# World Journal of Clinical Cases

## Contents

### REVIEW

1140 COVID-19: Gastrointestinal manifestations, liver injury and recommendations  
*Ozkurt Z, Çınar Tanrıverdi E*

### ORIGINAL ARTICLE

#### Retrospective Study

1164 Continuous intravenous infusion of recombinant human endostatin using infusion pump plus chemotherapy in non-small cell lung cancer  
*Qin ZQ, Yang SF, Chen Y, Hong CJ, Zhao TW, Yuan GR, Yang L, Gao L, Wang X, Lu LQ*

1172 Sequential sagittal alignment changes in the cervical spine after occipitocervical fusion  

#### Observational Study

1182 Importance of the creation of a short musculofascial tunnel in peritoneal dialysis catheter placement  
*Lee CY, Tsai MK, Chen YT, Zhan YJ, Wang ML, Chen CC*

1190 Clinical effect of methimazole combined with selenium in the treatment of toxic diffuse goiter in children  
*Zhang XH, Yuan GP, Chen TL*

1198 Clinical study on the minimally invasive percutaneous nephrolithotomy treatment of upper urinary calculi  
*Xu XJ, Zhang J, Li M, Hou JQ*

### SYSTEMATIC REVIEWS

1226 What are the self-management experiences of the elderly with diabetes? A systematic review of qualitative research  
*Li TJ, Zhou J, Ma JJ, Luo HY, Ye XM*

### META-ANALYSIS

1242 Comparison of the clinical performance of i-gel and Ambu laryngeal masks in anaesthetised paediatric patients: A meta-analysis  
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1255</td>
<td>Autogenous iliotibial band enhancement combined with tendon lengthening plasty to treat patella baja: A case report</td>
<td>Tang DZ, Liu Q, Pan JK, Chen YM, Zhu WH</td>
</tr>
<tr>
<td>1278</td>
<td>Unicentric Castleman disease was misdiagnosed as pancreatic mass: A case report</td>
<td>Zhai HY, Zhu XY, Zhou GM, Zhu L, Gao DD, Zhang H</td>
</tr>
<tr>
<td>1291</td>
<td>Primary central nervous system lymphoma presenting as a single choroidal lesion mimicking metastasis: A case report</td>
<td>Jang HR, Lim KH, Lee K</td>
</tr>
<tr>
<td>1311</td>
<td>Hydrogen inhalation promotes recovery of a patient in persistent vegetative state from intracerebral hemorrhage: A case report and literature review</td>
<td>Huang Y, Xiao FM, Tang WJ, Qiao J, Wei HF, Xie YY, Wei YZ</td>
</tr>
<tr>
<td>1320</td>
<td>Ultrasound-guided needle release plus corticosteroid injection of superficial radial nerve: A case report</td>
<td>Zeng Z, Chen CX</td>
</tr>
<tr>
<td>1326</td>
<td>Inverted Y ureteral duplication with an ectopic ureter and multiple urinary calculi: A case report</td>
<td>Ye WX, Ren LG, Chen L</td>
</tr>
<tr>
<td>1333</td>
<td>Multiple miscarriages in a female patient with two-chambered heart and situs inversus totalis: A case report</td>
<td>Duan HZ, Liu JJ, Zhang XJ, Zhang J, Yu AY</td>
</tr>
<tr>
<td>1349</td>
<td>Fatal rhabdomyolysis and disseminated intravascular coagulation after total knee arthroplasty under spinal anesthesia: A case report</td>
<td>Yun DH, Suk EH, Ju W, Seo EH, Kang H</td>
</tr>
</tbody>
</table>
## Contents

**World Journal of Clinical Cases**  
**Thrice Monthly Volume 10 Number 4 February 6, 2022**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1366</td>
<td>Imaging presentation of biliary adenofibroma: A case report</td>
<td>Li SP, Wang P, Deng KX</td>
</tr>
<tr>
<td>1373</td>
<td>Multiple gouty tophi in the head and neck with normal serum uric acid: A case report and review of literatures</td>
<td>Song Y, Kang ZW, Liu Y</td>
</tr>
<tr>
<td>1381</td>
<td>Toxic epidermal necrosis induced by ritodrine in pregnancy: A case report</td>
<td>Liu WY, Zhang JR, Xu XM, Ye TY</td>
</tr>
<tr>
<td>1394</td>
<td>External penetrating laryngeal trauma caused by a metal fragment: A Case Report</td>
<td>Qiu ZH, Zeng J, Zuo Q, Liu ZQ</td>
</tr>
<tr>
<td>1417</td>
<td>Hemizygous deletion in the OTC gene results in ornithine transcarbamylase deficiency: A case report</td>
<td>Wang LP, Luo HZ, Song M, Yang ZZ, Yang F, Cao YT, Chen J</td>
</tr>
<tr>
<td>1432</td>
<td>Inflammatory myofibroblastic tumor after breast prosthesis: A case report and literature review</td>
<td>Zhou P, Chen YH, Lu JH, Jin CC, Xu XH, Gong XH</td>
</tr>
<tr>
<td>1441</td>
<td>Eustachian tube involvement in a patient with relapsing polychondritis detected by magnetic resonance imaging: A case report</td>
<td>Yunayama D, Aoki A, Kobayashi H, Someya M, Okubo M, Saito K</td>
</tr>
</tbody>
</table>

**LETTER TO THE EDITOR**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1454</td>
<td>Rituximab as a treatment for human immunodeficiency virus-associated nemaline myopathy: What does the literature have to tell us?</td>
<td>Gonçalves Júnior J, Shinjo SK</td>
</tr>
</tbody>
</table>
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COVID-19: Gastrointestinal manifestations, liver injury and recommendations

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Abstract
Coronavirus disease 2019 (COVID-19) has caused a pandemic that affected all countries with nearly 270 million patients and 5 million deaths, as of as of December, 2021. The severe acute respiratory syndrome coronavirus 2 virus targets the receptor, angiotensin-converting enzyme 2, which is frequently found in human intestinal epithelial cells, bile duct epithelial cells, and liver cells, and all gastrointestinal system organs are affected by COVID-19 infection. The aim of this study is to review the gastrointestinal manifestations and liver damage of COVID-19 infection and investigate the severe COVID-19 infection risk in patients that have chronic gastrointestinal disease, along with current treatment guidelines. A literature search was conducted on electronic databases of PubMed, Scopus, and Cochran Library, consisting of COVID-19, liver injury, gastrointestinal system findings, and treatment. Liver and intestinal involvements are the most common manifestations. Diarrhea, anorexia, nausea/vomiting, abdominal pain are the most frequent symptoms seen in intestinal involvement. Mild hepatitis occurs with elevated levels of transaminases. Gastrointestinal involvement is associated with long hospital stay, severity of the disease, and intensive care unit necessity. Treatments and follow-up of patients with inflammatory bowel diseases, cirrhosis, hepatocellular carcinoma, or liver transplant have been negatively affected during the pandemic. Patients with cirrhosis, hepatocellular carcinoma, auto-immune diseases, or liver transplantation may have a greater risk for severe COVID-19. Diagnostic or therapeutic procedures should be restricted with specific conditions. Telemedicine should be used in non-urgent periodic patient follow up. COVID-19 treatment should not be delayed in patients at the risk group. COVID-19 vaccination should be prioritized in this group.

Key Words: COVID-19; Gastrointestinal manifestations; Liver injury; Liver transplantation; SARS-CoV-2
Coronavirus disease 2019 (COVID-19) has caused a pandemic that affected all countries with more than 238 million patients and nearly 5 million deaths, as of October, 2021[1]. The clinical outcome of COVID-19 infection is ranged from asymptomatic to death. Patients who are older, male, and have comorbidities such as diabetes mellitus, hypertension and cardiovascular diseases are regarded as the high-risk group for COVID-19 infection. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is spread throughout the system by angiotensin-converting enzyme 2 (ACE2) receptors found in endothelial cells[2]. Thus, COVID-19 infection is not limited to the respiratory system and spreads to all tissue of the body, and causes multisystemic diseases.

During COVID-19 infection, the gastrointestinal (GI) system is affected on varying degrees. Liver and intestinal involvements are the most common manifestations. Because of the SARS-CoV-2 virus found in both the oral mucosa and the intestinal tract endoscopy procedures have become risk procedures for nosocomial transmission from patients to healthcare professionals.

In another aspect, patients with chronic diseases such as chronic hepatitis, cirrhosis, irritable bowel syndrome, ulcerative colitis, and liver transplant have been affected by the pandemic transformation of hospitals. Treatment and control visits were canceled or postponed for an unknown period due to this extraordinary situation.

The aim of this study is to review the GI manifestations and liver damage of COVID-19 infection and investigate the severe COVID-19 infection risk in patients that have chronic GI disease, along with current treatment guidelines.

### PATHOGENESIS

SARS-CoV-2 virus enters into the target cell and tissue via ACE2 binding receptor[2]. ACE2 receptors have been found and expressed in intestinal enterocyte cells. Gastric and intestinal epithelial surfaces cilia of a glandular cell include ACE2 mainly in the cytoplasm. It has been rarely found in esophageal epithelial surfaces. Thus, viral nucleocapsid proteins are found in the gastric, duodenal, rectal glandular epithelial cells, but not in the esophagus[3-4]. Zou et al.[5] described that if tissue ACE2 expression > 1%, it would mean involvement by SARS-CoV-2, and accepted as a high-risk category. According to this theory, lower respiratory tract (2%), lung (> 1%), heart (> 7.5%), ileum (30%), esophagus (> 1%), kidney (4%), and bladder (2.4%) were sorted in high-risk category. Because liver and stomach had < 1% proportion of ACE2-positive cells, these tissues were accepted as low risk for COVID-19 infection[3].

After receptor binding, S protein enters the host cell by host proteases such as mucosa-specific transmembrane serine protease type 2 and 4 (TMPRSS2 and TMPRSS4), trypsin, elastase, cathepsin L, cathepsin B, factor X, and furin[6]. Then, viral replication of SARS-CoV-2 occurs[2].

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Zang et al[6] showed SARS-CoV-2 intestinal replication in human small intestinal enteroids. They found that TMPRSS2 and TMPRSS4 are important to virus entry into the host cell. Interestingly they showed also that when the virus is present in the intestinal lumen, it can be inactivated by colonic fluid, thus the virus has not been recovered from stool specimens.

In addition, the SARS-CoV-2 virus is also disrupting the normal intestinal flora, leading to GI symptoms, especially diarrhea[4].

During COVID-19 infection lung-derived CCR9+ CD4+ T cells increase and into the small intestine by increased CCL25[7]. Thus, intestinal inflammation occurs. Balance of the intestinal flora is disturbed. Interleukin (IL)-17A increases and it causes neutrophils migration, intestinal immune damage, diarrhea, and other GI symptoms[8]. When intestinal inflammation occurs, cytokines and bacteria also, can enter the lung by the bloodstream. Thus the lung inflammation increases. Additionally, the gut-liver axis, which refers to the bidirectional relationship of the portal vein between the intestine, microorganisms, and liver through the portal vein may also be affected. Host and microbial metabolites are transferred to the liver by the portal vein, and liver functions are affected[9].

Besides, ACE2 receptor is found in bile duct epithelial cell and liver. Therefore, virus replication occurs in the liver and bile ducts, and manifests as elevated liver enzymes, decrease albumin, and prolongation of prothrombin time.

### GI MANIFESTATIONS

The rates of GI symptoms are from 11% to 53%, and nearly half of the patients have at least one of the symptoms such as loss of appetite, nausea, vomiting, diarrhea, and abdominal pain[3]. GI manifestations rate was reported as 17.6% in a large series including 60 studies and 4243 patients[10]. In a meta-analysis that enrolled 47 studies and including 10890 patients, the most frequent GI manifestations reported was nausea/vomiting (7.8%), diarrhea (7.7%) and abdominal pain (2.7%)[11]. In a meta-analysis of 43 reports, including 18246 patients, the most frequent GI symptoms were diarrhea (11.5%), nausea, vomiting (6.3%), and abdominal pain (2.3%) [12]. Ferm et al [13] reported GI symptoms of 892 patients as diarrhea (19.8%), nausea (16.6%), vomiting (10.2%), loss of appetite (11.8%), abdominal pain (7.8%), and loss of taste (2.4%). At least one GI manifestation such as diarrhea, nausea, vomiting, or abdominal pain was found in patients with COVID-19 infection. The mean duration of GI symptoms was found to be 4 (3-7) d. In our series, which includes 430 cases, the prevalence of GI symptoms was 19.8%, and the most common GI symptoms were nausea/vomiting, abdominal pain, and diarrhea (10.4%, 6.1%, and 2.9%, respectively) [14]. The rates of GI manifestations in COVID-19 infection are shown in Table 1.

GI symptoms frequently start at an early period of the disease and 1-2 d before respiratory symptoms. GI manifestations were also reported more frequently in severe cases (17.1%) than that in non-severe cases (11.8%) [4,10].

Hospitalization rates of the patients who had GI involvement were found five times higher than others. It has increased 8 times in patients with diarrhea, as compared to without GI symptoms[15]. This finding supports the theory of SARS-CoV-2 gastro-intestinal entry and infection via the ACE2 receptor[2].

### INTESTINAL INVOLVEMENTS

ACE2 is frequently found in human small intestinal epithelial cells, and it is more strongly expressed in type II epithelial cells[5,16,17]. It is a key enzyme for the renin-angiotensins system that regulating intestinal inflammation and diarrhea[16,18]. Virus and/or pro-inflammatory cytokines may affect host cells. They may cause changing bowel flora. Thus watery diarrhea occurs. Lymphocytic infiltration in the esophageal epithelium, abundant infiltrating plasma cells and lymphocytes, and interstitial edema in the stomach, duodenum, and rectum lamina propria were found.

The most common symptoms of COVID-19 GI involvement are diarrhea and anorexia. Anorexia is present in most infectious diseases. The loss of taste and smell seen in COVID-19 infection contributes to anorexia. Patients become more anorectic and worse if cacosmia and/or cacousi are present.
Diarrhea is another common GI system symptom of COVID-19. At the onset of the pandemic, respiratory symptoms were dominant, and watery diarrhea was reported only 2%-10% in cases. However, in the summer season, diarrhea was observed more frequently up to 49.5%[19]. Diarrhea may be the first symptom in some patients and lasted for an average of 4-5 d, and even in some patients for 8-14 d[11].

Approximately 2%-19.5% of patients complained of diarrhea as the first symptom of the infection and in such cases, the virus genome could be isolated from stool and blood samples[20]. It is estimated that about half of admitted patients had at least one GI symptom, with these symptoms becoming more pronounced as the severity of the disease progressed. GI symptoms were found as high as 79.1%[16,19]. Patients with GI symptoms were also found to have a longer symptom time from onset to admission[4].

Viral gastroenteritis is characterized by non-bloody, watery diarrhea with abdominal cramps. Sometimes it is accompanied by fever and vomiting and nausea. The median duration of diarrhea was reported 5.4 ± 3.1 d (range, 1-14 d) and mostly self-limited[8,20].

A recent case report also documented SARS-CoV-2 GI infection-causing hemorrhagic colitis. In a fecal microscopic examination, leukocyte was detected in 5.2% and no red blood cells were found, which was consistent with viral diarrhea characteristics[21].

