCase protein, thus affecting the function of the GCase protein.

CONCLUSION

The current study verified that the p.L483P/p.S310G novel compound heterozygous mutation was the cause of GD. This mutation caused the disease probably by interfering with the biological function of the GCase protein. A follow-up study will be performed to assess the risk of developing PD in patients with the p. L483P variant.

FOOTNOTES

Author contributions: Zhang RJ, Wen XL and Zhang XL designed the study. Zhang XL and Wen XL performed the experiments. Wen XL and Wang YZ drafted the manuscript; and all authors have contributed to the revision of the manuscript.

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Informed consent statement: Informed written consent was obtained from the patient for the publication of this report and any accompanying images. This study was approved by the Ethics Committee of the Third Hospital of the Shanxi Medical University (approval no. SBQKL-2021-052) and in accordance with the principles of the Declaration of Helsinki.

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P-Editor: Wang JJ

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CASE REPORT

Short-term prone positioning for severe acute respiratory distress syndrome after cardiopulmonary bypass: A case report and literature review

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Abstract

BACKGROUND

Aortic dissection is a complex and dangerous cardiovascular disease, with many complications in the perioperative period, including severe acute respiratory distress syndrome (ARDS), which affects prognosis and increases mortality. Despite the effect of prone positioning (PP) in improving oxygenation in patients with severe ARDS, reports about PP early after cardiac surgery are few and such an opt-ion may be an issue in cardiac surgery patients because of the recent sternotomy.

CASE SUMMARY

A 40-year-old male patient diagnosed with acute type A aortic dissection on October 22, 2021 underwent ascending artery replacement plus total aortic arch replacement plus stent elephant trunk implantation under cardiopulmonary bypass. Unfortunately, he developed ARDS on postoperative day 1. Despite comprehensive treatment with aggressive pulmonary protective ventilation, fluid management with continuous renal replacement therapy, the condition continued to deteriorate and rapidly progressed to severe ARDS with a minimum oxygenation index of 51. We are ready to implement salvage therapy, including PP and extracorporeal membrane oxygenation (ECMO). Due to the large amount of pericardial mediastinal and thoracic drainage after thoracotomy, ECMO may result in massive postoperative bleeding. Prolonged prone ventilation is often inappropriate after thoracotomy. Therefore, we chose short-term PP for < 6 h. Finally, the oxygenation index greatly improved and the diffuse exudation in both lungs of the patient was significantly reduced with short-term prone positioning.

CONCLUSION
Intermittent short-term PP can improve early postoperative severe ARDS after acute aortic dissection.

Key Words: Aortic dissection; Short-term prone positioning; Acute respiratory distress syndrome; Oxygenation index; Cardiopulmonary bypass; Case report

Core Tip: Severe acute respiratory distress syndrome (ARDS) is often secondary to cardiac macrovascular surgery. Extracorporeal membrane oxygenation (ECMO) and prone positioning (PP) can improve pulmonary ventilation blood flow ratio and survival rate. We report a case of aortic dissection complicated with severe ARDS, in which intermittent short-term PP successfully improved oxygenation in the absence of ECMO. It is not an absolute contraindication to prone ventilation in the early postoperative period after thoracotomy. The use of intermittent short-term PP can improve the condition and avoid the complications caused by early PP after thoracotomy.

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INTRODUCTION

Aortic dissection is a complex and dangerous cardiovascular disease, with a high mortality rate, and surgical treatment is an effective way to save life[1-3]. Aortic dissection surgery is traumatic, requiring a long treatment time and deep hypothermia for circulatory arrest[1,2]. A large number of blood transfusions are often required, as well as ischemia-reperfusion due to extracorporeal circulation, so there are many postoperative complications, among which, the incidence of acute respiratory distress syndrome (ARDS) is high, especially in obese patients with acute renal impairment before surgery[1,2,4,5]. ARDS significantly increases postoperative mortality and prolongs ventilator use and intensive care unit (ICU) stay[3]. According to the Berlin definition, ARDS is characterized by acute onset with bilateral lung opacities not explained by cardiac failure and/or fluid overload (Table 1). Although extracorporeal membrane oxygenation (ECMO) and prone positioning (PP) are important parts in the comprehensive treatment plan of severe ARDS[6-10], ECMO can easily cause fatal bleeding in the case of abnormal coagulation. Standardized and timely PP can effectively improve oxygenation and respiratory mechanics, including increasing functional residual volume, reducing lung shunt, promoting pulmonary secretion discharge, and improving ventilation flow ratio[8,11-13], so as to reduce mortality rate[14]. Gu *et al*[15] used PP to treat severe hypoxemia after aortic dissection and achieved good results. Here, we report a case of successful improvement in oxygenation with postoperative severe ARDS with acute type A aortic dissection treated with PP.

CASE PRESENTATION

Chief complaints

A 40-year-old middle-aged man was admitted to hospital with sudden chest and back pain for 5 h.

History of present illness

The patient suddenly developed severe chest and back pain 5 h ago. The tearing-like pain continued without relief. Computed tomography angiography (CTA) of the thoracic and abdominal aorta was performed in a large class III general hospital in Chongqing. The examination showed acute type A aortic dissection.

History of past illness

The patient did not have any other medical history other than hypertension.

Table 1 Berlin definition and management of acute respiratory distress syndrome

Diagnostic criteria[5]	Onset within 1 wk of known clinical impairment or new/worsening respiratory symptoms; Bilateral shadows (on CXR or CT scan) not fully explained by effusions, lobar/lung collapse, or nodules; Respiratory failure not entirely explained by heart failure or fluid overload		
Oxygenation impairment[5]	Mild; 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg with PEEP or continuous positive airway pressure ≥ 5 cmH_2O	Moderate 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg with PEEP ≥ 5 cmH_2O	Severe PaO_2/FiO_2 ≤ 100 mmHg with PEEP ≥ 5 cmH_2O
Risk factors for ARDS[5,16,17]	Infectious risk factors: Pneumonia, nonpulmonary sepsis	Noninfectious: Aspiration of gastric contents, severe trauma, pulmonary contusion, noncardiogenic shock, inhalation injury, severe burns, pancreatitis, drug overdose, multiple transfusions or TRALI, pulmonary vasculitis, drowning	
Oxygen therapy	Intubation/mechanical ventilation (most patients)Noninvasive ventilation for mild ARDS		
Fluid management	Aim for central venous pressure < 4 mmHg or PAOP < 8 mmHg to ↓ pulmonary; Oedema		
Prone positioning			
ECMO			
Decreased oxygen consumption; Increased oxygen delivery[7]	Antipyretics, sedatives, analgesics and paralysis agents; Inotropics to ↑ filling pressure (if no pulmonary edema); Restrict transfusions to maintain hemoglobin to 7–9 g/dL; Inhaled vasodilators (NO, prostacyclin and prostaglandin E1) to ↑ V'/Q' matching		

ARDS: Acute respiratory distress syndrome; CXR: Chest X-ray; CT: Computed tomography; ECG: Electro-chemical grinding; FIO_2: Fraction inspired oxygen; PaO_2: Partial pressure of arterial oxygen; PAOP: Pulmonary artery occlusion pressure: PEEP: Positive end-expiratory pressure; TRALI: Transfusion-related acute lung injury; V'/Q': Ventilatory blood flow ratio.

Personal and family history

The patient had a 20-year history of heavy smoking, two packs per day, with no specific family history.

Physical examination

Physical examination revealed persistent tearing pain in the chest and back.

Laboratory examinations

Renal function test showed that creatinine rose to 237.6 mmol/L.

Imaging examinations

Thoracic and abdominal aorta CTA (Figure 1) showed aortic false lumen formation.

FINAL DIAGNOSIS

(1) Acute aortic dissection (Standford type A); (2) acute kidney injury (AKI) grade II; (3) coagulation dysfunction; (4) acute myocardial injury; (5) hypoproteinemia; and (6) high-risk stage 3 hypertension.

TREATMENT

After preoperative examination, the patient underwent ascending aortic and total aortic arch replacement plus stented elephant trunk implantation under general anesthesia and cardiopulmonary bypass. He was transferred to the ICU in critical condition for continued treatment after surgery. During the operation and on the day of admission to ICU, 4 U of red blood cells, 850 mL of plasma, 20 U of cryoprecipitate, and 2 U of platelets were transfused.

Despite combined treatment with lung protective ventilation, fluid management with continuous renal replacement therapy, and airway secretion clearance, the disease continued to deteriorate and rapidly progressed to severe ARDS. The oxygenation index (OI) dropped from normal to a minimum of 51. We were ready to give emergency rescue measures, including prone ventilation and ECMO, and

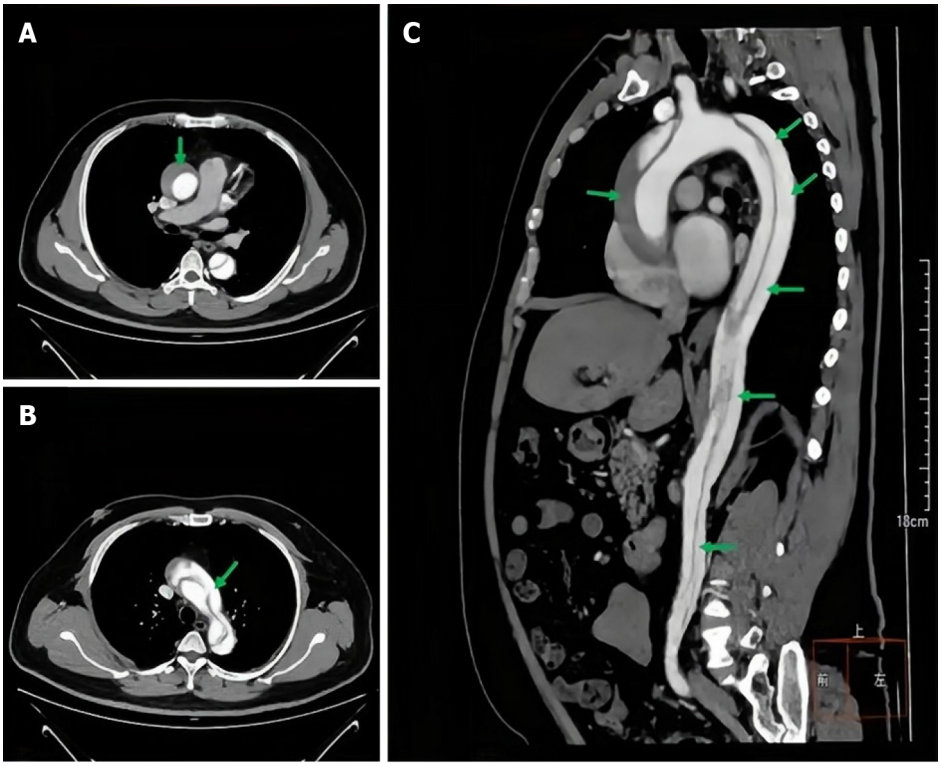

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Figure 1 Enhanced computed tomography scan of the patient's aorta. A: Transverse computed tomography (CT) scan of the ascending aorta; B: Cross-sectional CT images of aortic arch; C: Sagittal CT scan of the aorta. The green arrows indicate the aortic dissection.

immediately assessed the feasibility of both approaches. Due to the large amount of drainage from the mediastinal pericardium and chest cavity after thoracotomy, we ruled out ECMO because of the potential risk of massive bleeding. The patient was treated with PP. Prior to treatment, bedside chest radiography was used to assess the lung condition (Figure 2A). The treatment guidelines suggested that PP time should be ≥ 12 h[6]. Although PP has a positive effect on patients with severe ARDS, it may be difficult in cardiac surgery patients because of the recent sternotomy. Because of the patient's obesity and large amount of mediastinal pericardial and thoracic drainage fluid after thoracotomy, prolonged PP could have increased the risk of drainage tube compression, resulting in poor drainage. Finally, we chose PP for no more than 6 h, and 12 h after the end of PP, the prone position ventilation treatment was performed again. During this period of treatment, we assessed drain patency every hour and monitored circulatory changes in real time to prevent inadequate drainage leading to fatal acute cardiac tamponade. We dynamically followed-up the patient by blood gas analysis. After 4 d of PP, chest X-ray showed that the diffuse exudation from both lungs was significantly reduced (Figure 2B). OI was significantly improved and showed an overall upward trend during PP (Figure 3).