SARS-CoV-2 invades the GI system and excretes in the stool. SARS-CoV-2 nucleic acid was detected in the stool of up to nearly 54% of patients[22,23]. The results of these studies indicate that the GI tract is a site where SARS-CoV-2 invades and it is released[23].

The incidence of GI symptoms in patients with COVID-19 in Wuhan was significantly higher than the national level. In a meta-analysis study, the rates of diarrhea were found as 7.7 (7.2 to 8.2) in 10676 cases worldwide, 5.8 (5.3 to 6.4) in 38612 cases from China, and 18.3 (16.6 to 20.1) in 2064 cases from countries other than China[11]. Diarrhea may be developed as side effects of the drugs used.

SARS-CoV-2 virus RNA was present in stool samples 35.7%-54.5% in the patients with diarrhea and even in those who have not diarrhea. But this positivity found was not correlated with the disease symptoms and the presence of diarrhea[24]. The viral load in stool was reached to a very high levels (mean viral load 4.7 log10 copies per mL) in patients with diarrhea[10]. Cheung et all[10] also found SARS-CoV-2 positivity 48.1% at the same time both respiratory secretions and stool samples, and 70.3% in only stool samples. Meanwhile, the rate of viral RNA positivity in stool sample were found longer than respiratory sample[22,25]. The virus can be found positive in the stool even after it has been cleared from the respiratory system. Gupta et al[22] reported that 53.9% of stool samples were RNA positive, and fecal shedding time ranged from 1 d to 33 d, even after negative respiratory results. Thus the rate of stool viral RNA positive and respiratory secretion negative was found as 70% in patients with COVID-19. Fecal virus shedding may continue up to 47 d, and 13 d after from respiratory system becomes negative[22]. Interestingly, it was found that steroid usage causes longer time viral shedding from stool[10].

Fecal viral shedding causes environmental contamination and mechanical vectors may be contributing to virus distribution[26]. Although SARS-CoV-2 is an envelope virus, it was found viable 14 d at 4 °C, and 2 d at 20 °C in sewage[25,27]. Additionally, the virus can be stable on surface and viable for up to 7 d on stainless steel, plastic, cardboard[28].

### Table 1 Gastrointestinal manifestations in coronavirus disease 2019

<table>
<thead>
<tr>
<th>Gastrointestinal manifestations</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal involvement</td>
<td>11-79</td>
</tr>
<tr>
<td>Anorexia</td>
<td>34-67</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2-49.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1-16</td>
</tr>
<tr>
<td>Nausea</td>
<td>1-16</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.7-9.2</td>
</tr>
<tr>
<td>Liver injury</td>
<td>15-53</td>
</tr>
</tbody>
</table>
These findings have shown that SARS-CoV-2 may be transmitted by direct fecal-oral route or indirect contamination of hands through the contaminated household environmental surface[29].

Treatment of COVID-19 diarrhea

There is no specific treatment for viral diarrhea. Hydration is the main treatment of diarrhea and vomiting. Tian et al[30] reported that The National Health Commission of the People’s Republic of China showed that symptomatic treatment and adequate hydration were essential to prevent electrolyte imbalance. Some medications such as dioctahedral montmorillonite powder and loperamide can be used for diarrhea. Probiotics may be given for intestinal dysbiosis and antispasmodics may be given for abdominal pain[30]. Dioctahedral montmorillonite powder and loperamide may be used to treated diarrhea. Antispasmodics may be given for abdominal pain. Besides, probiotics may be useful for gut dysbiosis.

Enteral nutrition and digestive tract function are important for therapy. Enteral nutrition is needed for providing energy, restoring and maintaining the normal physiological function of the GI tract, and microecology with mucosal immunity[16]. Parenteral nutrition is used in only patients who have been intubated, have GI system lesions, and intolerant to enteral nutrition. Enteral nutrition should be reversed immediately.

SARS-CoV-2 virus in the stool may be transmitted through contact with hands. Additionally, feces particles widespread air and may be inhaled by other persons. Therefore, when cleaning digestive tract secretions of COVID-19, patients should be attentive and all protective equipment should be worn, hand hygiene should be provided, and hospital or house environmental surfaces should be also properly disinfected[16].

INFLAMMATORY BOWEL DISEASE AND COVID-19

The number of ACE2 receptors is at high levels in patients with inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn’s disease. Burgueño et al[31] found that ACE2 and TMPRSS2 expression were the highest in ileum and colon respectively. The drugs given to the patients lead to immunosuppression, and they predispose them to SARS-CoV-2. Both their immunosuppressive therapy and increased ACE2 receptors make this group of patients susceptible to COVID-19 infection. Thus, it is estimated that patients who have been given biological agents are at-risk group. But clinical experience showed that the risk of the patient IBD diseases is similar to that of other persons[11]. IBD patients with comorbidity, and/or who are elderly (> 70), use prednisolone per day (> 20 mg), biologic agents and have used steroid in the last 6 wk, who have moderately or severely active diseases, short gut syndrome, and who need parenteral nutrition are at the high-risk group.

During the COVID-19 pandemic, patients with IBD can be treated. The International Organization for the Study of Inflammatory Bowel Diseases, Crohn’s and Colitis UK, and Crohn’s and Colitis Foundation recommended ongoing medical treatment for IBD[32]. Thiopurines therapy has increased the risk of viral infection, but mesalamine has not such an effect. Steroids can be used in the pandemic period, because steroids are not damaged clinical course of COVID-19. Vedolizumab can be continued. Ustekinumab may be given by infusion route[4].

Patients should be questioned or screened in terms of SARS-CoV-2 infection before beginning the immunosuppressive therapy.

Elective endoscopy and surgery of IBD patients should be postponed. Indications of the endoscopy of IBD patients are given as follows: (1) Confirmation of a new diagnosis in moderate to severe IBD; (2) Evaluation of severe acute flare up of ulcerative colitis; (3) Evaluation of partial or subacute bowel obstruction; and (4) Developing cholangitis in patients with IBS who has primary sclerosing cholangitis[4].

Screening for COVID-19 infection is recommended if patients need endoscopy or surgery.

GUT MICROBIOME

Dysbiosis may lead to epithelial inflammation and increase ACE2 expression by changing dietary amino acid homeostasis. ACE2 regulates the intestinal uptake of
trypotphan. Tryptophan increases antimicrobial peptides (AMPs) through the mammalian Target of Rapamycin (mTOR) pathway. AMPs change the composition of gut microbiota. Butyrate-producing bacteria stimulate the immune system cells (macrophages, dendritic cells, and T cells), IFN-1 and anti-inflammatory ILs[33]. SARS-CoV-2 binds to ACE2 and inhibits balance in microflora. In the intestinal system, ACE2 expression has regulated by gut bacteria. Bacteroides species downregulate ACE2 expression in the murine gut[33,34]. Proinflammatory gut microbiome increases ACE2 expression and may cause favorable conditions in the gut epithelium for SARS-CoV-2 infection[8,33]. SARS-CoV-2 may prevent nutrient absorption and disrupt intestinal homeostasis by binding to ACE2. Diarrhea in COVID-19 infection may be explained by ACE2-dependent regulation of the gut microbiota. Alterations in the gut and/or lung microbiome by ACE2 might also be associated with cardiopulmonary pathology[35]. Downregulation of ACE2 decreases AMP’s secretion, and causes increased pathogen survival and gut dysbiosis.

Zuo et al[36] investigated changing of gut microbiota of patients with COVID-19 during hospitalization. They found the depletion of beneficial commensals and increasing opportunistic pathogens. Gut dysbiosis continued after viral clearance from the respiratory tract. In this study, Coprobacillus, Clostridium ramosum, and Clostridium hathewayi were found to correlate with the disease severity. Opposite Faecalibacterium prausnitzii (an anti-inflammatory bacterium) was found inverse correlated with severe outcome. Bacteroides species down-regulate ACE2 expression in murine guts, and correlated inversely with viral load in fecal samples from patients. Fecal microbiota alterations were found to be associated with both fecal viral load and the severity of the disease[36].

Yeoh et al[37] found that gut microbiome was significantly altered in patients with COVID-19 compared with non-COVID-19 individuals whether patients had been given medication or not. In stool samples, Faecalibacterium prausnitzii, Eubacterium rectale, and Bifidobacteria remained low at 30 d after disease improving. These changes were found to correlate with disease severity and elevated cytokines and other blood markers. Therefore, they suggest that the gut microbiome has played important role in the severity of COVID-19 infection by modulating host immune responses. Additionally, dysbiosis after improving the disease may contribute to persistent symptoms in long COVID-19[37].

Prolonged gut microbiome dysbiosis in COVID-19 is associated with fecal virus shedding and disease severity. These data provide a new therapeutic target and modulation of the gut microbiota may be useful to supportive therapy of COVID-19.

Additionally, some drugs used in COVID-19 treatment such as chloroquine and corticosteroids have been shown to interact with gut microbiome[2].

Recommendations
The treatment strategies improving microbiota may be useful to decrease disease severity. Unless secondary bacterial pathogens present, antibiotic usage should be avoided in COVID-19 viral pneumonia. Microbiota and host cytokine pathway interactions are best understood and should be considered as developing new treatment approaches[38].

The microbiome also affects the immune response to the vaccine. Sufficient antibody levels after vaccine would not occur if the human has dysbiosis[39]. Dietary changes, giving probiotics and prebiotics, and avoiding antibiotic usage are mandatory to improve microbiota. Probiotics may improve diarrhea by intestinal micro ecological balance and prevent secondary bacterial infections[16]. Probiotics may have potential use for reducing symptoms of upper respiratory tract infections in overweight and obese people, and older age[40].

LIVER MANIFESTATIONS
Liver injury in COVID-19
Although, SARS-CoV-2 is a respiratory virus, liver involvement is frequently seen in the COVID-19 infection. SARS-CoV-2 enters into the cell by binding ACE2 receptors. ACE2 receptors are found in many systems of the body such as lungs, liver, heart, kidney, and blood vessels[36,41]. There is more ACE2 receptor expression in bile duct epithelial cells (cholangiocytes 57.7%) markedly higher than in liver cells (hepatocytes 2.6%)[42]. Overexpression of ACE2 receptors in cholangiocytes causes liver injury. Liver damage probably occurs secondary to bile duct cell injury[4].
Cholestatic hepatitis is not the usual liver involvement pattern in COVID-19 infection[41,42]. Hepatic ACE2 receptor expression was highly elevated in females. This may explain the better clinical outcome of COVID-19 infection in females[41-45]. Multifactorial causes lead to liver damage during COVID-19 infection, such as direct virus cytopathic effect, inflammation, intrahepatic immune activation, microvascular thrombosis, hepatic congestion, disruption of the gut liver axis, drug toxicity, multidrug interactions[46-48]. Causes of liver injury are summarized in Figure 1.

Liver injury may occur by direct virus cytopathic effect by lysis or by inducing apoptosis[49-53]. The virus-specific protein 7a has been induced a caspase-dependent apoptosis pathway that presence in cell lines of different organs such as lung, kidney, and liver. The virus was detected by the low viral load in liver tissue[54]. Moreover, it was showed that the virus can be replicated in hepatocytes, and spike proteins found cytoplasm[55].

These findings suggest that SARS-CoV-2 could directly affect liver tissue and may cause cytopathic effect in hepatocytes[41,55]. Wang et al[56] showed that SARS-CoV-2 caused mitochondrial swelling, endoplasmic reticulum dilatation, glycogen granule decrease, and cell membrane dysfunction in hepatocytes. Massive hepatic apoptosis and some binuclear hepatocytes were reported in the same study. Both ultrastructural and histological evidence indicated a typical lesion of viral infection. Immunohistochemical results showed scarce CD4+ and CD8+ lymphocytes. No obvious eosinophil infiltration, cholestasis, fibrin deposition, granuloma, massive central necrosis, or interface hepatitis were observed[56].

Secondly, immune-mediated liver injury, source from pro-inflammatory cytokines (IL-1, IL-6, tumor necrosis factor), chemokine, and inflammatory cells produced against the SARS-CoV-2, are another important causes of liver damage[3,17,55,57]. Cytokine storm and mass syndrome also create liver injury. Elevated levels of all inflammatory and coagulopathy markers such as IL-2, IL6, chemokines, CRP, ferritin, D-dimer, and lactate dehydrogenase (LDH) correlated the severity of disease and poor outcome[3,57].

Viral-induced cytotoxic T cells (CD8) are also another important pathogenesis for viral infections[3,58]. Coagulation dysfunction and endothelial damage are found to be the main cause of liver injury in COVID-19 infection. Lagana et al[59] describe mitochondrial swelling, endoplasmic reticulum dilatation, and cell membrane dysfunction in liver biopsy samples of 40 COVID-19 patient autopsies. They found viral RNA and viral replication in hepatocytes. Polymerase chain reaction (PCR) positivity was found in 55% of patients in liver tissue[59]. PCR positivity and viral load were found correlated with histological results or liver enzymes. Mild and moderate micro-vesicular steatosis (75%), mild lobular necroinflammation (mild acute hepatitis) (50%) and portal inflammation (50%), and sinusoidal microthrombi (15%) were reported as the most common findings[59]. Mild lobular and portal activity showed in post-mortem liver autopsy specimen examinations[60].

Water degeneration and infiltrates (neutrophils, Kupffer cells and plasmocytes) were detected in lobules, sinusoidal, and portal areas[3,61,62]. Histopathological examination of 48 COVID-19 positive patients, acute vascular changes such as terminal vessel dilations, thrombosis and luminal ectasia, and chronic changes manifest fibrous thickening of the vascular wall observed in the portal and sinusoidal vessels were reported from post-mortem examination[59,62].

Intranuclear or intracytoplasmic viral inclusions were seen in patients with COVID-19 infection. Bile duct damage and liver failure signs were not seen in liver samples of severe COVID-19 patients[63].

Histopathological changes may be occurred due to direct viral effect, hypoxia or drugs.

Drugs such as antivirals, anti-inflammatory drugs, anticoagulants, antibiotics, and which are used underlying chronic diseases that are used during the COVID-19 infection contribute to liver injury[41,55]. Multi-drug usage and their interactions have also caused hepatotoxicity.

Another important cause of liver involvement is hypoxia that is a result of pneumonia. Even under oxygen therapy, hypoxic liver injury may occur.

Gut vascular barrier and dysbiosis (microbiota alterations) may be other causes contributing to liver damage due to indirect effect of toxic compound of opportunistic microorganisms.