OUTCOME AND FOLLOW-UP

After intermittent short-term PP, the OI improved greatly and the diffuse exudation in both lungs of the patient was significantly reduced.

DISCUSSION

Surgery is the main treatment for type A aortic dissection[2,16]. Several medical centers have reported that severe hypoxemia is likely to occur after thoracotomy under cardiopulmonary bypass (CPB)[17], especially in the patients with long-term smoking, obesity, early renal damage and prolonged CPB.

Severe hypoxemia rapidly progresses to severe ARDS, with high mortality[4,18-21]. A study from LUNG SAFE (Large observational study to Understand the Global impact of Severe Acute respiratory Failure) showed a mortality as high as 46% for severe forms of ARDS[22]. ARDS can have pulmonary (pneumonia, aspiration, pulmonary contusion, pulmonary embolism, *etc.*) or extrapulmonary (sepsis, acute severe pancreatitis, cardiopulmonary bypass, severe trauma, burns, *etc.*) causes[5,22-24], and the prominent clinical feature is hypoxemia. It is believed that ischemia–reperfusion injury and the release

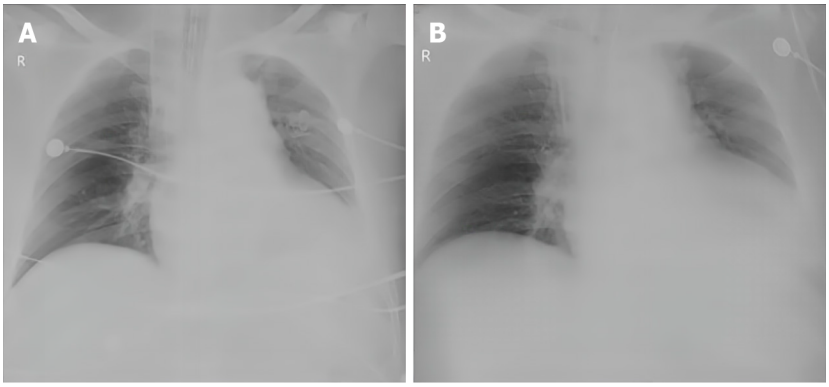

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Figure 2 Bedside X-ray images of the patient before and after prone position ventilation. A: X-ray image before prone position ventilation: Diffuse exudation of both lungs; B: X-ray image after three of intermittent prone position ventilation.

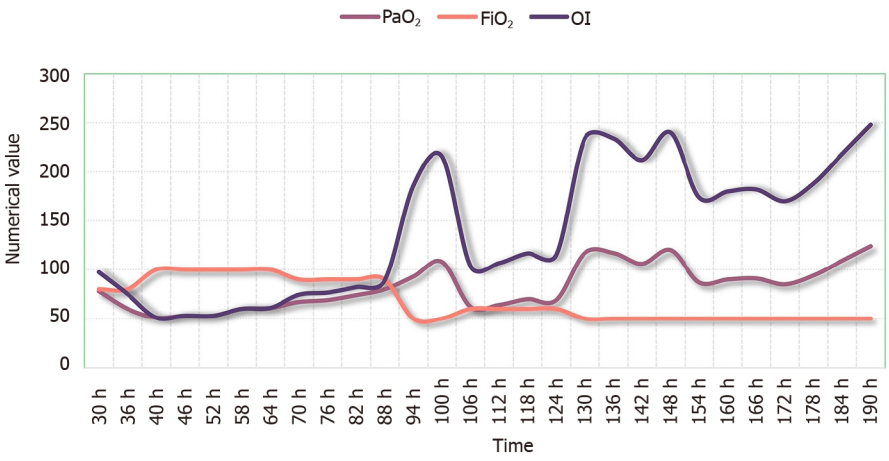

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Figure 3 Improvement of oxygenation index with prone position ventilation. PaO_2: Partial pressure of arterial oxygen; FIO_2: Fraction of inspired oxygen; OI: Oxygenation index.

of large amounts of inflammatory mediators and circulatory arrest during CPB are responsible for ARDS after cardiac surgery[17,20].

Globally, ARDS accounts for 10% of ICU admissions[25]. Although the pathogenesis of ARDS is gradually being revealed and therapeutic approaches have made significant progress, its morbidity and mortality are still high[7,26]. PP has been proven to effectively improve the prognosis of ARDS patients and reduces ventilator-induced lung injury[14,27]. In addition, PP can shorten the duration of mechanical ventilation and ICU length of stay. When lung protective mechanical ventilation cannot prevent hypoxia or hypercapnia, ECMO may also be considered in patient with severe ARDS[9]. However, even with ECMO support, the mortality rate for severe ARDS is still high. The EOLIA trial showed that in very severe ARDS, the mortality rate was 35% in patients treated with ECMO compared to 46% in patients without ECMO support[28]. Kono *et al*[29] reported a case that they chose V-V ECMO for Severe Respiratory Failure after Acute Aortic Dissection Surgery. Although PP and ECMO are both options for severe ARDS, ECMO is often not available in general healthcare centers and can easily cause fatal bleeding in patients with abnormal coagulation function. Therefore, PP may be a reliable treatment when ECMO is not an option. Although there are indications and contraindications for the implementation of PP in clinical settings (Table 2), ARDS patients can eventually obtain better therapeutic effect from PP as long as individualized treatment is carried out[30,31]. Gu *et al*[15] found that PP is a safe and feasible option for severe hypoxemia patients after acute type A aortic dissection surgery. The etiology of severe ARDS after cardiac surgery is different from that caused by severe lung infection. Prolonged prone ventilation is often inappropriate after thoracotomy. Therefore, we chose to perform PP for no longer than 12 h, as recommended by Griffiths *et al*[6]. On the premise of ensuring the stability of the thoracic structure and the patency of the pericardial mediastinal drainage tube after thoracotomy, we chose PP for < 6 h at a time, and continued prone position ventilation treatment after 12 h in the supine position, and achieved a good therapeutic effect.

Table 2 Criteria and recommendations for prone ventilation in acute respiratory distress syndrome

Indications	Severe ARDS ($PaO_2/FiO_2 \leq 100$ mmHg with PEEP ≥ 5 cmH_2O;); within 48 h after onset of ARDS; mean arterial pressure > 65 mmHg
Contraindications (absolute and relative)	Acial/neck trauma or spinal instability; Raised intraocular pressure or recent ophthalmic surgery, facial trauma, or recent oral maxillofacial surgery in last 15 d; Elevated intracranial pressure; Severe hemodynamic instability, unstable cardiac rhythms; Hemoptysis, unstable airway (double lumen endotracheal tube), new tracheostomy < 15 d, lung transplant; Recent sternotomy or more than 20% body surface burn; Grossly distended abdomen; Second or third trimester pregnancy, grossly distended abdomen; Venous thromboembolism treated < 48 h
Implementation method[8]	Requires 3-5 people, close attention to ETT and central lines; a demonstration video; and checklist are available; Preparation: Preoxygenation, empty stomach, suction; ETT/oral cavity, remove ECG leads and reattach to back, repeated zeroing of hemodynamic transducers; Support and frequently reposition pressure points: Face, shoulder, anterior pelvis
Prone positioning time[31]	12-16 h per protocol
Possible complications	Vascular catheter kinking; Elevated intraabdominal pressure; Facial pressure ulcers, facial edema, brachial plexus injury (arm extension); Cardiac arrest
Time to stop	PaO_2/FiO_2 remained > 150 mm Hg 4 h after supinating (with PEEP < 10 cm H_2O and FiO_2 < 0.6)

ARDS: Acute respiratory distress syndrome; ETT: Endotracheal tube; ECG: Electrochemical grinding; FIO_2: Fraction inspired oxygen; PaO_2: Partial pressure of arterial oxygen; PEEP: Positive end-expiratory pressure.

Therefore, we believe that it is feasible to perform prone ventilation in the early postoperative period in patients with aortic dissection. However, it is necessary to formulate an individualized plan, which not only achieves a better therapeutic effect, but also minimizes the associated potential risks, such as acute cardiac tamponade due to poor drainage of the diaphragmatic drainage tube.

CONCLUSION

The occurrence of ARDS after aortic dissection is high, and simple lung protective ventilation and fine fluid management are often ineffective. For patients with severe ARDS after CPB for aortic dissection, intermittent short-course PP may be useful when there is no ECMO support or when the risk associated with ECMO is high.

FOOTNOTES

Author contributions: Niu BL contributed to the study conception and design; Yang JH, Gan YX, Feng XY and Wang S contributed to the data collection and analysis; Yang JH wrote the manuscript; Niu BL and Wang S revised the manuscript; All authors have read the manuscript and approved the final version to be published; Yang JH and Wang S contributed equally to this work.

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CASE REPORT

Congenital nephrogenic diabetes insipidus arginine vasopressin receptor 2 gene mutation at new site: A case report

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Abstract

BACKGROUND

Congenital nephrogenic diabetes insipidus (CNDI) is a rare hereditary disorder. It is associated with mutations in the arginine vasopressin receptor 2 (AVPR2) gene and aquaporin 2 (AQP2) gene, and approximately 270 different mutation sites have been reported for AVPR2. Therefore, new mutations and new manifestations are crucial to complement the clinical deficiencies in the diagnosis of this disease. We report a case of a novel AVPR2 gene mutation locus and a new clinical manifestation.

CASE SUMMARY

We describe the case of a 48-d-old boy who presented with recurrent fever and diarrhea 5 d after birth. Laboratory tests showed electrolyte disturbances and low urine specific gravity, and imaging tests showed no abnormalities. Genetic testing revealed a novel X-linked recessive missense mutation, c.283 (exon 2) C>T (p.P95S). This mutation results in the substitution of a proline residue with a serine residue in the AVPR2 protein sequence. The diagnosis of CNDI was confirmed based on the AVPR2 gene mutation. The treatment strategy for this patient was divided into two stages, including physical cooling supplemented with appropriate amounts of water in the early stage and oral hydrochlorothiazide (1-2 mg/kg) after a clear diagnosis. After follow-up of one and a half years, the patient gradually improved.

CONCLUSION

AVPR2 gene mutations in new loci and new clinical symptoms help clinicians understand this disease and shorten the diagnosis cycle.

Key Words: Congenital nephrogenic diabetes insipidus; Arginine vasopressin receptor 2

gene mutation; New site; Diarrhea; Case report

Core Tip: In this case, a pediatric patient with congenital nephrogenic diabetes insipidus harbored a mutation in the arginine vasopressin receptor 2 (AVPR2) gene at a new locus. In addition, the diarrhea observed in this case is likely related to the novel AVPR2 gene mutation. Therefore, the description of new mutations and new manifestations are crucial to complement the clinical deficiencies in the diagnosis of the disease. We report a case harboring an AVPR2 gene mutation at a new locus and a new clinical manifestation.

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INTRODUCTION

Congenital nephrogenic diabetes insipidus (CNDI) is a rare nephrogenic hereditary disorder. Approximately 90% of CNDI cases harbor arginine vasopressin receptor 2 (AVPR2) mutations transmitted by X-linked recessive inheritance. Less than 10% of CNDI cases harbor aquaporin 2 (AQP2) mutations that are autosomal recessive or dominant mutations, and the genetic causes are unknown in approximately 2% of CNDI cases. To date, approximately 290 AVPR2 gene variants that may cause CNDI have been reported in the Human Gene Mutation Database[1], including approximately 177 missense mutations [2]. The disease often develops in infancy and early childhood, during which growth retardation, frequent vomiting, and hyperthermia represent the more common symptoms[1]. Growth retardation is considered a serious complication of CNDI. In addition to urinary complications, short stature and CKD are common[3]. Intracranial calcification and epilepsy are rare complications. New mutation sites and new clinical manifestations are constantly being reported. In this case, a pediatric patient with CNDI and a AVPR2 gene mutation at a new locus is reported. In addition, the diarrhea observed in this case is likely related to the AVPR2 gene mutation at the new locus. We discussed the new mutation and new phenotype together with information reported in the literature to improve clinicians' understanding of CNDI and guide the clinical diagnosis of this disease.

CASE PRESENTATION

Chief complaints

A 48-d-old Chinese boy presented with fever and diarrhea for one month.

History of present illness

A 48-d-old boy presented with recurrent fever and diarrhea 5 d after birth. In the following month, the child developed repeated fever, diarrhea, and a body temperature fluctuating between 37.1 °C and 38.4 °C. The fever was irregular, and the diagnosis could not be confirmed after 3 hospitalizations at the local hospital. To further confirm the diagnosis, the child was admitted to our hospital for treatment, and the admission symptoms included clear consciousness, general spirit, fever, diarrhea, no dehydration, sunken nose bridge, dry skin, normal diet, normal sleep, and normal urination.

History of past illness

The patient had no previous medical history.

Personal and family history

The patient's parents deny any family history.

Physical examination

The patient's temperature was 38.1 °C, pulse 140 beats/min, respiratory rate 35 breaths/min, blood pressure 70/40 mmHg, and weight 5 kg. No abnormalities were found in other system examinations.

Laboratory examinations

Blood test analysis showed an electrolyte imbalance: K, 5.5 mmol/L; Na, 149.5 mmol/L; Cl, 112.6 mmol/L; Ca, 2.61 mmol/L; and P, 1.98 mmol/L. Urinalysis showed that the specific gravity of urine was less than 1.005. Routine blood cell count, erythrocyte sedimentation rate, routine stool examination, 10 items regarding prenatal and postnatal care, 6 items regarding immunity, tuberculosis antibody test, Epstein-Barr virus nucleic acid quantitative detection, cytomegalovirus nucleic acid quantitative detection, infectious disease screening, genetic testing, glucose monitoring test and other results were normal.

Imaging examinations

Color Doppler ultrasound of the superficial lymph node, lung, heart, gastrointestinal tract, liver, gallbladder, spleen, abdominal lymph node and kidney revealed normal findings.

Genetic examinations

An AVPR2 gene mutation, c.283 (exon2) C>T (p.P95S), was identified. This mutation was a hemizygous mutation in the 2nd exon of the AVPR2 gene. The C nucleotide at position 283 became a T nucleotide, which led to an amino acid change. The amino acid at position 95 was mutated from proline to serine [p.Pro95Ser (p.P95S)]. This mutation was a missense mutation and a novel mutation locus in the AVPR2 gene. The mother of the proband is a carrier of this gene mutation, and the father harbors no abnormal mutations in this gene. The specific genetic test results and family pedigree are shown in Figures 1 and 2. The test results showed that the proband had a hemizygous mutation, which was consistent with X chromosome recessive inheritance. Because the child had intractable diarrhea and a possible pathogenic variant of diarrhea could not be excluded, we tested related genes. No abnormalities in JAK3 (severe combined immunodeficiency, autosomal recessive, T-B+NK-), ZAP70 (selective T-cell deficiency) or PLEC (epidermolysis bullosa and pyloric atresia) were noted in the genetic testing.

FINAL DIAGNOSIS

Based on the clinical symptoms of fever and diarrhea at admission, we performed auxiliary examinations to clarify the diagnosis and exclude related diseases. Furthermore, a genetic diagnosis of a c.283 (exon 2) C>T (p.P95S) mutation of the AVPR2 gene is of great significance in the diagnosis of CNDI, and the reference standards are stated here: (1) CNDI is a rare inherited disease that is caused by mutations in AVPR2 or AQP2[1]; (2) Mutations in either AVPR2 or AQP2 result in a genetic disease known as nephrogenic diabetes insipidus[4]; (3) CNDI results from mutations in the AVPR2 or AQP2 genes[5]; and (4) AVPR2 mutations result in X-linked recessive NDI, the most common form of inherited NDI[6]. As a result, the patient was finally diagnosed with CNDI.

TREATMENT

After the child was admitted to the hospital, we did not confirm the diagnosis in a timely manner. Treatment during this period included physical cooling supplemented with appropriate amounts of water. However, this approach does not fundamentally solve the problem. Two weeks after discharge from the hospital, we confirmed the diagnosis based on the results of genetic testing. Oral hydrochlorothiazide (1-2 mg/kg based on the child's body weight) was administered twice a day. After taking the medication for one year, the doctor adjusted the medication according to the child's physical condition and took it orally thereafter (1-2 mg/kg, twice a day). Tables 1 and 2 present the changes in the condition of the child before and after the oral administration of hydrochlorothiazide.

OUTCOME AND FOLLOW-UP

The child attended follow-up at the outpatient clinic after discharge, and the family members were instructed to monitor the changes in the child's body temperature, stool, diet and height. The follow-up period lasted approximately one and a half years. The child's condition is relatively stable now with 1400-1600 mL/d water intake, and other aspects of growth and development are similar to that noted in normal children.

DISCUSSION

In 1992, van den Ouweland *et al*[7] reported for the first time that patients with X-linked recessive

Table 1 Clinical presentations of the child before oral administration of hydrochlorothiazide

Date	Temperature (max)	Fever time interval/day	Diarrhea/times/day
October 30, 2020	38.1 °C	0	6
October 31, 2020	37.2 °C	0.5	3
November 1, 2020	38.7 °C	0	7
November 2, 2020	38.5 °C	0	6
November 3, 2020	37.9 °C	0	5
November 4, 2020	37.5 °C	0	5
November 5, 2020	37.9 °C	0	5
November 6, 2020	38 °C	0	6
November 7, 2020	37.6 °C	0	5
November 8, 2020	38.2 °C	0	7
November 9, 2020	37.9 °C	0	6
November 10, 2020	38.5 °C	0	7
November 11, 2020	37.9 °C	0	6

Table 2 Clinical presentation of the child after oral administration of hydrochlorothiazide

Date	Temperature (max)	Fever time interval/day	Diarrhea/times/day
November 25, 2020 to December 8, 2020	38.1 °C	1-2	5
December 9, 2020 to January 9, 2021	38.4 °C	3	3-4
January 10, 2021 to April 9, 2021	37.7 °C	7	3-4
April 10, 2021 to July 9, 2021	37.5 °C	20	2-3
July 10, 2021 to October 9, 2021	37.9 °C	25	2-4
October 10, 2021 to January 9, 2022	37.5 °C	32	1-2
January 10, 2022 to April 9, 2022	37.2 °C	45	1-2
April 10, 2022 to July 9, 2022	36.7 °C	70	1

nephropathy insipidus harbor AVPR2 gene mutations and gradually began to study the genetics of CNDI at home and abroad. CNDI patients show symptoms of polyuria and polydipsia from birth and typically develop irritability[8], feeding difficulties, weight loss, dry skin, poor skin elasticity, sunken eyes and other dehydration manifestations in the first week after birth. High fever and constipation are frequently noted[9,10]. Common symptoms in male patients include polyuria, polydipsia, fever of unknown etiology, convulsions, and vomiting. These symptoms typically appear shortly after birth, and relatively mild symptoms are generally noted in women[11]. In this case, the child also had symptoms of long-term recurrent fever. Schrager *et al*[12] reported on fever in CNDI patients but did not further clarify the mechanism of the fever. Some researchers believe that this intermittent high fever is a common complication of the dehydration state, which mainly occurs in very young children[9]. Based on the fact that the fever can be further relieved after the patient drinks water, some scholars consider it to be a dehydration fever[13]. In addition to the fever symptoms, the child we described also had obvious symptoms of diarrhea. In this regard, we hypothesized that the patient's repeated fever is caused by dehydration as a result of diarrhea. It is well known that the main symptom of CNDI patients is polyuria[5,14-16]. To date, there have been no reports of diarrhea associated with this disease. Genetic testing of the AVPR2 gene revealed the c.283 (exon 2) C>T (p.P95S) mutation, which was considered to be associated with diarrhea symptoms in this patient. This presentation potentially represents another new complication of the disease. This new clinical manifestation potentially results from this novel mutation locus.

Research on the pathogenesis of CNDI has been previously reported in detail. Under physiological conditions, AVP secreted by the posterior pituitary increases in the presence of hypovolemia or hypernatremia, which binds to the type 2 receptor AVPR2 located on the basolateral side of collecting duct cells[9], and activated AVPR2 initiates a signal transduction cascade. This process includes the activation of adenylate cyclase by stimulating Gs protein[4], resulting in increased intracellular cyclic

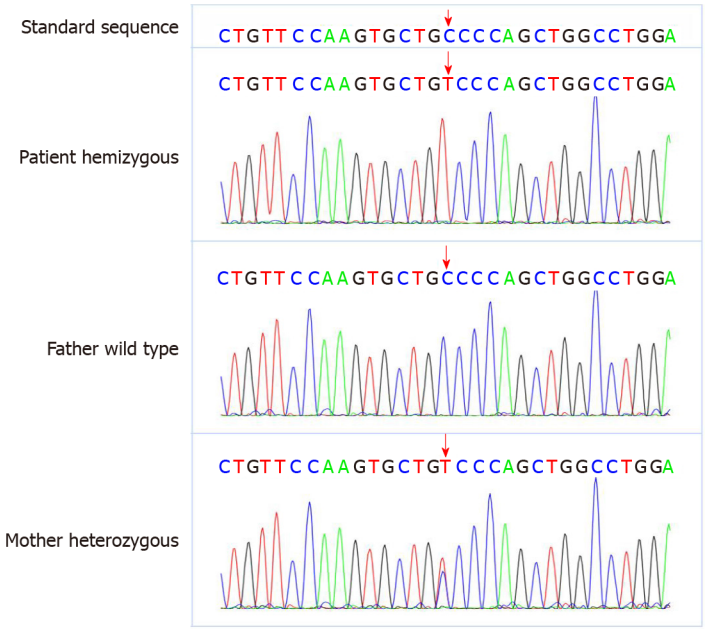

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Figure 1 Genetic testing results of the child indicated a arginine vasopressin receptor 2 gene mutation, c.283 (exon2) C>T (p. P95S). This was a hemizygous mutation in the 2nd exon of the arginine vasopressin receptor 2 (AVPR2) gene. The base C at position 283 became base T, which led to the change of amino acid. The amino acid at position 95 was mutated from proline to serine, p. P95S (p. Pro95Ser). This mutation was a missense mutation and a new mutation site in the AVPR2 gene. The mother of the proband is a carrier of this gene mutation, and the father has no abnormal mutation in this gene.