The liver injury might develop more frequently in patients with chronic liver disease (CLD). CLD was found as a risk factor for prolonged hospitalization, and fatal course of the COVID-19[3].
In the COVID-19 infection, except CLD, usually mild hepatitis has been seen[3]. Pathologic liver function test results have been found to increase in nearly half of the patients with COVID-19[3,41]. Liver injury is also seen particularly in severe cases[4,63]. Hepatic involvement usually manifests elevated liver enzymes, sometimes decreasing albumin and rarely increasing bilirubin levels. Elevated levels of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), LDH, hyperbilirubinemia, prolonged prothrombin time, and hypoalbuminemia may be found as laboratory findings of liver injury. Alteration of liver function tests may be described as parenchymal, cholestatic, and mixed type. ALT and/or AST 3-fold increase in the values above the upper limit of normal (ULN) in parenchymal form; ALP or GGT values 2-fold higher according to the ULN in cholestatic, and with both parenchymal and cholestatic pathologies present in the mixed type. The rates of parenchymal, cholestatic, and mixed form liver injuries were reported as 75%, 29.2%, and 43.4%, respectively in COVID-19 infection. Most of all were found the hepatocellular pattern, and ALT-AST levels rarely increase > 5 × ULN[48]. In a meta-analysis investigating 47 studies and including 10890 patients, elevation of ALT and AST were found as 15.0% and 20% in countries other than China[11]. The rates and ranges of ALT and AST elevations were 2.5%-50.0% to 2.5%-61.1% respectively[55]. In a case series including 1100 patients with COVID-19 infection, AST and ALT levels were (56% and 28%) higher in a severe case than that of mild-moderate ones (18% and 29%)[42] AST was found correlated with mortality[56]. In another study, AST/ALT, LDH, and bilirubin were found to increase by 25%, 20%, and 3% respectively. But, ALP was reported as normal in nearly all patients in the same study. Bilirubin and ALP levels did not markedly increase in COVID-19. Elevation rates of bilirubin were reported between 0%-35.3%[55]. Elevated total bilirubin was found in 16.7% COVID-19 patients from China[11]. The peak of increased bilirubin was reported at 5 d (4 to 12) after discharge. Hyperbilirubinemia and elevated ALT, ALP, and GGT levels were especially found in male patients, but hypoalbuminemia was frequently seen in males[3]. 

Although ALP and GGT tests usually normal values, GGT elevation found 37.6% of patients with non-alcoholic fatty liver disease (NAFLD)[55,64]. Despite elevated GGT level was reported in 41% of patients in another study, GGT usually increase in the severe patient[41,55,64]. The GGT elevation develops from drug toxicity more than obstruction and usually is not associated with ALP elevation[55]. Although GGT is a
cholangiocyte injury marker, its levels did not increase in all COVID-19 patients. It was only found high in severe patients.

Hypoalbuminemia was found correlated with the disease severity and fatal course [13,41,65,66].

AST levels usually increase more than AST in liver diseases and other viral infections, but AST levels higher ATL in COVID-19 infection[63]. Elevated AST could reflect zone 3 injuries of the hepatocyte cells. Zone 3 is the biggest reservoir of AST and susceptible to hypoxia. AST is found in the cytosol and the mitochondria. AST release increases due to the mitochondrial damage by the virus. The relationship between SARS-CoV-2 and mitochondrial proteins may be causing AST elevation. AST also produced from skeletal muscle, cardiac, kidney and lung tissue[67]. Thus, an elevated AST reflects not only the liver but also a multi-organ damage. Severe pneumonia causes liver injury through a hypoxic situation. Cytokine storm and endothelial activation cause multiorgan and liver damage in COVID-19 infection.

It was found that AST/ALT ratio > 1 provides predict mortality, severe pneumonia and intensive care unit (ICU) required in patients with ICU and severe pneumonia [68]. AST/ALT ratio, total bilirubin, and ALT/ALP ratio may estimate outcomes in cirrhotic COVID-19 patients[69].

The incidence of liver injury ranges from 15% to 53%[4]. The rates alteration of liver function test having been reported in 19%-76% of COVID-19 cases[48]. In a meta-analysis, hepatic injury developed in 23.70% total, 31.66% in non-severe and 44.63% in severe patients with COVID-19 infection[70]. ALT and AST elevations were reported as 39.58% and 49.68% in severe and 24.15% and 19.40% in non-severe disease. AST elevation was more than ALT in the severe COVID disease[70]. ALP and GGT elevation was reported as 7.48% and 27.94%, respectively. ALP (11.33% vs 4%) and GGT elevations (46.90% vs 18.66%) were found to have a relationship with the disease severity. Hypoalbuminemia (61.27% vs 18.80%) and hyperbilirubinemia (31.04% vs 9.24%) also correlated with disease severity. The authors suggested that the most frequent abnormality was hypoalbuminemia. Except ALP value, other liver tests were significantly abnormal in severe patients[70].

In another meta-analysis screening 15407 COVID-19 patients, liver injury was reported 23.1% at an early period, and 24.4% at a course of the disease[71]. Liver injury was found 48.5% at the first two weeks of admission of hospitalization, and it was reported peaked 10 d (7-12) after being discharged[3,72]. Liver injury has been seen 26.7% in patients with severe pneumonia[3]. Elevation of ALP levels is rare and it is reported only in patients with multi-organ and liver failure or death from COVID-19 infection[73].

In meta-analysis, elevated ALT, AST, and bilirubin levels were found correlated with the severity of the disease[74]. Liver injury is associated with 9-fold greater risk of severe disease, an increased intensive care need, intubation, and fatality.

Liver damage presence at admission is suggested as an independent prognostic factor for COVID-19[75]. It was reported that patients with liver damage had a higher mortality rate (28.9% vs 9.0%), male gender (65.1% vs 40.8%), and systemic inflammatory response syndrome (53.5% vs 41.3%). Grade-2 liver damage was reported more in males than females. Grade of liver damage was also reported as a predictor of death (hazard ratio: 1.377). The proportion of liver injury of ICU patients (61.5%) was higher than non-ICU patients (25.0%)[75]. Alteration of liver functions rates was reported between in 58.06% to 78% fatal cases[13,41,76].

Liver injury was found correlated with prolonged hospitalization, the severity of the disease, GGT, ferritin, lower albumin, and CD4+ T cells and B lymphocyte[36,77]. Serum albumin levels were also significantly lower in patients who died due to the infection. Increased CRP, procalcitonin, IL-6, and ferritin with decreased albumin and platelet have been correlated with liver injury[42,78]. Decreased lymphocyte count and male gender was also found important for liver injury and poor outcome. CT imaging may be a predictor of liver damage and predict a severe outcome. Acute liver failure due to COVID-19 infection has been rare[78,79]. Thus SARS-CoV-2 should not be considered as a hepatotropic virus.

Multiorgan failure and other systemic complications may be developed from a secondary nosocomial infection acquired from the ICU. In our series, we found albumin and AST levels to be correlated with the severity of the disease, presence of pneumonia, intensive care requirement, and prolonged hospitalization times. Intensive care needs was in 9.6% of patients with liver damage[14].

**Drug-inducing hepatotoxicity**

Drug usage is another cause of elevation of liver function tests. In a meta-analysis that included 20874 COVID-19 patients, the drug toxicity rate was reported as 25.4%[71].
Antivirals (favipiravir, remdesivir, lopinavir/ritonavir, chloroquine, oseltamivir, and ribavirin) drugs used anti-inflammatory effect (tocilizumab), antipyretics (acetaminophen), and many other drugs used during the treatment during COVID-19 infection may lead to hepatotoxicity[3]. The hepatotoxic effect has developed in severe patients and/or in the presence CLD[3,63,80,81].

The hepatotoxic drug should be excluded in patients with liver injury. Because most drugs used treatment of COVID-19 (e.g., oseltamivir, lopinavir/ritonavir, and chloroquines) are metabolized in the liver.

In a study, the drugs (antivirals, antibiotics, antipyretics) used the previous hospitalization were found unrelated to liver injury[41]. GGT and bilirubin elevation are usually seen in the usage of antiviral against SARS-CoV-2.

Lopinavir/ritonavir, an antiretroviral protease inhibitor, can cause transient and usually mild elevations in liver enzymes. Lopinavir plasma levels increase in advanced liver diseases, therefore it should be carefully used. The liver injury developed in 57.8% of patients given lopinavir or ritonavir. Most hepatotoxicity effect developed in COVID-19 patients give lopinavir/ritonavir or ribavirin[82]. A restart of the drug is not recommended[11]. Nearly 2.5 fold increase of liver enzyme reported in patients given remdesivir[83].

Favipiravir may cause a hepatotoxic effect and there are no data available on favipiravir usage in patients with CLD[84].

Azithromycin-induced liver injury, that hepatocellular type, was rare and has been developed 1-3 wk after initiation. It was spontaneously recovered[41,85].

Chloroquine rarely causes hepatotoxicity possibly due to hypersensitivity. Two acute liver failures were reported by hydroxychloroquine[41]. It should be used carefully in patients with CLD because hydroxychloroquine can concentrate in the liver tissue[11]. Although dose adjustments are not needed in patients with hepatic failure, it should be carefully used because of both cardiac and hepatic adverse effect [41,85,86].

In a randomized-controlled double-blind study, remdesivir found responsible hepatotoxicity in 23% of patients[87]. Serum bilirubin and aminotransferases had been elevated in remdesivir group[36,87,88]. Liver injury and encephalopathy were reported by remdesivir. It was reported that acetyl cysteine had successfully improved a patient’s encephalopathy and liver failure due to remdesivir[3,88]. Remdesivir has not experienced liver cirrhosis. Increased transaminase levels have been reported in up to 22.6% of the patients[87].

Prednisolone is one of the most frequent drugs used in severe COVID-19 patients for anti-inflammatory effect. But if it is used for a long time at a high dose, it may cause hepatitis B virus (HBV) reactivation and spontaneous bacterial peritonitis in patients with decompensated liver cirrhosis[41].

Another anti-inflammatory drug tocilizumab (an IL-6 inhibitor) should not be used in decompensated cirrhosis[41]. Tocilizumab may cause mild serum elevations of aminotransferase and bilirubin levels, which are usually short and asymptomatic periods[41]. Tocilizumab may cause reactivation of HBV, in the patient given HBV should be screened and antiviral therapy should be given according to the guidelines[41,89].

In patients receiving lopinavir/ritonavir, remdesivir, or tocilizumab, liver functions should be monitored. Usage of these drugs is not contraindicated in liver injury. But in patients who have AST or ALT levels > 5 × ULN, these drugs may be excluded[88].

ACE inhibitors and ACE2 receptor blockers usage was not found correlated with the disease severity[3]. Other anti-hypertensive drugs and ACE-related drugs were found not different with respect to the disease outcome. Antibiotics, nonsteroidal anti-inflammatory drugs, ribavirin, or interferon were not found associated with liver functions. But lopinavir and ritonavir may cause 4.4-5-fold increase by dose-dependent in liver function tests[3].

Cytokine release syndrome in severe COVID-19; IL-6 receptor antagonist tocilizumab may be the key to reduce mortality[63].

Ivermectin may cause a minor, self-limiting liver enzyme elevation. Dose adjustments are not needed in patients with liver failure.

**Recommendations**

Most liver injuries in COVID-19 are mild and spontaneously recover and it requires no special treatment. If liver injury persists, chronic underlying diseases such as hepatitis B and C should be considered[30]. Although there was no evidence of hepatitis reactivation or decompensation, patients with underlying chronic hepatitis or other CLDs should be closely monitored[11]. Drug interactions and drug-induced hepatotoxicity should be kept in mind. Multidrug interaction must be regularly monitored.
American Association for the Study of Liver Diseases (AASLD) recommends that unnecessary imaging should be avoided[90]. Because of its anti-inflammatory and immunomodulation activity, ursodeoxycholic acid may be added treatment especially in patients with liver injury. Recommended dose is 13-15 mg/kg per day[91]. Further detailed analyses are required. European Association for the Study of the Liver (EASL) and APASL recommendations related to hepatic care in the COVID-19 pandemic have been published[48,92]. The use of diagnostic procedures, supervision of patients with CLDs, and liver transplantation have been described[48].

PRE-EXISTING LIVER DISEASES AND COVID-19

CLDs
COVID-19 infection may lead to liver damage by several routes in patients with existing CDL. Additional hepatic injury induced by SARS-CoV-2 might lead to hepatic failure in patients with compromised hepatic reserves[48,68]. Immunosuppressive effect of drugs or COVID-19 may lead to viral reactivation in patients with chronic viral hepatitis[48,68]. Drugs used for infection such as antivirals, anti-inflammatory, antipyretic, and antibiotics may lead to hepatotoxicity.

Although it seems that patients with CLD are not at greater risk for acquiring the infection, those with cirrhosis, hepatocellular carcinoma (HCC), NAFLD, autoimmune liver diseases or liver transplant may have a greater risk for developing liver injury and severe COVID-19[93]. Disease severity and liver damage develop depending on CLD, presence of advanced fibrosis or cirrhosis[47]. Similarly, other infections in the liver, hepatocytes are probably more affected in patients with underlying CLD.

Kim et al[94] reported that 867 patients with CLDs acute liver disease (ALD), decompensated cirrhosis, and HCC have higher mortality during COVID-19 infection. The severity of COVID-19 infection, male gender, and low liver CT density were found causative factors that are strongly related to liver injury (odds ratios: 6.543, 3.387, 2.936, respectively)[4,95].

CIRRHOSIS
It is estimated that pre-existing cirrhosis is a risk factor for higher severity and mortality in COVID-19[48,96]. Patients with cirrhosis have an increased risk for both decompensation and development acute or chronic liver failure during COVID-19 infection[55]. Cirrhosis-associated immune dysfunction may cause severe disease course[41,48]. Increased Child-Pugh class was correlated with severe course. But whether the increase of complications is related to cirrhosis such as liver failure, hepatic encephalopathy, and upper GI bleeding during COVID-19 has not been known.

Acute or chronic liver failure may develop in patients with cirrhosis due to ACE2 overexpression in bile duct cells and inflammatory response. The increased inflammatory response may cause liver failure and death in cirrhotic patients[55]. These patients have a higher bacterial infection risk.

An international multicenter study investigated the role of pre-existing liver disease in COVID-19. A total of 745 patients from the United Kingdom hospital network with COVID-19 (386 patients with cirrhosis and 359 without cirrhosis), enrolled in this study. Mortality was found very high (32%) in cirrhotic patients and low (8%) in non-cirrhotic cases. In addition, mortality and other prognostic markers were associated with the degree of liver decompensation, and mortality was found as 19% in Child-Pugh class A, 35% in B, and 51% in C. Child-Pugh class A, B, C found also correlated with ICU (40%, 62%, 79%) and invasive ventilation requirement (52%, 74%, 90%)[97]. The main cause of death was reported as respiratory failure (71%). Acute liver failure had developed in 46% of patients with cirrhosis, and 21% of these patients had no respiratory symptoms. Age, liver disease stage, and alcohol-induced liver disease (ALD) were found to be risk factors for mortality in COVID-19[97]. It was reported that 5 of 21 (23%) pre-existing cirrhotic patients died during COVID-19 infection[94]. Thus cirrhotic patients have increased the risk of COVID-19, higher risk for severe disease, and increased risk for hepatic decompensation[98].
Regular screenings and monitoring procedures for patients with compensated cirrhosis should be postponed. In patients who have decompensated cirrhosis, particular measures should be carried out for those patients with cirrhosis admitted to non-COVID-19 hospital [48,99]. Patients with cirrhosis should receive the best standard of care according to the guideline. Patients with cirrhosis who developed SARS-CoV-2 infection are at high risk of hepatic decompensation, severe COVID-19 and death. To prevent decompensation and decrease the risk of hospitalization, guidelines on prophylaxis of spontaneous bacterial peritonitis, GI hemorrhage, and hepatic encephalopathy should be closely followed. Particular effort should be made to patients with cirrhosis who are admitted, and these patients manage in a designated non-COVID-19 ward. Patients with new or worsening hepatic decompensation or acute-on-chronic liver should be tested for SARS-CoV-2 even in the absence of respiratory symptoms. Early admission should be considered for patients with cirrhosis who developed COVID-19 infection. Vasoconstrictor therapy should be given with a considerable caution among critically ill patients with cirrhosis and COVID-19. Because they may lead to pulmonary pressure and decrease cardiac output [48]. All patients should receive vaccination for COVID-19, Streptococcus pneumonia, and influenza.