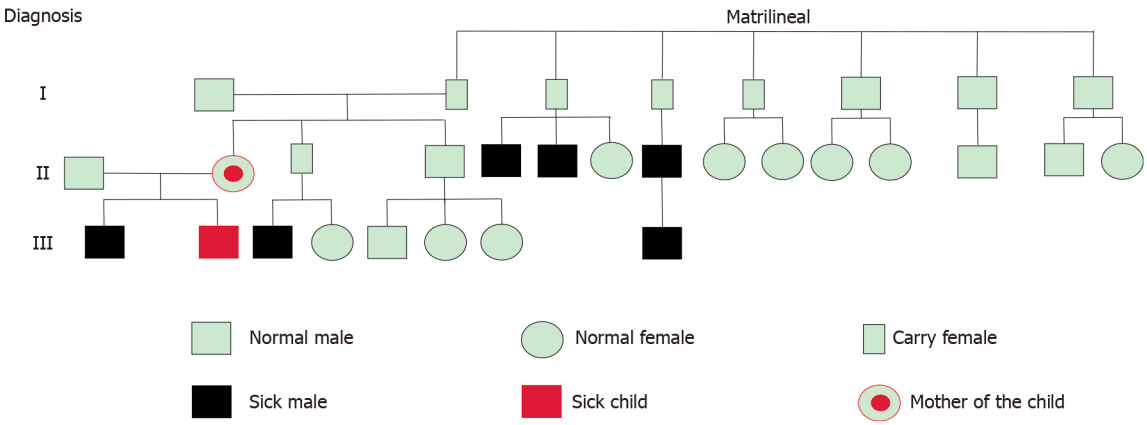

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Figure 2 Family pedigree of patients.

adenosine monophosphate (cAMP) levels, activation of protein kinase A (PKA), and phosphorylation of AQP2. The phosphorylation of three monomers in the AQP2 tetramer results in the redistribution of the AQP2 homotetramer, transportation of AQP2 from storage vesicles to the apical membrane, and increased permeability of collecting duct chief cells to water[9,17]. The important regulatory role of AVPR2 can be clarified from the pathogenesis process. This mechanism also represents the theoretical basis for direct sequencing of AVPR2 in neonates with familial susceptibility to CNDI as a rapid diagnostic tool for CNDI in clinical practice[14].

According to classification standards, researchers have categorized AVPR2 gene mutations into three categories: Type I mutants result in proteins that reach the cell surface but cannot bind to their ligands, type II mutant receptors are damaged and cannot reach the cell surface, and type III mutant proteins are improperly transcribed[11]. The diarrhea in this case likely resulted from the AVPR2 gene c.283 (exon 2) C>T hemizygous mutation, which caused the substitution of proline at position 95 to serine. This substituted based is surrounded by leucine at position 94 and leucine at position 96. Glutamine reacts to form new hydrogen bonds. The formation of new amino acid sequences leads to improper folding of the AVPR2 along with protein conformation changes. Thus, the protein is retained in the intracellular endoplasmic reticulum (ER)[5,15]. This effect may alter some properties of the protein, causing it to become harmful[1]. The accumulation of this harmful product affects the intestinal mucosa or intestinal

muscle layer of infants and young children through a specific channel or by releasing a specific factor. These children have weak intestinal function and are easily affected; thus, clinical symptoms of diarrhea will occur. Alternatively, the formation of new amino acid sequences leads to misfolding of the AVPR2, which enables the rapid degradation of certain peptides[15] and may also produce harmful proteins that affect the body's brain-gut axis function. Another hypothesis is that mutations in the AVPR2 gene do not cause alterations in expression, ER retention, or constitutive endocytosis. Rather, the symptoms are due to the abnormal function of the mutant receptor[1]. The function of the protein may cause intestinal flora disturbances. Currently, this is only a hypothesis for the mechanism by which diarrhea symptoms develop, and further studies involving a definitive functional analysis of this mutation are needed. In this study, the c.283 (exon2) C>T (p.P95S) mutation in the AVPR2 gene and the symptoms of diarrhea are reported. However, the effect on protein structure and function is unclear. The next step is to analyze the function of the receptor to verify the specific impact of the mutation on the receptor, provide a theoretical basis for emerging clinical complications, and propose possible treatment strategies for specific functional defect[1].

CNDI is a severe form of DI that is difficult to treat and typically results from genetic defects[15]. Currently, there is no specific treatment method for CNDI, and treatment mainly focuses on improving symptoms in clinical practice, such as guiding patients to supplement sufficient fluids, a low-sodium diet, a low-protein diet, and the oral administration of some drugs[5,18]. Based on advancements in molecular biology technology, some new therapeutic methods exhibit great potential in treating children with CNDI. Currently, these methods mainly involve the following mechanisms: (1) AVPR2 antagonists and cell-permeable AVPR2 antagonists act as molecular chaperones and are mainly administered to patients with AVPR2 missense mutations[19]. Targeting chemical and molecular chaperones appropriately corrects the point mutations that cause misfolded disease-causing proteins, rescuing mutant proteins from ER retention and allowing correctly folded proteins to be delivered in cells[19,20]; (2) AVPR2 agonists, some of which are cell permeability agonists, can bind AVPR2 mutants trapped in the ER, but they do not stabilize their conformation and can directly activate AVPR2 mutants within these cells by signaling to transmit a preformed receptor-G protein-adenylate cyclase complex. The subsequent generation of cAMP activates PKA, resulting in AQP2 phosphorylation and plasma membrane expression, thereby attenuating the NDI phenotype[4,19]; (3) Some classic treatment modalities, including vasopressin analogs, prostaglandin receptor agonists, hormone receptor agonists, and cGMP phosphodiesterase inhibitors, can bypass the defective AVPR2 signaling pathway. The main mechanism of this therapeutic approach is the increase in cytoplasmic cAMP and activation of cAMP-independent pathways[4,18,19]; and (4) Gene therapy can be used to edit the genome of somatic cells or embryos to correct the mutated genes[19]. However, only theoretical studies have been performed at present due to ethical concerns related to this treatment method. Some newer potential drugs have also been reported, such as the AKAP-PKA interfering agent FMP-API-1, which is similar to vasopressin. FMP-API-1/27, a derivative of FMP-API-1, is the first low-molecular-weight compound found to phosphorylate AQP2 more efficiently than existing drug candidates. AKAP-PKA-interfering agents have the potential to be developed into new therapeutic drugs and become potential therapeutic options [21]. The AMPK activator NDI-5033 can improve the urine concentration of NDI animals and is expected to be a potential therapy for CNDI caused by AVPR2 mutations[22]. Although numerous mutations with different functional defects hinder the development of specific treatments[23], the clinical safety, efficacy and long-term performance of these new potential treatments cannot be determined. With the development of technology and clinical safety evaluation improvements, these issues will be resolved in the near future.

CONCLUSION

This case describes a c.283 (exon 2) C>T (p.P95S) mutation of the AVPR2 gene in a child with CNDI with clinical symptoms of fever and diarrhea. Because children with CNDI do not exhibit the hallmark symptoms of chronic polyuria and polydipsia[14], the clinician experiences uncertainty in the early diagnosis process, which leads to a prolonged clinical diagnosis time. Many clinicians have considered CNDI when faced with infants with a fever of unknown etiology[10]. However, the onset of CNDI is insidious, and the condition may be misdiagnosed or missed. If the child has other rare or unreported phenotypes, the course of the disease lasts for a long time. Especially in neonates, CNDI can be life-threatening because patients may develop severe dehydration, and repeated severe dehydration and hypernatremia can lead to intellectual disability[24]. This case broadens the genotype and phenotype spectrum of rare cases of CNDI caused by AVPR2 mutation and provides a basis for studying the molecular biology of AVPR2[25]. In addition, with research on the physiology and pathology of CNDI, the mechanism of these rare phenotypes will be understood.

FOOTNOTES

Author contributions: Yang LL reviewed the literature and contributed to manuscript drafting; Xu Y and Qiu JL reviewed the manuscript and guided its revision; Zhao QY participated in the clinical care of patients and collected data; Li MM and Shi H contributed to patient follow-up; Zhao QY and Qiu JL as the co-corresponding author of this manuscript; and all authors commented on previous versions of the manuscript and issued final approval for the version to be submitted.

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CASE REPORT

Development of dilated cardiomyopathy with a long latent period followed by viral fulminant myocarditis: A case report

Seung Do Lee, Hyo Jin Lee, Hye Ree Kim, Min Gyu Kang, Kyehwan Kim, Jeong Rang Park

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Abstract

BACKGROUND

The clinical course of acute myocarditis ranges from the occurrence of a few symptoms to the development of fatal fulminant myocarditis. Specifically, fulminant myocarditis causes clinical deterioration very rapidly and aggressively. The long-term prognosis of myocarditis is varied, and it fully recovers without leaving any special complications. However, even after recovery, heart failure may occur and eventually progress to dilated cardiomyopathy (DCM), which causes serious left ventricular dysfunction. In the case of follow-up observation, no clear guidelines have been established.

CASE SUMMARY

We report the case of a 21-year-old woman who presented with dyspnea. She became hemodynamically unstable and showed sustained fatal arrhythmias with decreased heart function. She was clinically diagnosed with fulminant myocarditis based on her echocardiogram and cardiac magnetic resonance results. After 2 d, she was readmitted to the emergency department under cardiopulmonary resuscitation and received mechanical ventilation and extracorporeal membrane oxygenation. An implantable cardioverter defibrillator was inserted for secondary prevention. She recovered and was discharged. Prior to being hospitalized for sudden cardiac function decline and arrhythmia, she had been well for 7 years without any complications. She was finally diagnosed with dilated cardiomyopathy.

CONCLUSION

DCM may develop unexpectedly in patients who have been cured of acute fulminant myocarditis and have been stable with a long period of remission. Therefore, they should be carefully and regularly observed clinically throughout long-term follow-up.

Key Words: Myocarditis; Fulminant; Dilated cardiomyopathy; Outcome; Remission; Case report

Core Tip: While dilated cardiomyopathy (DCM) has been well-known as a complication in patients who develop fulminant myocarditis, it is still unclear when DCM might occur. We report the case of a young woman who developed DCM after 7 years of remission without any special complications after recovering from viral myocarditis. No case of DCM development has been reported after such a long latent period of normal cardiac function after a full recovery from viral fulminant myocarditis. We, therefore, suggest that clinicians be aware that DCM can develop unexpectedly and that careful clinical monitoring is required regularly.

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INTRODUCTION

Myocarditis, an inflammation of the myocardium, is also defined as inflammatory cardiomyopathy characterized by worsening cardiac dysfunction and cardiac remodeling in terms of the size, shape, and structure of the heart[1]. Etiologies of acute myocarditis include various infections, autoimmune diseases, hypersensitivity reactions, and toxic reactions to drugs and toxins[1]. Clinical presentations of myocarditis vary from asymptomatic or with mild symptoms of chest pain, dyspnea, or palpitations to high-risk cardiac conditions with severe heart failure (HF), refractory arrhythmias, cardiogenic shock, and sudden cardiac death[2].

Regarding the severity and prognosis of myocarditis, most patients successfully recover, and the clinical course is mostly self-limited. However, in a study, nearly 30% of individuals reportedly developed dilated cardiomyopathy (DCM)[3]. Furthermore, prompt and aggressive treatment can help achieve complete recovery in patients who develop a fulminant presentation with severe left ventricular (LV) dysfunction[4]. Although studies have found that patients with myocarditis have poor long-term clinical outcomes[5-7], the outcomes and follow-up strategies after full recovery require further investigation.

Herein, we present a case of delayed development of DCM after a long remission period of fulminant myocarditis.

CASE PRESENTATION

Chief complaints

A 21-year-old woman who presented with dyspnea, tachycardia, and hypotension was transferred to our emergency department.

History of present illness

She was admitted to the local hospital for 2 d for upper abdominal discomfort and constipation.

History of past illness

She had a history of cesarean delivery a year before.

Personal and family history

She had no history of family history of any heart disease.

Physical examination

Her initial vital signs were as follows: Blood pressure of 137/67 mmHg, pulse rate of 184 beats per min, respiration of 40 breaths per minute, and a body temperature of 36.7 ℃. Other general examinations were not remarkable. Atrial fibrillation was detected, and the rate still increased even after the administration of digitalis. Her systolic blood pressure suddenly dropped, so she received electric defibrillation

at 100 J, and her hemodynamic status was stabilized with a sinus heart rhythm.

Laboratory examinations

Remarkable laboratory findings were highly elevated levels of liver enzymes, *i.e.*, aspartate aminotransferase of 3381 U/L (reference, < 37 U/L) and alanine aminotransferase of 1197 U/L (reference, < 41 U/L); extremely increased B-type natriuretic peptide level of 2233 pg/mL (reference range, 0-100 pg/mL); mild hypokalemia, with serum potassium concentration of 3.2 mmol/L (reference range, 3.3-5.1 mmol/L); white blood cell count of 11710 × 10^3/mm^3; and C-reactive protein of 10.7 mg/L. Other than that, no abnormal findings, including cardiac enzymes, were found.

Imaging examinations

Her initial chest X-ray imaging showed remarkable cardiomegaly and bilateral pulmonary edema (Figure 1A). The initial transthoracic echocardiography (TTE) demonstrated dilated left atrium and LV and severe LV systolic dysfunction with an ejection fraction (EF) of 24% (Figure 2A; Supplementary Video 1). Mild mitral regurgitation and a small amount of pericardial effusion were found. On day 7 of hospitalization, cardiac magnetic resonance (CMR) imaging revealed endocardial edematous change and delayed gadolinium enhancement from the interventricular septum to the inferior wall of the LV (Figure 3). The myocardial perfusion of contrast was normal on CMR. Liver ultrasonography to rule out severe hepatic illness revealed only mild-to-moderate fatty liver.

FURTHER DIAGNOSTIC WORK-UP

She was diagnosed with acute myocarditis based on her acute clinical presentation and CMR findings. Increased liver enzymes improved dramatically with diuretic therapy and were thought to be the result of hepatic congestion following HF. After clinical stabilization, she was discharged and outpatient follow-up was arranged. However, she was readmitted at night of the same day that cardiopulmonary resuscitation was performed. On arrival, endotracheal intubation was performed, and repetitive defibrillation continued throughout the day. Severe arrhythmias, including ventricular fibrillation, ventricular tachycardia, and supraventricular tachycardia, recurred with hypotension. Subsequently, amiodarone and dobutamine were infused, and extracorporeal membrane oxygenation (ECMO) was initiated for circulatory support. As a result, her vital sign stabilized, and fatal arrhythmia was not observed. ECMO was discontinued, and an implantable cardioverter defibrillator (ICD) was inserted for secondary prevention.

On the second visit to the emergency department, the levels of cardiac enzymes were increased: Creatinine kinase-MB, 35.4 ng/mL (reference, < 5 ng/mL) and troponin-I, 2.67 ng/mL (reference range, 0-0.04 ng/mL). High neutralizing antibody titers to Coxsackie B1 virus (titer 1:64) were confirmed, and autoantibodies were negative. Although endomyocardial biopsy was not performed, she was clinically diagnosed with fulminant myocarditis based on TTE and CMR findings on clinical presentation. For HF, beta blockers, angiotensin receptor blockers, and diuretics were prescribed. TTE on day 21 revealed improved EF up to 40%.

One year later, the cardiomegaly detected by chest X-ray imaging was improved, and her follow-up LVEF recovered to normal range (Figures 1B and 2B; Supplementary Video 2). In the 7-year follow-up outpatient care, her condition and ICD without medications were regularly checked up. During the follow-up, she did not present any symptoms or signs, and there was only one event of inappropriate shock as a response to sinus tachycardia.

On the 8th year, paroxysmal atrial fibrillation and rapid ventricular response were detected by ICD recording, and the LVEF decreased to 42%, which means that she had a relapse of HF (Figures 1C and 2C; Supplementary Video 3). There was no definite evidence of aggravating factors regarding her disease such as medication, alcohol, infection, and even emotional stress. She presented dry cough, ankle edema, and chest discomfort gradually. Guideline-based medications were started again, and her condition symptomatically improved.

FINAL DIAGNOSIS

Initially, the patient was clinically diagnosed with fulminant myocarditis based on TTE and CMR findings on clinical presentation. The patient was finally diagnosed with DCM with a long remission period after viral fulminant myocarditis.

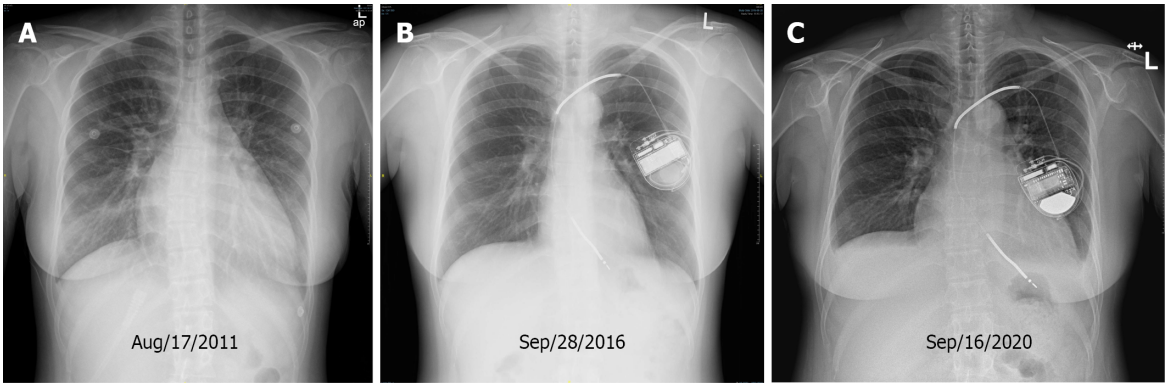

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Figure 1 Serial chest X-ray images. A: Cardiomegaly and pulmonary edema were observed at the initial presentation; B: Cardiac silhouette of the following image was normalized; C: Overt cardiomegaly and pleural effusion developed, and recurrent dilated cardiomyopathy was finally diagnosed.

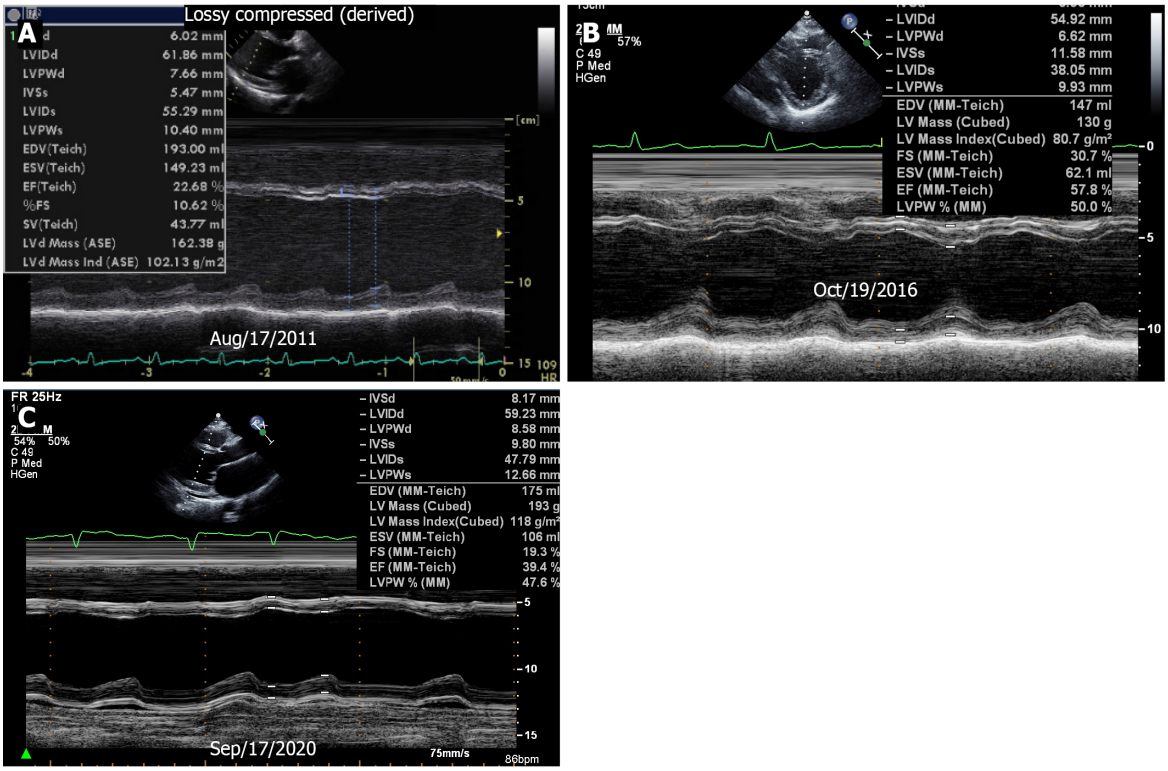

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Figure 2 Transthoracic echocardiography. A: Baseline echocardiography showed dilated left ventricular (LV) dimension and severely decreased LV ejection fraction (EF); B: Preserved LVEF at one year follow-up; C: The last M-mode image showed dilated LV and low LVEF again. Movies of the serial change of 4-chamber views showed the same findings.

TREATMENT

She was given an angiotensin receptor blocker, a vitamin K antagonist, and digitalis as conventional treatment for DCM and atrial fibrillation.

OUTCOME AND FOLLOW-UP

The most recent imaging performed on March 2021 showed a slight improvement in LVEF (47%). She is currently not experiencing any clinical adverse events.

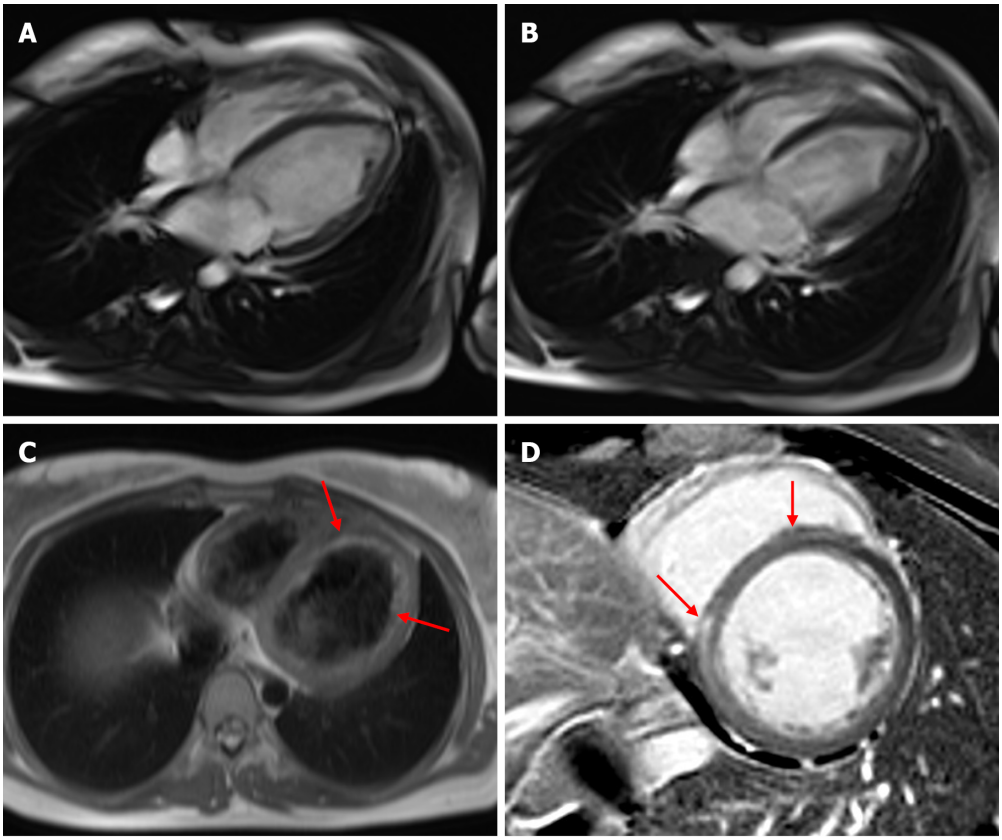

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Figure 3 Cardiac magnetic resonance. A and B: Decreased left ventricular systolic function was observed (A: Diastole and B: Systole); C: A T2-weighted image shows diffuse endocardial edema (arrow); D: A T1-delayed image revealed late gadolinium enhancement in the mid-layer of the interventricular septum (arrow).