There was no emergent situation for chronic viral hepatitis at COVID-19 pandemic. However, despite both studies demonstrating associations between severity of liver disease and poor outcome, it remains unknown whether the presence of chronic viral hepatitis influences prognosis.

In a case series including 1099 patients with COVID-19, the rate of chronic HBV (CHB) was found to be 2.1%. Only one patient with CHB had severe disease, thus it was considered CHB has not a negative effect on the outcome of COVID-19 [55].

Drugs of the patients with chronic HBV and chronic hepatitis C virus (HCV) should be continued if they have been receiving treatment. To follow, local laboratory test results should be sending and telemedicine should be applied. Prescriptions should be sent to the patients by mail or telephone to minimize disease transmission [48].

Interferon-alpha usage has an unknown impact, therefore, alternative agents should be used for patients with HBV during the COVID-19 pandemic [48].

In chronic HBV and HCV patients with COVID-19 infection, hepatitis treatment should be postponed until recovery. Patients with both COVID-19 and HBV flare-up, should be made on a case basis. IL antagonists such as tocilizumab and baricitinib used to mass syndrome might cause reactivation of HBV. In such a case antiviral prophylaxis should be given to prevent reactivation of HBV [4,48].

It was estimated that the balance between inflammation-promoting and inflammation-suppressing macrophage (M1 and M2) is insufficient in NADFL patients, it may cause the progression of COVID-19 [41,101].

In patients with CLD and/or NASH, ACE2 expression has increased, and cytokine production has been exaggerated associated with COVID-19. During the COVID-19 infection, it was shown that NASH patients have a high risk for complication progression to severe COVID-19, prolonged liver function disorder and poor outcomes. Additionally, patients with NASH have prolonged virus clearance time (17.5 ± 5.2 d vs 12.1 ± 4.4 d) [4,65,102].

In other studies, it was reported that NASH was not associated with severe disease [48,103,104]. Further research is needed to understand the impact of COVID-19 in NASH.
EASL-European Clinical Microbiology and Infectious Diseases recommendations related to NASH

During the COVID-19 pandemic, patients should be aware that a sedentary lifestyle has a negative effect on their metabolic conditions and contributes to increasing NASH degree. To prevent disease progression, lifestyle changes should be recommended in relation with nutritional guidance, weight loss advice, and diabetes management[48].

HCC

The mortality rate of COVID-19 is high in cancer patients. Chemotherapy within the last 14 d significantly increased the severity of COVID-19 infection. Liver cancer is one of the most frequent cancers with 782 thousand deaths in 2018[105,106]. More than 90% of liver cancer is HCC. HCC usually develops as a result of underlying CLD, such as chronic HBV or HCV infection, ALD, and NAFLD. The majority of cases of HCC are found in the Asian-Pacific region[106]. Since Asia-Pacific region has more experience both in HCC and in COVID-19 than anywhere else. Thus experts prepare some recommendations of the management of HCC in the era of COVID-19[106].

Recommendations

HCC is a highly malignant and aggressive tumor, therefore its diagnosis and treatment should not be delayed due to the COVID-19 pandemic. Because patients may develop poor outcomes, HCC patients should be closely monitored during COVID-19 infection. To minimize the exposure to the SARS-CoV-2, telemedicine may be used for screening HCC patients[48]. More intensive surveillance and early admission of HCC patients have been recommended. Systemic treatments and evaluation for liver transplant should be continued according to the guideline. Although 2 mo delay is reasonable, ADDSL recommended that HCC patients at-risk group (cirrhosis and chronic hepatitis B) continue both being monitored and therapy. The treatment should be continued and curative treatments should be periodized but other treatments such as vascular interventions and systemic therapy should be postponed. The risks and benefits of delaying surveillance should be told to the patients and documented. Images of patients with liver masses should be evaluated with an expert radiologist before the visit. Digital patient visits may be planned to discuss the diagnosis and management of liver tumors. If COVID-19 infection present, diagnosis and treatment of HCC patients should be postponed until the viral clearance[106].

HCC treatments should not be delayed[90]. HCC risk stratification scores should be used. Patients at an increasingly higher risk group (elevated alpha-fetoprotein levels, advanced cirrhosis, chronic hepatitis B, NASH/diabetes) should be prioritized for liver transplant[48,99]. In patients with COVID-19, immunosuppressive therapies should be temporally withdrawn and kinase inhibitors should be taken on a case basis[48]. Imaging examination to detect recurrence at the early stage should not be postponed[106].

AUTOIMMUNE HEPATITIS

In patients with autoimmune hepatitis (AIH), immunosuppressive therapy makes those patients at greater risk for severe infection and should be prioritized for early testing. If elevated liver enzymes developed in AIH patients during COVID-19 infection flare-up should be considered and confirmation through biopsy should be made[90]. EASL-European Society of Clinical Microbiology and Infectious Diseases (ESCMID) advises withdrawn immunosuppressive therapy in such patients[48]. Withdrawing especially for antimetabolites, should only be considered after consultation of an expert and under special situation (such as in severe COVID-19 with medication-induced lymphopenia, or presence of other superinfection)[48].

There are some observational studies related to corticosteroid usage and predis-position for severe COVID-19 infection[48,107]. The World Health Organization suggests minimizing high-dose prednisolone but to continue small doses to avoid adrenal insufficiency[48,107].

Patients with autoimmune CLD have a high risk for COVID-19 infection because of their suppressed immune function[69]. Reducing immunosuppressive therapy is not recommended in patients with autoimmune liver disease, to prevent SARS-CoV-2 infection[48]. Reductions should only be considered in only some conditions such as...
drug-associated lymphopenia and bacterial/fungal superinfection in cases of severe COVID-19. To decrease systemic glucocorticoid exposure budesonide is recommended as a first-line agent to induce remission in patients without cirrhosis who have a flare of AIH.

In patients who developed COVID-19, corticosteroid dosing should be decreased. Change with dexamethasone may be considered in only hospitalized patients. There is not a specific recommendation for patients with primary biliary cholangitis, primary sclerosing cholangitis, or immunoglobulin G4-related disease.

Patients should be vaccinated for Streptococcus pneumonia, influenza and COVID-19.

LIVER TRANSPLANTATION AND COVID-19

Clinical outcome in liver transplant patients with COVID-19

Data related to liver transplant recipient patients with COVID-19 infection are still limited. However, patients with liver transplants have a high risk for COVID-19 infection due to their suppressed immune function by immunosuppressive therapy [108]. The clinical course of COVID-19 infection is different in immunosuppressed transplant recipients from that in non-immunosuppressed patients.

An Italian center reported no increase in the hospitalization among > 300 children who followed for liver transplantation, AIH, or hepatoblastoma. SARS-CoV-2 positivity developed only in 3 of 13 hospitalized children, who have liver transplantation or giving chemotherapy for hepatoblastoma [109].

In a large liver transplant series including 151 patients, 6 patients became infected SARS-CoV-2, and 2.7% of long-term recipients died, but all 7.5% of short-term recipients survived [110]. Immunosuppressive regimen discontinued three cases, acute respiratory distress syndrome (ARDS) rapidly developed in and caused death. Becchetti et al [111] reported that fever and dyspnea were found more frequent in the long-term than that of short-term recipients (91% vs 63%, and 59% vs 29% respectively). Computed tomography scan and pulmonary radiography showed typical features of the disease in 24 (43%) and 25 (40%) cases, respectively. These pathologies can be attributed to the long-term use of immunosuppressant medications [112]. In a European study conducted 19-transplant centers enrolled 57 liver transplant recipients with COVID-19 (16 outpatients and 41 hospitalized), mortality was found as 17%. ARDS developed 19% and hospitalization was needed in 72% of patients. Total fatality rates found were 12% and 17% in hospitalized patients, most of whom had cancer [111].

In an Italian study (13%) of 24 liver transplant recipients with COVID 19 were admitted to the ICU and 5 (21%) of them died [113]. A Swiss Transplant Cohort Study (a prospective observational multicenter study) reported 21 solid organs transplant patients. In five patients had liver transplant, steroids and calcineurin inhibitors continued the same dose. They reported that the clinical course was not different from other people [114].

In transplant recipients with COVID-19, liver injury is relatively seen less frequent, but acute kidney injury is more common probably due to calcineurin inhibitors usage [58,102,103].

Qin et al [115] observed a case of COVID-19 in a patient who underwent liver transplantation. Tacrolimus and glucocorticoids continued but decreased to lower doses. Another post-transplant patient recovered from severe COVID-19 pneumonia after gradual withdrawal from immunosuppression therapy and given low-dose corticosteroid [111].

Recommendations

EASL-ESCMID recommended that liver transplantation recipients should be restricted to patient with poor prognosis with acute/acute-on-chronic liver failure, end-stage liver disease (elevated MELD score), and HCC. Hospital stay time should be short and consultation from other clinics should be restricted. Complications such as peritonitis or encephalopathy should be followed to prevent hospitalization. Streptococcus pneumonia and influenza vaccination should be given [48]. COVID-19 vaccine should be applied. EASL-ESCMID recommendations on liver transplant recipients and candidates are shown in Table 2 [48].

SARS-CoV-2 screening should be used both hospitalized patients with acute decompensation or acute liver failure. COVID-19 screening should be applied to both donors and recipients before transplantation [113]. COVID-19 screening is recomme-
Table 2 European Association for the Study of the Liver-European Clinical Microbiology and Infectious Diseases recommendations for liver transplantation[48]

**EASL-ECCMID recommendations**

<table>
<thead>
<tr>
<th>Liver transplant recipients</th>
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<tbody>
<tr>
<td>Reduction of immunosuppressive therapy should only be considered under special circumstances such as drug-induced lymphopenia, superinfection in case of severe COVID-19</td>
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<tr>
<td>LT recipients have high anxiety for COVID-19, and therefore their follow-up and treatment compliance may be impaired</td>
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<tr>
<td>Drug levels of calcineurin inhibitors and rapamycin inhibitors should be closely monitored. Because drugs used COVID-10 treatment such as hydroxychloroquine or protease inhibitors may interact them</td>
</tr>
<tr>
<td>Early admission should be made for LT recipients with COVID-19 infection</td>
</tr>
<tr>
<td>LT recipients, who have underlying malignancy, sarcopenia, graft dysfunction and metabolic disease are at-risk group for a severe COVID-19 infection</td>
</tr>
<tr>
<td>All patients should receive vaccination for <em>Streptococcus pneumonia</em>, influenza and COVID-19</td>
</tr>
</tbody>
</table>

**Liver transplant candidates**

| Patients on the LT waiting list with decompensated cirrhosis are at high risk of severe COVID-19 |
| LT should be prioritized for patients with poor short-term prognosis including those with acute liver failure, ACLF, high MELD score (including exceptional MELD points), and HCC at the upper limits of the Milan criteria |
| All donors for should be screening for SARS-CoV-2 infection by PCR and recommend |
| Both LT donors and recipients should be questioned clinical history, performed chest radiology, and SARS-CoV-2 testing |
| Consent for transplantation should include the potential risk of nosocomial COVID-19 |
| LT candidates should be informed that infection with SARS-CoV-2 in patients undergoing major surgery is associated with an increased risk of severe COVID-19 and death |
| Living-donor transplantations should be considered on a case-by-case basis and include careful risk stratification of donor and recipient, incorporating a combination of clinical history, chest radiology, and SARS-CoV-2 testing |

EASL: European Association for the Study of the Liver; ECCMID: European Clinical Microbiology and Infectious Diseases; LT: Liver transplantation; ACLF: Acute-on-chronic liver failure; MELD: Model for end-stage liver disease; HCC: Hepatocellular carcinoma.

COVID-19 AND GI TUMOURS

The COVID-19 pandemic negatively affected diagnosis and treatments of other
# Table 3 Recommendations for gastrointestinal system tumors during coronavirus disease 2019 pandemic

<table>
<thead>
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<th>Recommendations for gastrointestinal system tumors[116]</th>
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<tbody>
<tr>
<td>Social distancing mandates that every in-person interaction between patients and the health care system be scrutinized and only essential physical contacts between patients and health care professionals occur to diminish the risk of viral exposure to patients. Thus, minimize blood tests, scans and routine tests. Telephone and telemedicine visits should replace routine face-to-face clinic visits whenever possible. Whenever COVID-19 is clinically suspected or confirmed, systemic treatments should be suspended, and surgery should be postponed unless an urgent procedure is necessary (EOR). Whenever surgery is indicated, SARS-CoV-2 testing should be considered. There are insufficient data to recommend in favor or against an open versus minimally invasive approach. Proven benefits of minimally invasive surgeries of reduced length of stay and complications should be considered individually. Nevertheless, whenever minimally invasive surgeries are indicated, the use of devices to filter released CO₂ for aerosolized particles or techniques to treat the intra-abdominal gas whenever it should be emptied, is strongly advised. Central venous catheter flushing intervals should be increased to every 60 (younger and fit patients) or every 90 (older, frail patients with multiple comorbidities) days (EOR). For early stage (cT1/2 cN0) colorectal, biliary, hepatocellular, esophagus and gastric tumors, where neoadjuvant treatment is not standard, consider deferring surgical resection to up to 8 weeks. If delays beyond 8 wk are expected, repeat staging exams (EOR). Radiation schedules should be hypofractionated, whenever possible. Follow-up imaging and appointments should be reserved for those with symptoms suggestive of disease relapse. Asymptomatic patients not on active treatment should avoid imaging and follow up appointments, delaying tumor markers and colonoscopies, for example, for until the pandemic is over (EOR). In such cases, if possible, telemedicine or telephone consultation is indicated. DYPD screening is indicated whenever possible, before the use of fluoropyrimidines. Adjuvant treatment for colon and other gastrointestinal tumors, when recommended, should start in 4 wk to 8 wk after primary tumor resection. Monitoring blood counts at every cycle can be done by telemedicine if patients are asymptomatic. Infusional 5FU should be substituted for capecitabine in the following regimens: FOLFOX, cisplatin and 5FU, monotherapy, or when combined with radiotherapy. Exceptions are patients with severe renal dysfunction (creatinine clearance ≤ 30 mL/min); in patients with moderate (30 mL/min to 50 mL/min) renal dysfunction when upfront dose reduction of 25% is recommended. In curative-intent treatments, we encourage to maintain dose-intensity with the use of colony-stimulating growth factor (CSGF), if needed (EOR). In the metastatic setting, consider dose-reduce chemotherapy instead of adding CSGF, if the latter requires more hospital visits (EOR). In the metastatic setting, omit bolus 5FU in FOLFOX or FOLFIRI regimens to minimize toxicity (EOR). Whenever possible, chemotherapy holidays may be considered in patients with low-volume metastatic disease, who are responding or experiencing tumor stabilization and when there is no major risk of complications for site-specific progression (e.g., peritoneum, biliary obstruction). If maintenance is considered to be beneficial instead of chemo holidays (e.g., more aggressive disease), prefer capecitabine alone, without bevacizumab[116]. Standard second or further lines of anticancer therapies should be recommended for ECOG 0 or 1 patient. Preferably, when there is clinically relevant overall survival gain demonstrated by randomized phase III trials (e.g., second-line for colorectal cancer) Anti-PD1 immune checkpoint inhibitors are recommended in second or further lines of treatment for all gastrointestinal malignancies with microsatellite instability, regardless of the diagnostic method. For those in which immunotherapy monotherapy is indicated, we recommend the 6 wks' schedule with pembrolizumab. Multidisciplinary team discussions (MDT) by web conferencing systems are highly encouraged. We think MDT are key to help with decisions about risks and benefits of cancer-directed therapies during the COVID-19 pandemic. In all cases, clinical individual judgment is advised and decisions should be shared with patients. Additionally, the anticipated survival benefit for each patient versus the risks of exposure to the virus should be discussed with patients, taking into consideration the individual’s comorbidities and degree of frailty, as well as caregivers and family members at home. Clinical trial enrollment. Patients who are candidates for clinical trials should be encouraged to enroll in the following situations: studies testing orphan drug indications, experimental treatments where benefits are very likely to outweigh the risks (e.g., immunotherapy combo of ipilimumab and nivolumab for microsatellite unstable metastatic colorectal cancer (CheckMate 8HW-NCT 04008030) or rare tumors. However, institutions and principal investigators should discuss and align with sponsors and Institutional Research Ethical Boards about how to minimize hospital visits (e.g., all lab and image tests performed in one single day), implement telemedicine in certain moments of trial conduction (lab checks for fit patients who are tolerating well the trial therapy, for example), extend intervals between hospital visits, if possible. For patients already on trial, treatment should continue based on clinical judgement that should balance tolerance versus benefit. The same principles cited above to decrease hospital visits should be sought.</td>
</tr>
</tbody>
</table>