DISCUSSION

Fulminant myocarditis is a severe inflammatory myocardial disease often induced by cardiotropic viruses such as parvovirus, human herpes virus-6, coxsackie virus, human immunodeficiency virus, and cytomegalovirus[5]. Despite different clinical courses and outcomes, up to 30% of patients with acute myocarditis progressed to DCM, which is clinically defined by LV dilatation and systolic dysfunction [3]. The long-term poor clinical outcomes of patients with myocarditis have been reported[5,6], Escher *et al*[7] reported that about 50% of patients who suffered from acute myocarditis developed diastolic HF with preserved EF in a 6-year long-term follow-up period. However, it is unknown when DCM develops following the resolution of fulminant myocarditis.

In this case, we believed the patient had recovered completely from fulminant myocarditis, and she had been well with normal LVEF and normal diastolic function for 7 years. The paroxysmal atrial fibrillation event was the first sign of recurrent HF. It took 6 mo from the event of atrial fibrillation on the ICD to the onset of symptomatic HF. Studies and cases of recurrent myocarditis have been reported, with different intervals and varying causes[8,9]. However, we believe that our case is consistent with the study of Escher *et al*[7] in that the patient developed a long-latency relapse of HF because her symptoms and signs aggravated gradually. Recently, inflammatory cardiomyopathy, including DCM following acute myocarditis, has been recognized. Latent myocarditis caused by persistent virus and chronic inflammation is the major pathology of inflammatory cardiomyopathy, and it is commonly reported as a chronic and progressive impairment[10,11]. In another aspect, Spotnitz and Lesch[12] hypothesized the idiopathic dilated cardiomyopathy could be a late complication of healed viral myocarditis. Ghanizada *et al*[5] demonstrated a higher risk of HF hospitalization and all-cause mortality among patients with myocarditis, even in patients without cardiovascular events and those on HF medications within the first year of discharge, compared to matched controls.

As DCM has been demonstrated to be one of the most common hereditary cardiomyopathies, genetic analysis of mutations for DCM became essential to determine the pathogenesis of the disease[13]. Our patient did not participate in the genetic test for cardiomyopathies because she had no family history related to cardiovascular disease and her medical history of myocarditis was apparent. However, further DCM genetic evaluation would be helpful to rule out any genetic cause for the development of DCM.

To the best of our knowledge, there has been no reported case of DCM developing after such a long latent period while maintaining normal LV function after a full recovery from viral fulminant myocarditis. To date, the long-term follow-up strategy after restoration of fulminant myocarditis has not been established. Moreover, the TRED-HF trial demonstrated a relapse of HF among patients who stopped pharmacological treatment after their LV function was restored[14]. Therefore, we suggest that continuous and regular follow-up and individualized pharmacologic treatment would be required in patients recovering from acute myocarditis. This precaution also should be taken in the case of COVID-19 myocarditis, which has been issued for a severe cardiovascular complication, as well as in some cases of COVID-19 mRNA vaccine-associated myocarditis.

CONCLUSION

We presented one clinical experience that even though patients who are thought to be fully recovered from acute fulminant myocarditis and seemed to be stable for a long-time follow-up period, may develop DCM unexpectedly and they should be clinically monitored at outpatient clinic carefully and regularly with a long period of follow-up.

FOOTNOTES

Author contributions: Park JR was the patient's cardiologist, reviewed the literature, and contributed to the critical revision of the manuscript; Lee SD reviewed the literature, interpreted the clinical findings, and contributed to the manuscript's drafting; Kang MG, Kim K, Lee HJ, and Kim HR contributed to the manuscript drafting; all authors have read and approved the final manuscript.

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CASE REPORT

Hoffa's fracture in a five-year-old child diagnosed and treated with the assistance of arthroscopy: A case report

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Abstract

BACKGROUND

Hoffa's fracture is a coronal-oriented fracture of the femoral condyle. It is rarely observed in pediatric patients that isolated coronal fracture of the medial femoral condyle accompanies an intact lateral femoral condyle. Only a few cases involving Hoffa's fracture of the medial femoral condyle have been reported in patients with undeveloped skeletons. Such a fracture cannot be observed by routine imaging examinations, thus resulting in possible misdiagnosis and further treatment challenges.

CASE SUMMARY

A 5-year-old boy with Hoffa's fracture of the medial femoral condyle suffered from right knee pain and severe swelling after being hit by a heavy object. The patient was misdiagnosed and initially treated in a local primary healthcare center. No improvement in his right knee's extension was observed following conservative treatment for 2 wk. The patient was transferred to our hospital, re-diagnosed using arthroscopy, and underwent open reduction and internal fixation. The therapeutic outcome was satisfactory with the screws removed 7 mo after fixation. At the final follow-up of 40 mo, the range of motion in the knee had recovered. There was no varus-valgus instability.

CONCLUSION

Hoffa's fracture is rarely seen in children aged 5 years, let alone in the medial condyle, and can easily be misdiagnosed due to limited physical and imaging examinations. Suspected Hoffa's fracture in preschool children should be confirmed based on arthroscopic findings. Open reduction and internal fixation should be performed to protect the articular surface and prevent long-term complications.

Key Words: Hoffa's fracture; Pediatrics; Medial femoral condyle; Missed diagnosis; Arthroscopy; Open reduction-internal fixation; Case report

Core Tip: Hoffa's fracture is a rare fracture pattern of femoral condyle, it has special coronal fracture slice. When it happens in children, this fracture is very easy to be missed. The medial condyle Hoffa's fractures are especially uncommon. We report Hoffa's fracture of the medial condyle in a 5-year-old child, the youngest patient ever reported, who was misdiagnosed in the first place. Eventually, we diagnosed the disease with arthroscopy and completed the operation with its assistance, successfully avoiding the radiation damage caused by computed tomography scans to toddler. Meanwhile, a clear and concise review of literature is also included in our study.

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INTRODUCTION

Hoffa's fracture, named after Albert Hoffa in 1904 following his detailed research on this disease[1], is an unusual fracture type on the coronal plane of the femoral condyle. Hoffa's fractures of the lateral femoral condyle are commonly seen, while Hoffa's fractures of the medial femoral condyle are rare, especially in individuals with undeveloped skeletons. The latest case was a 16-year-old girl with Hoffa's fracture of the medial femoral condyle reported by Jiang *et al*[2] in 2022. This type of fracture is an intra-articular fracture and is clinically treated under the same principles as a typical intra-articular fracture. But this type of injury is often misdiagnosed due to a lack of clinical suspicion and radiographic examinations. In this report, we present the case of a 5-year-old boy with unusual type of injury misdiagnosed in a local hospital. Arthroscopy was performed to confirm the medial Hoffa's fracture. Later, open reduction and internal fixation were successfully applied to the patient for treatment.

CASE PRESENTATION

Chief complaints

A 5-year-old boy was transferred to the Department of Orthopedics in our hospital due to right knee pain and swelling, and an inability to bear weight and extend the right knee.

History of present illness

The patient had right knee pain and an inability to extend the knee following 2 weeks of conservative treatment.

History of past illness

The boy had no history of severe diseases, surgery or long-term medication.

Personal and family history

The patient's family had no related diseases.

Physical examination

His right knee was swollen, skin was intact with tenderness on palpation, and limited mobility. No distal neurovascular deficits were observed. He was alert, articulate, and a reliable reporter. No other weakness, stiffness, or edema was found.

Laboratory examinations

Results of laboratory examinations were unremarkable.

Imaging examinations

X-Ray showed a stable fracture in the medial femoral condyle with no displacement (Figure 1). A local orthopedist suggested conservative treatment. Computed tomography (CT) is considered efficient in the diagnosis of adult Hoffa's fracture. However, in this case, the thick cartilage of the distal femoral epiphyseal area made it difficult to evaluate the fracture[1,3,4]. The area of high signal on magnetic resonance imaging (MRI) also indicated no severe displacement (Figure 2).

FURTHER DIAGNOSTIC WORK-UP

Arthroscopy was performed to confirm the diagnosis. Different from the findings on the imaging examinations, obvious fracture displacement of the cartilage was found (Figure 3).

FINAL DIAGNOSIS

Hoffa's fracture of the medial femoral condyle.

TREATMENT

Arthroscopic exploration and diagnosis were performed at the beginning of the operation. The presence of steps and micromovement at the fracture ends could be seen during arthroscopy. However, due to instability of the bone mass caused by the now old injury (more than 2 wk), it was difficult to achieve a satisfactory reduction *via* arthroscopy. Therefore, open reduction was scheduled (Figure 4). Two 3.0 mm partially-threaded cancellous screws placed perpendicular to the fracture line were used to reduce the fracture. To avoid epiphyseal injury, a screw of appropriate length was placed through the metaphysis. Countersunk screws were also placed through the articular cartilage.

OUTCOME AND FOLLOW-UP

Following open reduction and internal fixation, the patient wore a knee brace with 30° of knee flexion for approximately 2 wk. Afterwards, gradually begin to work on the range of motion of the knee. The patient was strictly instructed to avoid any weight-bearing bending until the sixth week, in order to minimize the shear force on his coronation. Partial weight-bearing began after the sixth week, then progressing to full weight-bearing (FWB) by the tenth week. At the six-month follow-up, he could walk without support. The knee range of motion was 5° to 100° (Figure 5). No angular deformity or limb-length discrepancy was observed. X-ray showed that the fracture healed well and there was no sign of femoral condyle collapse (Figure 6). The screws were removed after 7 mo. At the final follow-up of 40 mo, the KSS score was 100. The patient had full range of motion, with no varus-valgus instability (Figure 7).

DISCUSSION

Coronal plane fracture of the femoral condyle was named after Hoffa following his detailed research on this fracture in 1904[3]. Letenneur *et al*[5] classified this fracture into three different types. Accordingly, our patient developed a Type III fracture. This rare injury can also be classified into a medial, lateral and conjoint Hoffa's fracture based on the location of the fracture[6]. According to a review of the literature on Hoffa's fracture in the pediatric population (Table 1), 16 cases of Hoffa's fracture in pediatric patients were reported. Only 5 were located on the medial femoral condyle. Bali *et al*[7] first described an isolated Hoffa's fracture of the medial condyle in a patient with an undeveloped skeleton. Ranjan *et al*[6] described a Hoffa's fracture of the medial condyle in a 6-year-old girl. To date, only four cases of Hoffa's fracture of the medial condyle in pediatric patients has been reported. We aimed to report the fifth case in a 5-year-old patient, the youngest ever diagnosed.

Hoffa's fractures are mostly triggered by high-energy damage[8,9], and are more commonly seen in young adults. This injury is mainly caused by axial shear force affecting the posterior part of the femoral condyle when the knee is flexed[6]. Due to the anatomical features of the ectropion angle at the distal femur, when high-energy violence acts on the distal femur, it often acts firstly on the lateral condyle. As a result, lateral condyle fractures are more common than medial condyle fractures. Commonly, the cause of Hoffa's fractures in adults is vehicle accidents[7] while in pediatric Hoffa's fracture are usually caused by trivial injury or sports injury[10]. In this case, the injury was caused by a heavy object falling

Table 1 Review of the literature on Hoffa's fracture in the pediatric population

No.	Ref.	Sex	Age (yr)	Injury	Diagnostic tool	Location of fracture	Approach	Outcome
1	Agrawal *et al* [8], 2021	M	18	Road side accident	X-ray, CT	Conjoint	Medial parapetallar approach, with 2 (6.5 mm) PTCS in 1 condyle and one 6.5 and 4.5 mm PTCS in another condyle	0°-130° ROM
2	Kondreddi *et al*[9], 2014	-	17	Road traffic accident	X-ray		Lateral parapatellar arthrotomy, with four 4-mm cancellous screws (2 for each condyle) introduced antero-posteriorly through the non-articular surface, in a direction perpendicular to the fracture line	120° ROM
3	Julfiqar *et al* [20], 2019	M	12	Fall from height when his left knee was in the flexed position	X-ray		Open reduction and intraepiphyseal internal fixation using a 4.5 mm cannulated cancellous screw	0°-120° ROM
4	Chaudhary *et al*[12], 2020	M	11	Fall from a tree	X-ray		Open reduction and internal fixation using the Swashbuckler approach, lag screw technique with two 4 mm cancellous screws placed antero-posteriorly in the lateral condyle and one antero-posterior 4 mm cancellous screw and one Herbert screw placed postero-anteriorly in the medial condyle	0°-120° ROM
5	Lal *et al*[15], 2011	-	9	Fall from height	X-ray		Arthroscopy assisted internal fixation, with 4.5-mm cannulated cancellous screws, inserted from anterior to posterior just distal to the femoral physis	Cure
6	Harna *et al* [22], 2017	M	7	Hit by a speeding motor vehicle	CT		Swashbuckler approach, with 2.9 mm Herbert screws for compression	0°-130° ROM
7	Kumar *et al* [13], 2001	F	17	Fall from ladder	X-ray	Lateral femoral condyle	Reduction and fixation with two antero-posterior lag screws	Full ROM
8	Flanagin *et al* [10], 2011	M	14	Wrestling	Arthroscopy		Headless compression screws	Full ROM
9	Potini *et al* [14], 2015	M	14	Direct blow over knee	X-ray		Open reduction and rigid fixation with countersunk interfragmentary screws	5°–110° ROM
10	Tripathy *et al* [19], 2013	M	12	Fall while playing	CT		Open reduction and fixation with two partially threaded cancellous lag screws	Cure
11	Ashraf[16], 2019	M	12	Motor vehicle accident	X-ray, CT		Evaluation of the cruciateligaments and antero-posterior stability with arthroscopy, open reduction and internal fixation using two cannulated screws	Full ROM
12	McDonough *et al*[11], 2000	M	8	Road traffic accident	X-ray		Open reduction and internal fixation using two partially threaded cancellous lag screws	Full ROM
13	Jiang *et al*[2], 2022	F	16	Knee injury in a sprint race	X-ray, CT	Medial femoral condyle	Open reduction and fixation using three 3.5 mm partially threaded cancellous screws	0°-135° ROM
14	AlKhalife *et al* [3], 2018	M	12	Object dropped	CT		Open reduction and internal fixation through a medial parapatellar approach with the aid of a bone clamp and two 4.0 mm partially threaded cancellous screws, the screw heads placed through the articular cartilage were countersunk	15°–130° ROM
15	Bali *et al*[7], 2011	M	12	Traffic accident	CT		Open reduction and internal fixation with two large-fragment cannulated screws, which were buried under the articular surface of the knee	Cure
16	Ranjan *et al* [6], 2021	F	6	Fall	CT		Open reduction and fixation through the medial approach with two 4.5 mm partially threaded cannulated cancellous screws	0°–110° ROM
17	Current Study, 2022	M	5	Hit by object	Arthroscopy		Open reduction and internal fixation through the medial parapatellar approach, using two 3.0 mm partially threaded cancellous screws	Full ROM

CT: Computed tomography; PTCS: Partially threaded cannulated cancellous screws; ROM: Range of motion.

on the right knee. Since only a few cases have been reported, little is known about Hoffa's fractures in children, and McDonough *et al*[11] reported the first case of a non-healing Hoffa's fracture in an eight-year-old boy. According to our research (Table 1), X-ray is the most effective diagnostic tool for confirming pediatric Hoffa's fracture, followed by CT[12-14]. However, as the fracture is barely visible

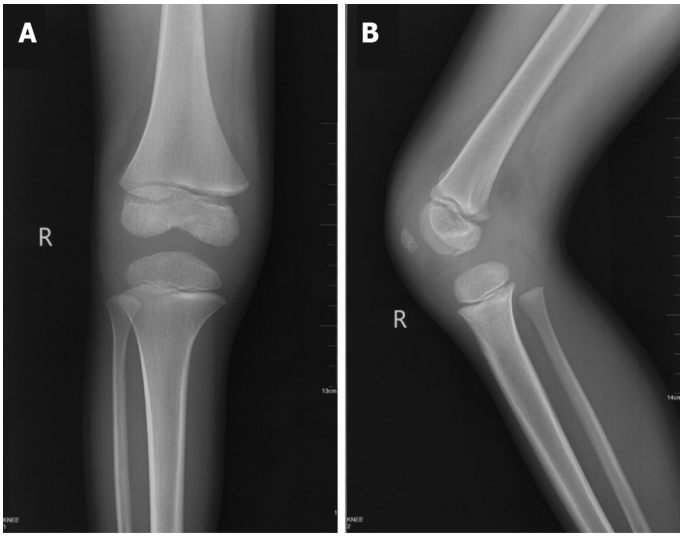

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Figure 1 X-ray before surgery shows a stable fracture in the medial femoral condyle with no displacement. A: Anterior-posterior view of X-ray; B: Lateral view of X-ray.

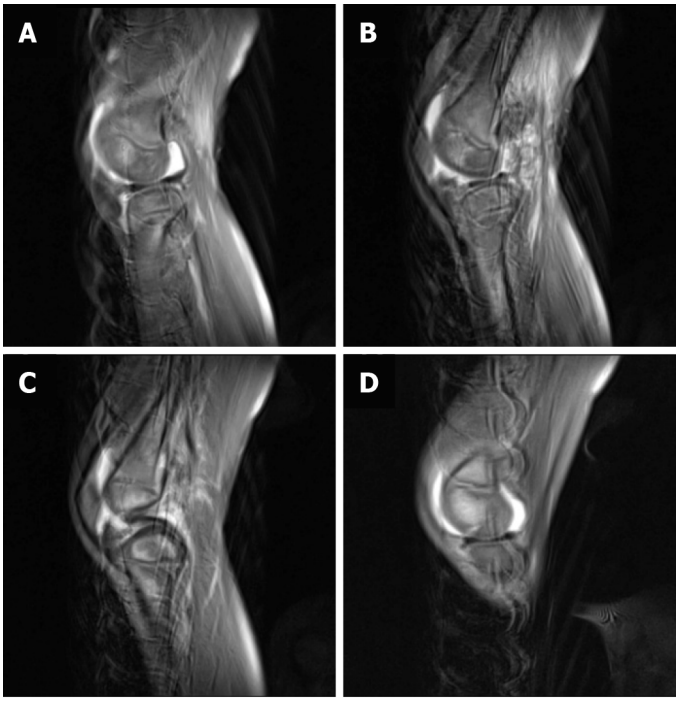

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Figure 2 Magnetic resonance imaging before surgery indicated no severe displacement. A: Sagittal slice of lateral condyle of femur; B: Most lateral slice of femoral intercondylar notch; C: Most medial slice of femoral intercondylar notch; D: Sagittal slice of medial condyle of femur.

on routine anteroposterior radiographs, misdiagnosis often occurs even in the lateral view. The fracture can be obscured by the intact anterior condyle in the anterior and posterior projections, if it is minimally displaced[15-17]. Therefore, it is wiser to carry out the gold standard investigation, which is CT[18]. However, in pediatric patients, the fracture line can be easily ignored, even on CT and MRI due to thick cartilage. In young patients, the diagnosis of Hoffa's fracture is often omitted based on past clinical experience. Three cases of misdiagnosed Hoffa's fracture in eight-year-old and two twelve-year-old boys were identified in previous literature, which were fixed with cannulated screws and successfully treated[11,16,19]. In this study, we report another case of nonunion of Hoffa's fracture in the medial condyle in a five-year-old boy who was initially misdiagnosed as having a stable fracture with no displacement. The patient was finally diagnosed with Hoffa's fracture by arthroscopy. Therefore, it is noteworthy that arthroscopy is critical in the diagnosis of pediatric Hoffa's fracture with inconclusive radiographs[10]. In our case, a CT scan was not performed on the injured knee due to difficulty in

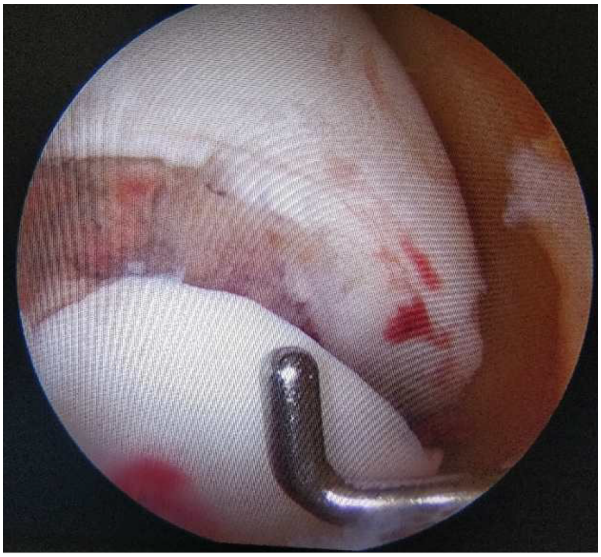

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Figure 3 Arthroscopy showed obvious fracture displacement of the cartilage.

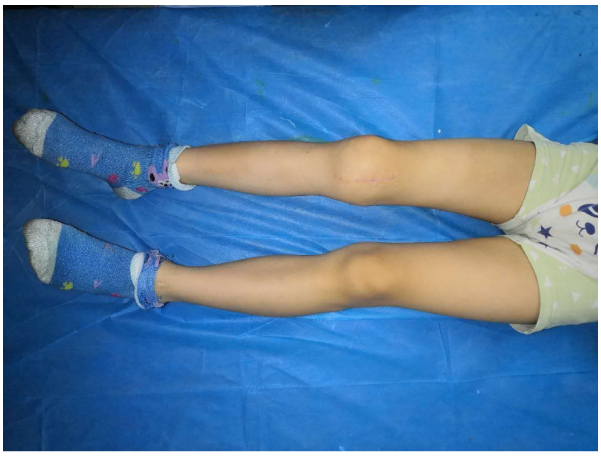

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Figure 4 The operation was completed using the medial parapatellar approach.

evaluating the fracture, thick cartilage of the distal femoral epiphysis and the patient's immature skeleton[1,3,4]. Avoiding CT exams can also prevent greater radiation exposure during CT scans than X-rays[20].