EOR: Expert opinion recommendation; ECOG: Eastern Cooperative Oncology Group; 5FU: 5 Florouracil; FOLFOX: Folinic acid, 5-fluorouracil, oxaliplatin; FOLFIRI: Folinic acid, florourasil, irinotekan.
patients with various diseases, including GI system cancer. Brazilian Gastrointestinal Tumors Group published evidence-based recommendations for GI cancers during the COVID-19 pandemic.[116]

These recommendations were based on scientific evidence, such as randomized clinical trials, meta-analyses, and large cohort studies. However, some recommendations performed an expert opinion. There are detailed recommendations and aimed to prioritize curative-intent cancer treatments during the pandemic, to support the treatment of aggressive tumors when effective therapies are available, to decrease the number of or delay oncological non-priority surgeries, to decrease hospital visits, to minimize anticancer therapy-related immunosuppression in a specific high-risk group.[116]. Recommendations related to GI cancers are showed in Table 3.

CONCLUSION
GI symptoms are common in patients with COVID-19. During the pandemic, SARS-CoV-2 infection should be kept in mind in patients who have acute GI symptoms. COVID-19 infection is usually associated with mild hepatic involvement. All with CLD appear to be at great risk of contracting an infection. However, it appears that patients with cirrhosis, HCC, autoimmune diseases, or liver transplantation may have a greater risk for severe COVID-19. COVID-19 treatment should not be delayed in patients at high-risk groups. Nutrition can be continued to improve important GI functions and clinical outcomes. Vaccines against SARS-CoV-2 have also been developed and are being widely used around the world. Like all chronic patients, COVID-19 vaccination should be prioritized in this group.

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Autoimmune Liver Disease, and Compensated Cirrhosis.


Retrospective Study

Continuous intravenous infusion of recombinant human endostatin using infusion pump plus chemotherapy in non-small cell lung cancer

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Author contributions: Qin ZQ and Yang SF designed and performed the research and wrote the paper; Chen Y, Hong CJ and Zhao TW designed the research and supervised the report; Yuan GR and Yang L designed the research and contributed to the analysis; Gao L and Wang X provided clinical advice; Lu LQ supervised the report; all authors gave final approval for the version to be submitted.

Institutional review board statement: This study was reviewed and approved by the ethics committee of Zhejiang Provincial People’s Hospital (People’s Hospital of Hangzhou Medical College) (2021QT290).

Informed consent statement: The ethics committee of Zhejiang Provincial People’s Hospital (People’s Hospital of Hangzhou Medical College) (2021QT290).

Abstract

BACKGROUND

Lung cancer is one of the deadliest cancers in the world with the highest incidence and mortality rate among all cancers. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of primary lung cancer. However, efficacy and safety of the current regimens for NSCLC is unsatisfactory. Therefore, there has been an increasing urgency for development of potential therapeutic therapies for NSCLC.

AIM

To investigate the therapeutic outcomes and safety of continuous intravenous infusion of recombinant human endostatin (Rh-endostain) using an infusion pump in retreated advanced NSCLC.

METHODS

Patients with retreated advanced NSCLC who were admitted to Zhejiang Provincial People’s Hospital from October 2017 to April 2019 were recruited. These patients received continuous intravenous infusion of Rh-endostain using an infusion pump. Objective response rate (ORR), clinical benefit rate (CBR), median progression-free survival (mPFS), and incidences of adverse events (AEs) were analyzed after treatment.

RESULTS

A total of 45 patients with retreated advanced NSCLC were included, and all of
INTRODUCTION

Lung cancer is one of the malignancies with the highest incidence and mortality worldwide[1]. By pathological typing, lung cancer is divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC, accounting for about 80%)[2]. Approximately 60%-70% of NSCLC patients are diagnosed at a late stage. The median survival of stage IV patients is less than nine months. Chemotherapy regimens for NSCLC mainly include platinum-containing double-drug chemotherapy or gemcitabine and docetaxel monotherapy[3]. However, the efficacy and safety of the current regimens is unsatisfactory. Therefore, the development and upgrade of treatments that are more effective, better tolerated, and less toxic is urgently warranted.

In 1971, Professor Folkman from the Harvard Medical School first proposed that the growth and spread of malignancies depended on tumor angiogenesis[4,5]. Vascular endothelial growth factor (VEGF) and its receptor are important factors in tumor angiogenesis. A synergistic effect may result from the combined use of antiangiogenic drugs and chemotherapy. Recombinant human endostatin (Rh-endostain, Endostar) was approved by the National Medical Products Administration in September 2005 for the treatment of NSCLC. Previous report revealed that Rh-endostain could inhibit angiogenesis. A synergistic effect may result from the combined use of antiangiogenic treatments that are more effective, better tolerated, and less toxic is urgently warranted.

Our results revealed that 5-day continuous intravenous infusion of Rh-endostain using infusion pump improved patient adherence and showed favorable efficacy and safety, which brought significant clinical benefits to advanced NSCLC patients.
Rh-endostain was usually administered by intermittent intravenous infusion, 3-4 times per day for 14 consecutive days. However, patients might have poor adherence to this dosing regimen, which remained to be optimized. Several clinical studies were conducted based on stability tests of the continuous intravenous infusion of Rh-endostain using an infusion pump[11-13]. In brief, the results showed that this administration regimen of Rh-endostain was convenient and guaranteed patient adherence. In addition, this administration regimen was conducive to maintaining the steady-state concentration of Rh-endostain in the blood, which was widely accepted and used clinically[14-19].

The present study observed the efficacy and safety of 5-d continuous intravenous infusion of Rh-endostain in advanced NSCLC patients, which may provide further valuable clinical data for the treatment of advanced NSCLC.

**MATERIALS AND METHODS**

**Baseline characteristics**

The medical records of 45 NSCLC patients who were treated at Zhejiang Provincial People's Hospital from October 2017 to April 2019 were retrospectively analyzed. Eligibility of the patients was assessed using the following inclusion criteria: (1) NSCLC confirmed by pathohistology or cytology; (2) Retreated advanced NSCLC (stage IV according to the American Joint Committee on Cancer staging system); (3) Eastern Cooperative Oncology Group performance status score, 0-2; (4) Measurable and evaluated lesions without contraindications; and (5) Data on the following examinations were available: routine blood and urine tests, liver and kidney function tests, cardiac enzyme profile, and electrocardiogram, computed tomography scan of the chest, abdomen and brain, and whole-body bone scan after two cycles of treatment. The patients were excluded if any of the following exclusion criteria were met: (1) Women who were pregnant or lactating; (2) Hemorrhagic tendency, history of thrombosis, or currently taking anticoagulant medication; (3) Abnormal organ functions and unable to tolerate the side effects of Rh-endostain and chemotherapy; and (4) The presence of other malignancies. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Zhejiang Provincial People’s Hospital (People’s Hospital of Hangzhou Medical College) (2021QT290). Individual consent for this retrospective analysis was waived.

**Treatment regimens**

Rh-endostain (Shandong Simcere-Medgenn Bio-pharmaceutical Co., Ltd., 15 mg/bottle) was administered concomitantly with chemotherapy. Rh-endostain was given by continuous intravenous infusion using an infusion pump at a dose of 210 mg for 5 consecutive days. Each treatment cycle lasted 21 d (q21d). The chemotherapy regimens included the following: (1) AP regimen: Pemetrexed 500 mg d1 + carboplatin Area under roc curve (AUC) = 5-6 (or cisplatin 75 mg/m²) d1 q21d; (2) GP regimen: Gemcitabine 1000-1250 mg/m² d1 + cisplatin 75 mg/m² (or carboplatin AUC = 5-6) d1 q21d; (3) Pemetrexed monotherapy: Pemetrexed, 500 mg/m² d1 q21d; and (4) Docetaxel monotherapy: Docetaxel, 60-75 mg/m² d1 q21d. Tumors were assessed as planned until disease progression.

**Clinical efficacy and adverse event evaluation**

Treatment efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria[20]. The efficacy indicators were as follows: complete response (CR, defined as disappearance of all target lesions, no new lesions, and return of tumor markers to normal, for at least 4 wk), partial response (PR, defined as the sum of the decrease in the maximum diameters of the target lesions by more than 30%, for at least 4 wk), stable disease (SD, defined as the sum of the decrease in maximum diameters of the target lesions, yet not reaching the standard of PR or being increased yet not reaching the standard of progressed disease), and progressed disease (PD, defined as the sum of the increase in the maximum diameter of the target focus by at least 20%, or the appearance of new lesions). Objective response rate (ORR) = (CR+PR)/(total number of cases in each group), and clinical benefit rate (CBR) were determined. Progression-free survival (PFS) was defined as the time from the first administration to disease progression confirmed by objective evidence or death due to any cause. Adverse events (AEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-
CTCAE version 5.0), and were recorded.

**Statistical analysis**
Data analysis were performed using SPSS 22.0 software. The ORR and CBR in patients with different pathological types of NSCLC who received different treatment regimens were compared using the \( \chi^2 \) test. \( P < 0.05 \) indicated a significant difference. All tests were two-sided. The survival curve was estimated using the Kaplan–Meier method.

**RESULTS**

**General information**
A total of 45 NSCLC patients who were treated at Zhejiang Provincial People’s Hospital from October 2017 to April 2019 were retrospectively analyzed in this study, and baseline characteristics were shown in Table 1. The median age was 65 years (Interquartile range: 35-83 years). Besides, 27 of the NSCLC patients in this study were male, with the rest 18 of the patients being female. Among them, 10 NSCLC patients (22.2%) were Squamous cell carcinoma, with the rest of them being Adenocarcinoma type. Besides, the chemotherapy drugs combined with Rh-endostain included AP (\( n = 2 \)), GP (\( n = 2 \)), Pemetrexed monotherapy (\( n = 16 \)) and Docetaxel monotherapy (\( n = 11 \)).

**Analysis of short-term clinical effects on NSCLC patients**
The clinical data of all 45 enrolled patients were evaluated. There were no cases of CR, 10 cases of PR, 28 cases of SD, and 7 cases of PD. ORR was 22.2%, CBR was 84.4%, and median progression-free survival (mPFS) was 5.3 mo (Figure 1). The patients were also stratified by pathological type and chemotherapy regimens. No significant differences were observed in patients with different types of NSCLC who received different treatments (\( P > 0.05 \)). Further details were provided in Table 2.

**AEs**
The following AEs were observed as follows decreased hemoglobin (34 cases, 75.6%), nausea/vomiting (32 cases, 71.1%), elevated transaminase (24 cases, 53.3%), leukopenia (16 cases, 35.6%), thrombocytopenia (14 cases, 31.1%), and constipation (1 case, 3.4%). None of the patients had leukopenia, nausea/vomiting, and constipation of grade III and above. Further details are provided in Table 3. Overall, the toxicity profile of the combination treatment in this study was acceptable and manageable.

**DISCUSSION**
Several studies evaluated the efficacy and safety of Rh-endostain plus platinum-containing double-drug chemotherapy. However, there were only limited data on the combination of Rh-endostain plus monodrug chemotherapy or platinum-containing double-drug chemotherapy as the second-line regimen and below in advanced NSCLC patients. Patients generally showed lower adherence to intravenous drip infusion in previous studies[21,22]. In the present study, the efficacy and safety of Rh-endostain administered by continuous intravenous infusion for five days using an infusion pump in retreated advanced NSCLC were assessed.

Our study was observational in nature. All the enrolled patients had stage IV NSCLC in which no driver genes were identified. The chemotherapy regimens used were primarily the platinum-containing double-drug regimen and monodrug therapy (monodrug therapy was favored as a later-line treatment or for patients in a poor general condition (PS ≥2), such as gemcitabine and docetaxel monotherapy). The above chemotherapy regimens combined with rh-endostain, as a targeted antiangiogenic agent, can normalize tumor vessels, sensitize tumor cells to chemotherapy, and improve patient prognosis. Our results showed that in the 45 enrolled patients, ORR was 22.2%, CBR was 84.4%, and mPFS was 5.3 mo. The incidences of hematological and non-hematological toxicities of grade III and above were low. No Rh-endostain-related cardiac functional abnormalities, as reported previously, occurred in our study. Furthermore, the efficacy was compared in patients with different pathological types and receiving double-drug or monodrug chemotherapy. However, no significant differences were identified. Rh-endostain combined with either double-drug or monodrug chemotherapy improved the efficacy in both lung adenocarcinoma and NSCLC. Our research findings lay the foundation for making clinical decisions on
Table 1 General information on 45 patients with advanced non-small cell lung cancer

<table>
<thead>
<tr>
<th>Features</th>
<th>Basic information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65 yr (35-83 yr)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
</tr>
<tr>
<td>Pathological type</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>10</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>35</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td></td>
</tr>
<tr>
<td>AP</td>
<td>13</td>
</tr>
<tr>
<td>GP</td>
<td>5</td>
</tr>
<tr>
<td>Pemetrexed monotherapy</td>
<td>16</td>
</tr>
<tr>
<td>Docetaxel monotherapy</td>
<td>11</td>
</tr>
</tbody>
</table>

AP: Pemetrexed + carboplatin; GP: Gemcitabine + cisplatin.