Conservative treatment of these fractures is unsatisfactory as the reduction in fracture fragments is difficult to achieve and to maintain by closure. This may lead to multiple complications such as avascular necrosis, nonunion, and malunion[4,15,21]. Therefore, as the ideal treatment[19], surgical stabilization and internal fixation are required to achieve a satisfactory clinical outcome. There is also controversy regarding the surgical approaches for pediatric Hoffa's fracture. The approaches described in previous literature include the lateral, medial and Swashbuckler approach (Table 1). It is generally accepted that surgical stabilization is necessary for a satisfactory clinical outcome after the treatment of Hoffa's fracture. The reason for this is that, closure reduction and cast/traction techniques are difficult to achieve and sustain the reduction of fracture fragments without soft tissue attachment. Therefore, this kind of injury is also prone to vascular necrosis and bone nonunion, which should be prevented by stable anatomical compression reduction and internal fixation. This can only be achieved by open/arthroscopic approaches[15]. In our case, we performed open reduction and internal fixation with the assistance of arthroscopy using a medial parapatellar approach. The outcome was satisfactory. The advantages of the guidance of arthroscopy include avoidance of soft tissue, decreased blood loss, and intraarticular visualization. Acute Hoffa's fracture with minimal communition and large fragments can also get benefit from arthroscopic fixation[21,22].

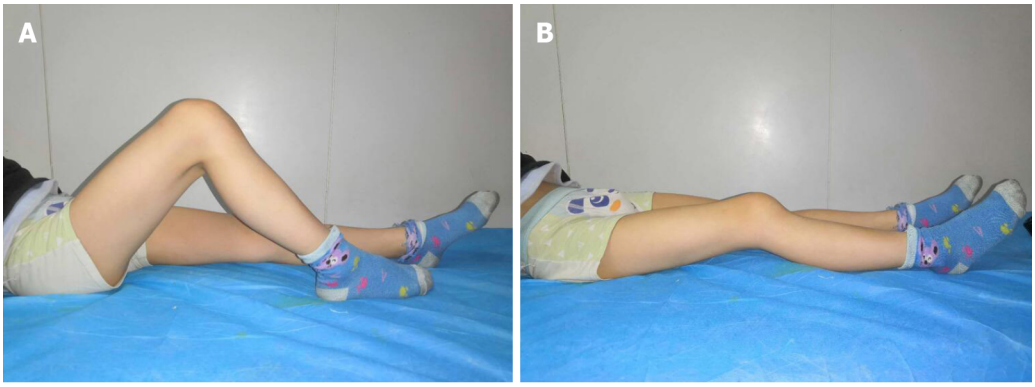

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Figure 5 Six months after surgery, the range of motion of the knee joint reached 5°-100°. A: Maximum flexion position; B: Maximum extension position.

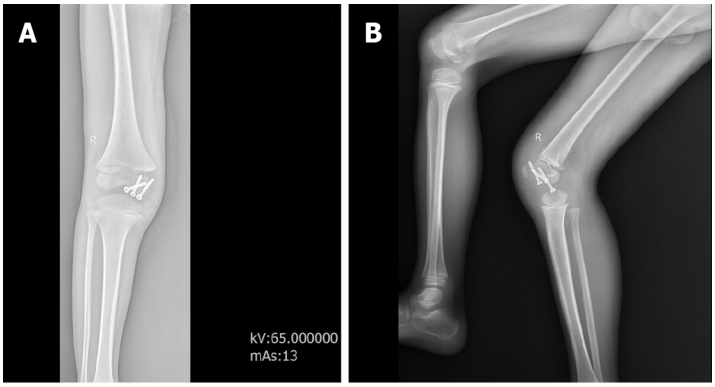

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Figure 6 Plain radiographs showed a well-healed fracture with no evidence of collapse of the femoral condyle. A: Anterior-posterior view of X-ray; B: Lateral view of X-ray.

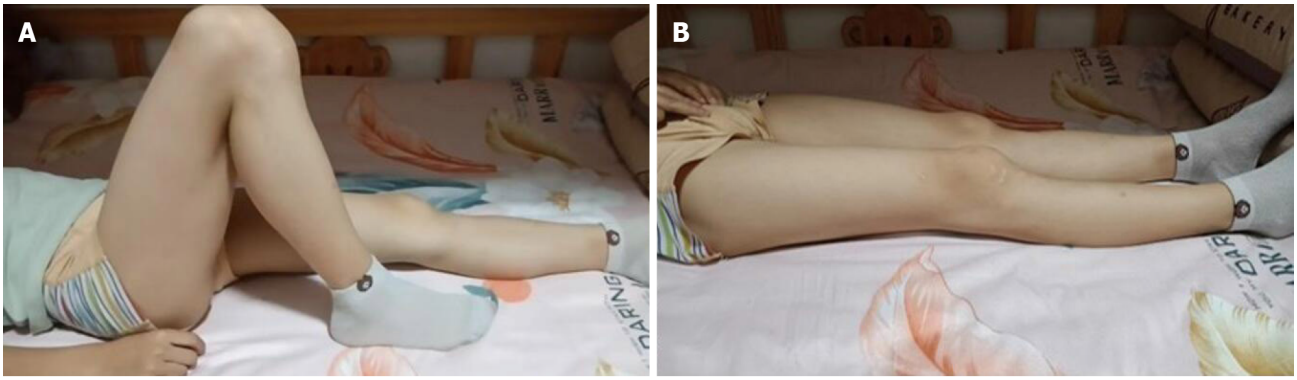

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Figure 7 At the final follow-up of 40 months, the patient had full range of motion. A: Maximum flexion position; B: Maximum extension position

CONCLUSION

We report Hoffa's fracture of the medial condyle in a 5-year-old child, the youngest patient ever reported, who was diagnosed and treated with the assistance of arthroscopy. We maintain that this rare fracture can be misdiagnosed easily. Healthcare practitioners should note of this when dealing with children's knee fractures. It is better to diagnose this fracture by arthroscopy in patients with skeletal immaturity. Treatment of this fracture with open reduction and internal fixation can prevent further long-term complications. However, arthroscopy-guided reduction and internal fixation may be a good option for patients who have a fresh fracture.

FOOTNOTES

Author contributions: Shi ZB provided this case and provided the relevant fund; Chen ZH and Wang HF drafted the majority of the manuscript; Wang HY, Li F, Bai XF and Ni JL collected all the materials; All authors have read and approved the final version.

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

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LETTER TO THE EDITOR

Precautions before starting tofacitinib in persons with rheumatoid arthritis

Raktim Swarnakar, Shiv Lal Yadav

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Abstract

Tofacitinib is an immunosuppressive and disease-modifying therapy in rheumatoid arthritis. It may result in many infections flaring up. It is important to take precautions of all kinds (cardiovascular, malignancy, infections etc.) before starting tofacitinib. In this article, we have highlighted important steps where we need to take precautions before starting tofacitinib.

Key Words: Tofacitinib; Rheumatoid arthritis; DMARDs; Disease-modifying; Precaution; Side-effects

Core Tip: Tofacitinib is a disease-modifying drug in rheumatoid arthritis. It has many side effects, especially in susceptible people. Before starting tofacitinib we must take precautions regarding cardiovascular status, infections and malignancy.

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TO THE EDITOR

We read with interest the article by Lin *et al*[1] where authors have reported one case report of recurrent herpes zoster (HZ) in rheumatoid arthritis (RA) patients treated with tofacitinib. We would like to highlight important aspects regarding tofacitinib,

Table 1 Precautions before tofacitinib starting in rheumatoid arthritis

Serial No.	Precautions[4,5]	Reasons
1	Persons with moderate-severe renal impairment or moderate hepatic impairment are recommended 5 mg once daily	In RA, multiple NSAIDS (non-steroidal anti-inflammatory drugs)/DMARDs themselves can cause liver or kidney injury. Furthermore, tofacitinib is hepatotoxic. It is metabolized in the liver largely through the cytochrome P450 3A4 pathway (cytochrome P 3A4)
2	Screening of infections like latent Tuberculosis, Hepatitis, cytomegalovirus, Epstein Barr Virus (EBV), BK virus	Reactivation of TB, and hepatitis can occur
3	Screening to check immunosuppressive conditions like human immunodeficiency virus (HIV) infection, Diabetes etc.	Reactivation of latent infections can occur
4	**Blood investigations to be done:** Routine complete hemogram, Liver function and kidney function tests, lipid profile and C-reactive protein Repeat complete blood count 1 to 2 mo following initiation, and every 12 wk after that Lipid profile should be monitored 4 to 8 wk after initiation of treatment	To rule out latent infections, liver, kidney status
5	Mantoux test, Chest X-ray and at times Interferon gamma release assay may be required.	To rule out latent TB
6	**Do not start tofacitinib:** If haemoglobin (Hb) levels are below 9 g/dL, absolute lymphocyte count is below 500 cells/mm^3, and absolute neutrophil count below 1000 cells/mm^3 In presence of any infection.	It may aggravate the infection
7	In renal transplant recipients	Renal transplant subjects receiving tofacitinib alongside immunosuppressive therapy are at increased risk of EBV associated post-transplant lymphoproliferative disorder
8	**Reproductive age group:** Women of reproductive potential should be counselled on the risk of possible infertility from tofacitinib **Pregnancy:** Treatment during pregnancy may increase the potential risk to the fetus **Lactation:** Discontinue breastfeeding as tofacitinib may be excreted in breast milk	Due to potential side effects of tofacitinib
10	Screening for malignancy and cardiovascular diseases	FDA (The United States Food and Drug Administration) released an updated boxed warning in September 2021 regarding the increased risk of death, major adverse cardiovascular events, malignancies and thrombosis with Janus kinase inhibitors compared with tumor necrosis factor-alpha inhibitors[4,5]

especially all the precautions to be taken before starting tofacitinib in cases of rheumatoid arthritis. Tofacitinib is a potent, selective Janus-associated kinase (JAK) inhibitor that preferentially inhibits JAK1 and JAK3. Tofacitinib exerts its mechanism of action by inhibiting intracellular cytoplasmic nonreceptor tyrosine kinase JAK enzymes, which participate in adaptive and innate immune responses in the process of immune-mediated inflammatory diseases[2]. The incidence of herpes zoster is found to be higher with tofacitinib than in the general RA population[3]. Tofacitinib increases the risk of HZ by which mechanism is not well understood but may be related to inhibition of interferon (IFN) signaling. Antiviral defenses depend on type I and II IFN signaling *via* the JAK/STAT pathway and it is inhibited by tofacitinib. Tofacitinib is United States Food and Drug Administration (FDA) approved drug for RA. Oral tofacitinib 5 mg twice daily is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant of, one or more disease-modifying antirheumatic drugs (DMARDs). It can also be used in sequence with first-line therapy methotrexate or conventional DMARDS or can also be used as monotherapy for RA. Detailed precautions are listed in Table 1.

Screening for malignancy and cardiovascular diseases

FDA released an updated boxed warning in September 2021 regarding the increased risk of death, major adverse cardiovascular events, malignancies and thrombosis with JAK inhibitors compared with tumor necrosis factor inhibitors[4,5]. Hence, before starting tofacitinib in a case of rheumatoid arthritis a doctor has to keep in mind those precautionary measures to avoid untoward adverse reactions or incidents.

FOOTNOTES

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