Table 2 Relationships between clinicopathological features and short-term efficacy

<table>
<thead>
<tr>
<th>Clinicopathological features</th>
<th>Case</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>ORR</th>
<th>CBR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.848</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>10</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>20.0%</td>
<td>80.0%</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>35</td>
<td>0</td>
<td>8</td>
<td>22</td>
<td>5</td>
<td>22.9%</td>
<td>85.7%</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.411</td>
</tr>
<tr>
<td>Dual-drug chemotherapy + Rh-endostain</td>
<td>18</td>
<td>0</td>
<td>5</td>
<td>11</td>
<td>2</td>
<td>27.8%</td>
<td>88.9%</td>
<td></td>
</tr>
<tr>
<td>Single-drug chemotherapy + Rh-endostain</td>
<td>27</td>
<td>0</td>
<td>5</td>
<td>17</td>
<td>5</td>
<td>18.5%</td>
<td>81.5%</td>
<td></td>
</tr>
</tbody>
</table>

ORR: Objective response rate; CBR: Clinical benefit rate; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressed disease.

Table 3 Incidences of adverse events, n (%)

<table>
<thead>
<tr>
<th>AEs</th>
<th>Any grade</th>
<th>Grade III and above</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>34 (75.6)</td>
<td>5 (11.1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>16 (35.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14 (31.1)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Elevated transaminase</td>
<td>24 (53.5)</td>
<td>7 (15.6)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>32 (71.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (3.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

AEs: Adverse events.

different chemotherapy regimens.

Some previous studies have reported similar findings. For example, five days of intravenous infusion of Rh-endostain using an infusion pump as first-line treatment achieved similar efficacy to a continuous intravenous drip in advanced NSCLC patients (PFS: 6.0 mo vs 3.8 mo, P = 0.10). In addition, the incidences of AEs did not increase[23]. The use of an infusion pump improved the adherence of patients to rh-endostain treatment. The short-term efficacy and tolerance of Rh-endostain using the
above treatment regimen with concurrent radiochemotherapy in unresectable stage III NSCLC were satisfactory[24]. Rh-endostain administered by continuous intravenous infusion using an infusion pump plus concurrent radiochemotherapy was associated with a low incidence of AEs in advanced NSCLC patients. These patients also reported a higher level of comfort and demonstrated better adherence. Therefore, the quality of medical care and nursing was improved[25].

Limitations in this retrospective analysis should never be neglected. For one thing, this was a retrospective study with a small sample size, and prospective clinical randomized controlled trials will be conducted for further validation of the efficacy and safety of continuous intravenous infusion of Rh-endostatin combined with chemotherapy in retreated advanced NSCLC. For another, heterogeneity of patients enrolled in this study should be further considered to reduce potential selective bias.

CONCLUSION

Taken together, 5-d continuous intravenous infusion of Rh-endostatin using an infusion pump improved patient adherence, bringing significant clinical benefits to the patients. Further clinical studies were warranted to further confirm the efficacy and safety of this regimen, in order to improve the prognosis of patients with advanced NSCLC.

ARTICLE HIGHLIGHTS

Research background
To date, current available treatment options for non-small cell lung cancer (NSCLC) are associated with significant limitations in safety and efficacy. Therefore, development and achievement of potential therapeutic therapies for NSCLC is necessary.

Research motivation
This study mainly evaluated the efficacy and safety of continuous intravenous infusion of recombinant human endostatin (Rh-endostain) using an infusion pump in patients with retreated advanced NSCLC.

Research objectives
This study aimed to investigate the efficacy and safety of continuous intravenous infusion of Rh-endostain in retreated advanced NSCLC patients.
Research methods
Forty-five patients from Zhejiang Provincial People’s Hospital received continuous intravenous infusion of Rh-endostain using an infusion pump. Objective response rate (ORR), clinical benefit rate (CBR), median progression-free survival (mPFS), and adverse events were analyzed after treatment.

Research results
In these 45 patients, ORR was 22.2%, CBR was 84.4%, and mPFS was 5.3 mo. The following AEs were observed as follows, decreased hemoglobin (34 cases, 75.6%), nausea/vomiting (32 cases, 71.1%), elevated transaminase (24 cases, 53.3%), leukopenia (16 cases, 35.6%), thrombocytopenia (14 cases, 31.1%), and constipation (1 case, 3.4%). None of the patients had leukopenia, nausea/vomiting, and constipation of grade III and above.

Research conclusions
Five-day continuous intravenous infusion of Rh-endostain using an infusion pump improved patient adherence, and brought about favorable efficacy and safety in retreated advanced NSCLC.

Research perspectives
Prospective clinical randomized controlled trials will be conducted for further validation of the efficacy and safety of continuous intravenous infusion of Rh-endostatin combined with chemotherapy in retreated advanced NSCLC.

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Sequential sagittal alignment changes in the cervical spine after occipitocervical fusion

Ce Zhu, Lin-Nan Wang, Tai-Yong Chen, Li-Li Mao, Xi Yang, Gan-Jun Feng, Li-Min Liu, Yue-Ming Song

Abstract

BACKGROUND
There are few studies regarding sequential changes in the sagittal alignment of the upper and lower cervical regions of the spine after occipitocervical fusion (OCF). In addition, no comparisons of cervical sagittal alignment (CSA) between patients with craniocervical junction disorders (CJDs) and normal populations have been reported.

AIM
To compare the CSA of patients with CJDs with that of normal controls and investigate the sequential changes in the CSA of the upper and lower cervical spine after OCF.

METHODS
Eighty-four patients who underwent OCF (OCF group) and 42 asymptomatic volunteers (control group) were included. Radiographic parameters, including the occipital to C2 angle (O-C2a), occipital and external acoustic meatus to axis angle (O-EAa), C2–7 angle (C2-7a), and pharyngeal inlet angle (PIA), were measured and compared pre- and postoperatively. The correlations among the parameters were analyzed using Pearson’s correlation test.

RESULTS
The O-C2a and PIA of the OCF group were smaller than those of the control group, while their O-EAa and C2-7a values were larger than those of the normal
publication of this case report and any accompanying images.

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

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

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**Specialty type:** Medicine, research and experimental

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**Peer-review model:** Single blind

**Peer-review report’s scientific quality classification**

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

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controls. There were no significant differences in O-C2a, C2-7a, or PIA in the OCF group at baseline, 1 mo, or the final follow-up after surgery. The Pearson’s correlation results showed that there were significant correlations between the O-C2a and C2Ta, C2-7a, C2-7 sagittal vertical axis (SVA), and PIA at 1 mo after OCF surgery and between O-C2a and O-EAa, C2Ta, C2-7a, C2-7 SVA, and PIA at the final follow-up.

**CONCLUSION**

Patients with CJDs have a more kyphotic upper CSA and a more lordotic lower CSA than normal controls. The effectiveness of OCF surgery in restoring CSA may be limited by the realignment of the craniocervical junction being neglected. The reduction in O-C2a after OCF surgery may increase C2-7a and decrease PIA.

**Key Words:** Sagittal alignment; Occipitocervical fusion; Craniocervical disorders; Cervical spine; Dysphagia

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**Core Tip:** Patients with craniocervical junction disorders had a more kyphotic upper cervical sagittal alignment (CSA) and a more lordotic lower CSA than normal controls. The decreased lordosis of the upper cervical spine caused by the weakness of paraspinal muscles and ligaments (OC2a) led to the gravity center of the cranium moving forward (C2Ta). To maintain horizontal gaze and normal C2-7 sagittal vertical axis, the lordosis of the lower cervical spine was increased (C2-7a). Moreover, the restoration of CSA after occipitocervical fusion (OCF) may be limited by neglecting the realignment of craniocervical junction. The reduction of the O-C2a after OCF would increase the C2-7a and decrease the pharyngeal inlet angle and lead to postoperative dysphagia.

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**INTRODUCTION**

The cervical spine can be classified into two parts: The upper cervical spine (C0-C2) and lower cervical spine (C3-C7). The sagittal alignments of the two parts are closely interrelated[1]. An imbalance in the upper and lower cervical regions of the spine can lead to poor cervical sagittal alignment (CSA), which correlates with headache, neck pain, and poor health-related quality of life (HRQOL)[2].

Several studies have explored the interrelationship between upper and lower CSA. Nojiri et al[1] and Lee et al[3] observed a significant negative correlation between the C0-2 and C2-7 angles in asymptomatic individuals. Huang et al[4] found that postoperative kyphosis in the lower cervical spine is associated with hyperlordotic atlantoaxial fusion. Kim et al[5] reported that anterior cervical disectomy and fusion in the lower cervical spine can induce improvements in regional lordosis at the surgical level and can subsequently cause changes in the upper cervical segment including upward inclinations of the C1 slope and C2 slope.

Occipitocervical fusion (OCF) was first described in 1927 and was suggested to be an effective and safe procedure for the surgical treatment of cranio cervical junction disorders (CJDs) caused by congenital deformities, trauma, rheumatoid arthritis (RA), and degenerative processes[6]. Matsubayashi et al[7] found that the occipital to C7 angle (O-C7a) is regulated by the T1 slope and that the corresponding O-C7a is divided into the occipital to C2 angle (O-C2a) and C2-C7 angle (C2-7a), which have negative correlations with each other and then maintain horizontal gaze. Korovessis et al[8] demonstrated that postoperative O-C2a, pharyngeal inlet angle (PIA), and T1-slope safely predict HRQOL outcomes following OCF for fresh trauma.
However, there are few studies regarding sequential changes in the sagittal alignment of the upper and lower cervical regions of the spine after OCF. In addition, to our knowledge, no comparisons of CSA between patients with CJDs and normal populations have been reported. Thus, this study had two purposes: (1) To compare the CSA of patients with craniocervical disorders with that of a normal control population; and (2) To investigate the sequential changes in and interrelationships of the sagittal alignment of the upper and lower cervical regions of the spine after OCF.

MATERIALS AND METHODS

This was a retrospective study that was approved by the ethics committee of West China Hospital of Sichuan University and informed consent was obtained from all the patients. All methods were carried out in accordance with relevant guidelines and regulations.

Patients with CJDs who underwent OCF (OCF group) between April 2010 and May 2019 were included in the study. The inclusion criteria were as follows: (1) Age ≥ 18 years; (2) Surgical treatment with OCF; (3) No history of spine surgery; and (4) At least 1 year of radiographic follow-up data with adequate visualization of the cervical spine on pre- and postoperative films. The exclusion criteria included a history of spine surgery or oropharyngeal surgery, and the presence of preoperative dysphagia, and dysphagia resulting from esophageal disease. For comparison, asymptomatic volunteers with no history of cervical disease or trauma and no neck, shoulder, or arm symptoms were also included in the study as a control group. These people were matched by age and sex with the patients in the OCF group.

All surgical procedures were performed by two senior surgeons from one medical team. We routinely used autologous iliac bones for fusion. The patients in the OCF group were divided into dysphagia and nondysphagia subgroups according to whether they had suffered postoperative dysphagia, as determined by face-to-face questioning or telephone interviews. Patients were defined as having dysphagia if they needed swallowing agents or pureed foods to avoid choking[9].

A lateral radiograph of the cervical spine was obtained at baseline, 1 mo, and the last follow-up after OCF surgery. The radiographic parameters assessed (Figure 1) were as follows based on previous studies[9-11]: O-C2a, which is the angle between the inferior end plate of C2 and the McGregor line that connects the hard palate and opisthion; the occipital and external acoustic meatus to axis angle (O-EAa), which is the angle formed by the McGregor line and the EA-line and connects the midpoint of the external acoustic meatuses and the midpoint of the inferior endplate of C2; the tilting angle (C2Ta), which is the angle formed by the inferior endplate of C2 and the EA-line; C2-7a, which is the Cobb angle between the lower endplate of C2 and C7; the T1 slope, which is the angle between the horizontal and the T1 superior endplate; the C2-7 sagittal vertical axis (C2-7 SVA), which is the horizontal distance between the C2 plumb line and the posterior corner of C7; and the PIa[10], which is the angle between McGregor line and the line that links the center of the C1 anterior arch and the apex of the cervical sagittal curvature (or bottom when the cervical alignment is kyphotic). Positive values indicated lordosis, while negative values indicated kyphosis. The C2-7 SVA value was considered to be positive if the C2 plumb line was located in front of the posterior upper corner of the C7 vertebral body, and it was considered to be negative if the C2 plumb line was behind the posterior upper corner of the C7 vertebral body[12]. To avoid intraobserver bias, all radiological parameters were measured by two attending spinal surgeons who were not involved in the surgery, and the average value of their measurements was used for analysis.

Analyses were performed with SPSS software (version 22.0; IBM Corp., Armonk, NY, United States). Values are presented as the mean ± SD. Quantitative data were analyzed using the Student’s t test or Mann–Whitney U test, as appropriate. Categorical data were analyzed by the χ² test or Fisher’s exact test. The relationships between variables were assessed using the Pearson’s correlation test. P < 0.05 indicated statistical significance.

RESULTS

A total of 84 patients were included in the OCF group. The average patient age was 50.5 ± 15.0 years, and 45.2% (38/84) of patients were male. CJDs were caused by deformities (n = 63), trauma (n = 12), and RA (n = 9). The fusion levels were O-C2 (n =
For comparison, 42 asymptomatic volunteers were enrolled in the control group. The differences in age and sex between the OCF group and control group were not significant (P = 0.738 and P = 0.851, respectively). The radiographic parameters in these two groups are listed in Table 1.

The radiological parameters of patients in the OCF group before surgery, 1 mo after surgery, and at the last follow-up after OCF surgery are reported in Table 1. There were no significant differences in O-C2a, C2-7a, or PIA at baseline, 1 mo after surgery, or the final follow-up after surgery (P > 0.05). Compared with the asymptomatic volunteers in the control group, the patients in the OCF group had significantly smaller O-C2a and PIA values after OCF surgery (P < 0.05) and significantly larger O-EAa, C2Ta, and C2-7a values (P < 0.05). The results of the Pearson’s correlation analysis of O-C2a and the other parameters showed that there were significant correlations between O-C2a and C2Ta (r = -0.840, P = 0.000), C2-7a (r = -0.333, P = 0.002), C2-7 SVA (r = 0.218, P = 0.046), and PIA (r = 0.744, P = 0.000) at 1 mo after OCF surgery and between O-C2a and O-EAa (r = 0.346, P = 0.001), C2Ta (r = -0.764, P = 0.000), C2-7a (r = -0.314, P = 0.004), C2-7 SVA (r = 0.293, P = 0.007), and PIA (r = 0.495, P = 0.000) at the final follow-up.

There were 20 patients with dysphagia and 64 patients without dysphagia in the OCF group. No significant intergroup differences were found in terms of age (52.2 ± 12.8 vs 49.9 ± 15.7, P = 0.555), fusion level (≤ C3/> C3: 16/4 vs 44/20, P = 0.405), the proportion of patients with RA (4/20 vs 6/64, P = 0.185), or the proportion of patients with AS (13/20 vs 40/60, P = 0.840). However, the proportion of female patients was significantly higher in the patients with dysphagia (16/20) than in the patients without (30/64) (P = 0.019). The details of the radiological parameters of the patients with and without dysphagia at baseline, 1 mo after the surgery, and the final follow-up after OCF surgery are shown in Table 3.

Figure 1 Representation of the radiographic measurements. O-C2a: The angle between the inferior endplate of C2 and the McGregor line; O-EAa: The angle formed by the McGregor line and the EA-line; C2Ta: The angle formed by the inferior endplate of C2 and the EA-line; C2-7a: The Cobb angle between the lower endplate of C2 and C7; T1 slope: The angle between the horizontal and the T1 superior endplate; C2-7 SVA: The horizontal distance between the C2 plumb line and the posterior corner of C7; PIA: The angle between McGregor line and the line that links the center of the C1 anterior arch and the apex of cervical sagittal curvature. O-C2a: O-C2 angle; O-EAa: Occipital and external acoustic meatus to axis angle; C2Ta: C2 tilting angle; C2-7a: C2-7 angle; SVA: Sagittal vertical axis; PIA: Pharyngeal inlet angle.

28), O-C3 (n = 31), O-C4 (n = 18), and O-C5 (n = 7). The postoperative follow-up period in the OCF group ranged from 12 to 78 mo (mean, 22.8 ± 16.6 mo).
Table 1 Radiological parameters of patients in the occipitocervical fusion and control groups

<table>
<thead>
<tr>
<th></th>
<th>OCF (n = 84)</th>
<th>Control (n = 42)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre-op</td>
<td>Post-op</td>
</tr>
<tr>
<td>O-C2a (°)</td>
<td>4.7 ± 15.3</td>
<td>4.6 ± 12.6</td>
</tr>
<tr>
<td>O-EAa (°)</td>
<td>101.1 ± 8.5</td>
<td>99.4 ± 7.7</td>
</tr>
<tr>
<td>C2Ta (°)</td>
<td>96.5 ± 17.3</td>
<td>94.8 ± 13.5</td>
</tr>
<tr>
<td>C2-7a (°)</td>
<td>24.8 ± 18.1</td>
<td>21.7 ± 16.1</td>
</tr>
<tr>
<td>T1 slope (°)</td>
<td>23.2 ± 9.5</td>
<td>23.4 ± 8.2</td>
</tr>
<tr>
<td>C2-7 SVA (cm)</td>
<td>1.4 ± 1.1</td>
<td>1.5 ± 1.1</td>
</tr>
<tr>
<td>PIA (°)</td>
<td>91.6 ± 10.3</td>
<td>89.3 ± 10.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> P < 0.05 compared with pre-op.  
<sup>b</sup> P < 0.05 compared with post-op.  
<sup>c</sup> P < 0.05 compared with final follow-up.

OCF: Occipitocervical fusion; Pre-op: Preoperative; Post-op: Postoperative; O-C2a: O-C2 angle; O-EAa: Occipital and external acoustic meatus to axis angle; C2Ta: C2 tilting angle; C2-7a: C2-7 angle; SVA: Sagittal vertical axis; PIA: Pharyngeal inlet angle.

Table 2 Pearson product moment coefficient (Pearson’s r value) between O-C2 angle and C2-7 angle and other parameters in the occipitocervical fusion and control groups

<table>
<thead>
<tr>
<th></th>
<th>OCF (n = 84)</th>
<th>Control (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r value</td>
<td>P value</td>
</tr>
<tr>
<td>O-C2a</td>
<td>-0.585</td>
<td>0.000</td>
</tr>
<tr>
<td>O-EAa</td>
<td>-0.872</td>
<td>0.000</td>
</tr>
<tr>
<td>C2Ta</td>
<td>-0.585</td>
<td>0.000</td>
</tr>
<tr>
<td>C2-7a</td>
<td>0.067</td>
<td>0.545</td>
</tr>
<tr>
<td>T1 slope</td>
<td>0.757</td>
<td>0.000</td>
</tr>
<tr>
<td>C2-7 SVA</td>
<td>0.023</td>
<td>0.837</td>
</tr>
<tr>
<td>PIA</td>
<td>0.540</td>
<td>0.000</td>
</tr>
<tr>
<td>T1 slope</td>
<td>0.040</td>
<td>0.000</td>
</tr>
<tr>
<td>C2-7 SVA</td>
<td>0.909</td>
<td>0.000</td>
</tr>
<tr>
<td>PIA</td>
<td>-0.546</td>
<td>0.000</td>
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</table>

O-C2a: O-C2 angle; O-EAa: Occipital and external acoustic meatus to axis angle; C2Ta: C2 tilting angle; C2-7a: C2-7 angle; SVA: Sagittal vertical axis; PIA: Pharyngeal inlet angle.

DISCUSSION

Previous studies have explored the relations between the alignments of the upper and subaxial cervical regions of the spine in asymptomatic volunteers[1,13,14]. Nojiri et al [1] enrolled 313 asymptomatic individuals in their study and investigated the relationships between the alignments of the upper and lower cervical regions of the spine. They observed significant negative correlations between O-C2a and C2-7a and between C1-2a and C2-7a. The correlation coefficient between O-C2a and C2-7a was larger than that between C1-2a and C2-7a. Sherekar et al[13] also reported that O-C2a was negatively correlated with C2-7a. Guo et al[14] found that O-C2a was larger in females than in males, whereas C2-7a was significantly larger in males. Both C2-7a and O-C2a correlated significantly with age. In our study, the mean values of O-C2a
Table 3 Radiological parameters of patients with dysphagia and without dysphagia

<table>
<thead>
<tr>
<th></th>
<th>Dysphagia (n = 20)</th>
<th>Without dysphagia (n = 64)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-C2a (°)</td>
<td>Pre-op</td>
<td>9.7 ± 10.7</td>
<td>3.2 ± 16.2</td>
</tr>
<tr>
<td></td>
<td>Post-op</td>
<td>0.9 ± 9.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.8 ± 13.3</td>
</tr>
<tr>
<td></td>
<td>Final follow-up</td>
<td>1.3 ± 9.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.8 ± 14.1</td>
</tr>
<tr>
<td>O-EAa (°)</td>
<td>Pre-op</td>
<td>104.2 ± 7.8</td>
<td>100.2 ± 8.6</td>
</tr>
<tr>
<td></td>
<td>Post-op</td>
<td>95.1 ± 8.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100.8 ± 6.6</td>
</tr>
<tr>
<td></td>
<td>Final follow-up</td>
<td>96.9 ± 6.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>99.7 ± 9.7</td>
</tr>
<tr>
<td>C2Ta (°)</td>
<td>Pre-op</td>
<td>94.5 ± 13.1</td>
<td>97.1 ± 18.3</td>
</tr>
<tr>
<td></td>
<td>Post-op</td>
<td>94.3 ± 14.1</td>
<td>94.9 ± 13.4</td>
</tr>
<tr>
<td></td>
<td>Final follow-up</td>
<td>95.6 ± 10.6</td>
<td>93.8 ± 14.0</td>
</tr>
<tr>
<td>C2-7a (°)</td>
<td>Pre-op</td>
<td>19.5 ± 14.3</td>
<td>26.4 ± 19.0</td>
</tr>
<tr>
<td></td>
<td>Post-op</td>
<td>26.9 ± 13.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20.0 ± 16.6</td>
</tr>
<tr>
<td></td>
<td>Final follow-up</td>
<td>27.9 ± 12.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19.6 ± 16.2</td>
</tr>
<tr>
<td>T1 slope (°)</td>
<td>Pre-op</td>
<td>21.5 ± 5.7</td>
<td>21.2 ± 11.1</td>
</tr>
<tr>
<td></td>
<td>Post-op</td>
<td>21.5 ± 6.8</td>
<td>24.4 ± 8.9</td>
</tr>
<tr>
<td></td>
<td>Final follow-up</td>
<td>22.7 ± 6.5</td>
<td>20.9 ± 9.1</td>
</tr>
<tr>
<td>C2-7 SVA (cm)</td>
<td>Pre-op</td>
<td>0.9 ± 0.9</td>
<td>1.6 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>Post-op</td>
<td>1.1 ± 1.3</td>
<td>1.6 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>Final follow-up</td>
<td>0.4 ± 1.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.2 ± 0.9</td>
</tr>
<tr>
<td>PIA (°)</td>
<td>Pre-op</td>
<td>95.0 ± 6.7</td>
<td>90.6 ± 11.0</td>
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<tr>
<td></td>
<td>Post-op</td>
<td>82.0 ± 5.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>91.6 ± 10.2</td>
</tr>
<tr>
<td></td>
<td>Final follow-up</td>
<td>86.3 ± 6.8&lt;sup&gt;abc&lt;/sup&gt;</td>
<td>89.5 ± 13.7</td>
</tr>
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</table>

<sup>a</sup>P < 0.05 compared with pre-op.
<sup>b</sup>P < 0.05 compared with post-op.

Pre: Preoperative; Post: Postoperative; O-C2a: Occipital and external acoustic meatus to axis angle; C2Ta: C2 tilting angle; C2-7a: C2-7 angle; SVA: Sagittal vertical axis; PIA: Pharyngeal inlet angle.
physiologic craniocervical neutrality and prevent related complications. This method allows patients to be in a comfortable position when they are awake and allows surgeons to adjust the craniocervical alignment before final fixation and fusion.

However, the results of our study showed that there were no significant changes in O-C2a or C2-7a from before to after OCF surgery. The O-C2a of the patients with craniocervical disorders at the last follow-up was still significantly smaller than that of the asymptomatic volunteers, while the C2-7a of those patients was larger. We considered the main reason to be that we focused on decompression, reduction, and fusion for the treatment of craniocervical disorders but neglected the importance of restoring craniocervical sagittal alignment.

Dysphagia was reported to be one of the most common complications caused by cervical sagittal malalignment after OCF, with an incidence ranging from 9.4% to 26.6%[9,10,19,20]. The mechanisms of postoperative dysphagia after OCF remain unclear and are speculated to be multifactorial. In the present study, O-C2a and PIA decreased significantly in the patients with dysphagia from before surgery to 1 mo after surgery, and the effect remained at the final follow-up, while C2-7a increased 1 mo postoperatively and remained the same at the last follow-up. However, the O-C2a, C2-7a, and PIA of the patients without dysphagia were comparable pre- and postoperatively. Pearson’s correlation test showed that postoperative O-C2a values correlated significantly with C2-7a and PIA values. Our results were consistent with those of previous reports describing the relationship between CSA and postoperative dysphagia after OCF[10,19,20]. Based on these results, we assume that the mechanism by which postoperative dysphagia is caused by a reduction in O-C2a is as follows: When O-C2a decreases after OCF surgery, the degree of subaxial lordosis (C2-7a) increases to compensate for the decrease in occipitocervical lordosis so that the individual can maintain a horizontal gaze. Then, the apex of cervical spine lordosis protrudes anteriorly (PIA↓), which can compress and narrow the oropharyngeal space directly and lead to dysphagia (Figure 2).

Previous studies evaluated many factors that might lead to postoperative dysphagia, such as O-C2a, fused segments, age, pathologies, and subaxial cervical positioning[19,21]. However, O-C2a was the only significant independent variable correlated with dysphagia. Consequently, operative positioning of O-C2 is the most effective way to avoid postoperative dysphagia. Bagley et al[18] advocated that preoperative halo immobilization might allow patients to have their head fixed in a particular position and prevent dysphagia. Wang et al[9] and Meng et al[11] recommended that surgeons avoid O-C2a reductions greater than 5° during OCF surgery to prevent postoperative dysphagia. Huang and Gonda et al[21,22] attempted to maintain patients’ head and neck neutrality by an algorithm based on the comparison of pre- and intraoperative X-rays and CT scans.

Our study has limitations. Although we found that the O-C2a, C2-7a, and PIA could not be corrected to the normal range by OCF while neglecting craniocervical realignment, we did not find a good method of restoring physiologic occipitocervical alignment in patients with CJDs. To date, there is no consensus on the best method to reestablish occipitocervical sagittal alignment because of its complexity. Many factors should be taken into account to restore optimal alignment, such as the duration of the craniocervical disease, cervical motions in different directions, the influence of the intraoperative position, variations across different techniques, and the impact on adjacent segments[19]. Therefore, more studies focusing on the basic biomechanics of the occipitocervical junction, the development of new instrumentations and techniques, and individualized treatment to restore ideal occipitocervical alignment are needed in the future. Moreover, our study was also limited by the retrospective nature and short follow-up period. Therefore, additional prospective studies with more patients and longer follow-up periods are needed to investigate both the clinical and radiographic outcomes of OCF patients.

CONCLUSION

Compared to a normal age-matched control population, patients with CJDs have a more kyphotic upper CSA and a more lordotic lower CSA. The effectiveness of the restoration of CSA provided by OCF surgery may be limited by the realignment of the craniocervical junction being neglected. The reduction in O-C2a after OCF surgery may increase C2-7a and decrease PIA.
Figure 2 A 43-year-old woman developed dysphagia after occipitocervical fusion surgery. A: The preoperative O-C2 angle (O-C2a), C2-7 angle (C2-7a) and pharyngeal inlet angle (PIA) were 11.1°, 10.8°, and 93.8°, respectively; B: The O-C2a and PIA decreased to -9.3° and 81.5°, respectively, while the C2-7a increased to 42.9° 1 mo postoperatively; C: At the 1-year follow-up, the O-C2a, C2-7a, and PIA were -8.9°, 38.2°, and 83.7°, respectively. O-C2a: O-C2 angle; C2-7a: C2-7 angle; PIA: Pharyngeal inlet angle.

ARTICLE HIGHLIGHTS

Research background
The studies regarding sequential changes of cervical sagittal alignment (CSA) after occipitocervical fusion (OCF) were limited.

Research motivation
The comprehension of sequential changes of CSA after OCF can help surgeons prevent postoperative complications after OCF.

Research objectives
To compare the CSA of patients with craniocervical junction disorders (CJDs) with that of normal controls and investigate the sequential changes in the CSA of the upper and lower cervical spine after OCF.

Research methods
Radiographic parameters including the occipital to C2 angle (O-C2a), occipital and external acoustic meatus to axis angle (O-EAa), C2–7 angle (C2-7a), and pharyngeal inlet angle (PIA) of the selected patients were measured and compared pre- and postoperatively.

Research results
The O-C2a and PIA of the OCF group were smaller than those of the control group, while their O-EAa and C2-7a values were larger than those of the normal controls. There were significant correlations between the O-C2a and C2Ta, C2-7a, C2-7 sagittal vertical axis (SVA), and PIA at 1 mo after OCF surgery and between O-C2a and O-EAa, C2Ta, C2-7a, C2-7 SVA, and PIA at the final follow-up.

Research conclusions
Patients with CJDs have a more kyphotic upper CSA and a more lordotic lower CSA than normal controls. The effectiveness of OCF surgery in restoring CSA may be limited by the realignment of the craniocervical junction being neglected. The reduction in O-C2a after OCF surgery may increase C2-7a and decrease PIA.

Research perspectives
This study provides novel insights for sequential changes of CSA after OCF.
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176 [PMID: 19412018 DOI: 10.1097/BSD.0b013e318168be6f]


Retrospective Study

Importance of the creation of a short musculofascial tunnel in peritoneal dialysis catheter placement

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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 obtained after each patient agreed to treatment by written consent.

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

Data sharing statement: No additional data are available.

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Abstract

BACKGROUND
Peritoneal dialysis (PD) catheter migration impedes the efficacy of dialysis. Therefore, several techniques involving additional sutures or incisions have been proposed to maintain catheter position in the pelvis.

AIM
To evaluate the efficacy of creating a short musculofascial tunnel beneath the anterior sheath of the rectus abdominis during PD catheter implantation.

METHODS
Patients who underwent PD catheter implantation between 2015 and 2019 were included in this retrospective study. The patients were divided into two groups based on the procedure performed: Patients who underwent catheter implantation without a musculofascial tunnel before 2017 and those who underwent the procedure with a tunnel after 2017. We recorded patient character-
Peritoneal dialysis (PD) is a widely applied therapy for long-term renal replacement. During PD, a catheter is essential for infusion and drainage of the dialysate. PD catheter implantation is performed by inserting a catheter through the abdominal wall and positioning the tip in the pelvic cavity, which is an ideal drainage site. However, in some patients, the catheter tip may migrate postoperatively, leading to flow dysfunction.

According to the guidelines published by the International Society for Peritoneal Dialysis (ISPD) in 2019[1], a 2.5-cm long musculofascial tunnel beneath the anterior sheath of the rectus abdominis is suggested to orient the catheter tip in the pelvis using the shape-memory of the straight catheter, which was first described in 1981[2]. Nevertheless, there is no current literature comparing the efficacy of this tunneling technique in reducing catheter migration with other procedures. Moreover, several studies[3-5] have described the “traditional” open surgical dissection technique without a musculofascial tunnel. However, those studies reported a higher catheter migration rate in comparison to other modified procedures, in which an additional skin incision[3] or supplementary sutures[5] were needed to “orient” the catheter downward.

In this study, we performed catheter insertion through the abdominal wall without a musculofascial tunnel before 2017 and noticed occasional catheter migration. In addition, postoperative plain abdominal radiographs were reviewed to determine the catheter angle in the event of migration.

RESULTS

The no-tunnel and tunnel groups included 115 and 107 patients, respectively. Compared to the no-tunnel group, the tunnel group showed lesser catheter angle deviation toward the pelvis (15.51 ± 11.30 vs 25.00 ± 23.08, P = 0.0002) immediately after the operation, and a smaller range of migration within 2 years postoperatively (13.48 ± 10.71 vs 44.34 ± 41.29, P < 0.0001). Four events of catheter dysfunction due to migration were observed in the no-tunnel group, and none occurred in the tunnel group. There was no difference in the two-year catheter function survival rate between the two groups (88.90% vs 84.79%, P = 0.3799).

CONCLUSION

The musculofascial tunnel helps maintain catheter position in the pelvis and reduces migration, thus preventing catheter dysfunction.

Key Words: Catheter migration; Peritoneal dialysis; Tenckhoff catheter implantation; Renal replacement

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subsequent year, we introduced the musculofascial tunnel technique as a routine procedure in our center. This retrospective study aimed to examine the efficacy of creating a short musculofascial tunnel beneath the anterior sheath of the rectus abdominis in PD implantation by comparing the catheter migration rates with those of PD implantation following the traditional procedure.

MATERIALS AND METHODS

Patients
We retrospectively analyzed the medical records of patients who underwent PD catheter implantation from 2015 to 2019 at our hospital. The same surgical team performed all of the procedures, and all patients underwent open dissection surgery. Patients were divided into two groups: Patients who underwent catheter implantation without a musculofascial tunnel before 2017 and those who underwent the modified procedure with a tunnel after 2017. This retrospective study was approved by the Research Ethics Committee of NTUH (202106072RINA).

Operation
All patients received local anesthesia with intravenous sedation. The left side was preferred for surgery as the patients might be considered for future kidney transplantation using a right-sided approach. A 2–3-cm vertical incision was made over the lower rectus abdominis, and a small opening was created over the anterior sheath at the lower part of the incision. We then split the rectus abdominis bluntly to open the posterior sheath and peritoneum. After placing a purse-string suture, a 41 cm straight catheter with two cuffs (Covidien, Mansfield, United States) was inserted blindly toward the pelvis. In the no-tunnel group, the catheter was extracted from the rectus abdominis via the same opening in the anterior sheath, and the deep cuff was left in the muscle layer (Figure 1, left). In the tunnel group, we pierced the anterior sheath approximately 1-2 cm superior to the previous opening to extract the catheter and left the deep cuff beneath the sheath (Figure 1, right). A subcutaneous tunnel was created similarly in both groups to exit the site and orient the catheter downward.

Measurement of the catheter angle
Postoperative plain film radiographs were reviewed to determine the angle of the catheter (Figure 2A). The catheter was placed into the pelvis perpendicularly during the procedure (ideal angle 0°). The angle of the catheter was calculated based on the axis of the catheter 5 cm below the deep cuff. All patients underwent radiography on the same day of the operation. We also reviewed all available radiographs taken within 2 years following the implantation. All angles of the catheter direction were recorded. The maximal migration angle was defined as the maximal disparity between any two measurements within the 2 years.

Catheter survival
Overall catheter survival was determined at the time when patients discontinued PD for any reason. Therefore, patients were included if catheter function remained normal, but PD was ceased due to factors not attributed to the catheter itself, such as death, transplantation, personal choice, inguinal hernia, or subsequent abdominal surgery. The data of patients included in this category were censored.

Statistical analysis
Continuous variables are presented as mean ± SD. A two-sample t-test with Welch’s correction was used to compare nominal data sets. Data proportions were compared using Fisher’s exact test. Two-sided P values < 0.05 were considered statistically significant. We presented the data using Kaplan-Meier curves for the overall and functional catheter survival rates and analyzed them using a log-rank test. Statistical analysis was performed using the software GraphPad Prism 9.1.0 (GraphPad Software, LLC, CA, United States).
Table 1 Comparison of baseline characteristics between the “no-tunnel” and “tunnel” groups

<table>
<thead>
<tr>
<th></th>
<th>No-tunnel (n = 115)</th>
<th>Tunnel (n = 107)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr, mean ± SD)</td>
<td>57.03 ± 17.88</td>
<td>58.49 ± 16.38</td>
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</tr>
<tr>
<td>Male, n (%)</td>
<td>64 (55.65)</td>
<td>67 (62.62)</td>
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<tr>
<td>BMI (kg/m², mean ± SD)</td>
<td>23.85 ± 4.27</td>
<td>24.16 ± 4.07</td>
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</tr>
<tr>
<td>Cause of ESRD, n (%)</td>
<td></td>
<td></td>
<td>0.1434</td>
</tr>
<tr>
<td>GN</td>
<td>26 (22.61)</td>
<td>23 (21.50)</td>
<td></td>
</tr>
<tr>
<td>Polycystic kidney</td>
<td>2 (1.74)</td>
<td>5 (4.67)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17 (14.78)</td>
<td>26 (24.30)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>70 (60.87)</td>
<td>53 (49.52)</td>
<td></td>
</tr>
<tr>
<td>History of abdominal surgery, n (%)</td>
<td>22 (19.13)</td>
<td>18 (16.82)</td>
<td>0.7279</td>
</tr>
</tbody>
</table>

* A two-tailed Fisher’s exact test was used for categorical variables, and a two-tailed unpaired t-test was used for continuous variables.

SD: Standard deviation; ESRD: End-stage renal disease; BMI: body mass index; GN: Glomerulonephritis.

Table 2 Events leading to the cessation of peritoneal dialysis

<table>
<thead>
<tr>
<th></th>
<th>No-tunnel (n = 115), n (%)</th>
<th>Tunnel (n = 107), n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low efficiency</td>
<td>4 (3.48)</td>
<td>2 (1.87)</td>
<td>0.6845</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>11 (9.57)</td>
<td>6 (5.61)</td>
<td>0.3186</td>
</tr>
<tr>
<td>Abdominal wall leak</td>
<td>1 (0.87)</td>
<td>(0.93)</td>
<td>&gt; 0.9999</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>1 (0.87)</td>
<td>0 (0.00)</td>
<td>&gt; 0.9999</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>0 (0.00)</td>
<td>2 (1.87)</td>
<td>0.2312</td>
</tr>
<tr>
<td>Personal choice</td>
<td>2 (1.74)</td>
<td>0 (0.00)</td>
<td>0.4984</td>
</tr>
<tr>
<td>Transplantation</td>
<td>4 (3.48)</td>
<td>2 (2.80)</td>
<td>&gt; 0.9999</td>
</tr>
<tr>
<td>Death</td>
<td>4 (3.48)</td>
<td>10 (9.35)</td>
<td>0.0975</td>
</tr>
</tbody>
</table>

* A two-tailed Fisher’s exact test was used for categorical variables.

RESULTS

Demographic data of the patients
This study included 222 patients who underwent PD catheter implantation from 2015 to 2019. Among these patients, 115 underwent the procedure without a musculofascial tunnel before July 2017, and 107 underwent the modified procedure with a tunnel starting from August 2017. There was no difference in age, sex ratio, or primary renal disease incidence between the no-tunnel and tunnel groups (Table 1). In addition, no differences in body mass index or abdominal surgery history were observed between the two groups.

Postoperative position of the catheter
The absolute value of the catheter angle was significantly smaller in the tunnel group than in the no-tunnel group (15.51 ± 11.30 vs 25.00 ± 23.08º, P = 0.0002). Moreover, there were fewer cases of catheter migration greater than 45 in the tunnel group than in the no-tunnel group (1.87% vs 13.04%, P = 0.0018).

Catheter migration in the 2 years following surgery
All patients had at least one radiograph taken in the two-year period following catheter placement. Patients who underwent catheter placement with an associated musculofascial tunnel displayed a significantly lower shift in the catheter angle than the patients who underwent catheter placement without a tunnel (Figure 2B, 13.48 ± 10.71 vs 44.34 ± 41.29º, P < 0.0001), implying that the catheter tip remained more stable.
Figure 1 A schematic presentation of the “no-tunnel” (left) vs the modified “tunnel” methods (right) for catheter implantation.

Figure 2 Comparison of catheter angle and migration. A: Shows the catheter direction on a plain radiograph (upper) and catheter angle deviation (lower). The absolute value of the angle was significantly greater in the no-tunnel group than in the tunnel group (lower, **P = 0.0002** by unpaired t-test); B: The maximal difference in catheter angle. The tunnel group had a smaller range of catheter migration (**P < 0.0001**).

in the pelvic cavity when the musculofascial tunnel was created.

**Catheter complications**

Dysfunction of the catheter due to migration was observed in four patients over the two-year follow-up period, and all affected patients were in the no-tunnel group. In addition, both groups had two cases of catheter obstruction due to omental wrapping. PD was resumed successfully in all four patients following laparoscopic omentectomy.

**Catheter survival**

At the end of the two-year follow-up period, more than 70% of patients in both groups continued PD (Figure 3). The most common reasons for discontinuation were peritonitis and death (Table 2). After censoring the causes of discontinuation that were not attributed to the catheter (mentioned above), we performed a “function” survival analysis of the catheter, which revealed a two-year survival rate of 88.90% and 84.79% in the tunnel and no-tunnel groups, respectively. Although the survival curve seemed superior in the tunnel group, the difference was not statistically significant (**P = 0.3799**).
DISCUSSION

Catheter migration is a common complication following catheter implantation, with a reported incidence of 10%-30% [6,7]. This retrospective study demonstrated that PD catheter orientation was improved by creating a short musculofascial tunnel. Further, this tunnel helped maintain catheter position within the pelvis of all patients throughout a two-year follow-up period. In contrast, four patients in the no-tunnel group (3.4%) experienced catheter dysfunction due to migration.

Various current modifications for open surgery [4,5] involve performing additional incisions or sutures to extend the catheter route, reducing malfunction episodes, and prolonging catheter survival. However, our musculofascial tunnel modification required only a brief extension of surgical time and did not necessitate a significant procedure alteration. In addition, according to our experience, there is no need to make a long skin incision for the tunnel.

Laparoscopic surgery is also a practical method for rectus sheath tunneling or pre-peritoneal tunneling [8] to prevent catheter migration. However, general anesthesia with a muscle relaxant is necessary for laparoscopy, increasing anesthesia-related risk and prolonging perioperative preparation. Moreover, laparoscopic surgery is associated with additional costs for anesthesia and surgical instruments.

We suggest placing the catheter approximately 1.5 cm outside the purse-string suture of the peritoneum with the inner cuff just beneath the anterior fascia. This placement allows the catheter to be well fixed away from the peritoneum, thus preventing possible peritonitis induced by a tissue reaction around the deep cuff [9]. In addition, when discontinuing the use of the catheter, it is easier to remove the inner cuff in the presence of a musculofascial tunnel because the cuff lies superior to the rectus abdominis. On the contrary, the inner cuff is buried deeply in the rectus abdominis near the peritoneum in the no-tunnel method. Thus, increasing the risk of injuring the peritoneum and intestines during removal of the cuff due to extensive dissection.

This study had several limitations. First, this was a retrospective study conducted in a single center. As patients underwent different procedures in two separate periods, bias in patient selection and care was inevitable. However, we compared the patient characteristics between the two groups, and there were no significant differences in terms of kidney disease status and factors related to surgical concerns. In addition, all operations were performed by the same surgical team (Lee CY and Chen CC). Therefore, perioperative preparation and surgical materials remained unchanged throughout the study; thus, we believe that bias was minimal although present. Second, the patients in the study had an average body mass index of 24 kg/m², which is similar to that of most Asians but lower than those of Europeans and Americans [10]. The thickness of subcutaneous adipose tissue is critical for determining incision length, and deep subcutaneous adipose tissue may result in technical difficulty during open surgery. Further investigation involving patients with a high body mass index is needed in the future.
CONCLUSION

The results from this study provide evidence supporting the ISPD guideline for improving the quality of PD care. However, the addition of a short musculofascial tunnel, a simple but usually neglected step in catheter implantation, helped tilt the catheter and orient it downward toward the pelvis, which reduced catheter migration and prevented catheter dysfunction. This preemptive modification does not require specialized training, and therefore, can be readily adopted by surgical teams.

ARTICLE HIGHLIGHTS

Research background
Creation of a musculofascial tunnel is usually neglected in the procedure of peritoneal dialysis catheter implantation.

Research motivation
We would like to see if the tunnel reduces catheter migration.

Research objectives
Patients undergoing peritoneal dialysis implantation with or without a musculofascial tunnel were retrospectively reviewed.

Research methods
Plain film after catheter implantation were reviewed to compare the migration angle.

Research results
Patients with the musculofascial tunnel had lower migration rate.

Research conclusions
Creating of a musculofascial tunnel is an important step for reducing catheter migration.

Research perspectives
Long term follow up is need for the function survival benefit.

ACKNOWLEDGEMENTS

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REFERENCES

Lee CY et al. Musculofascial tunnel for peritoneal dialysis catheter


Retrospective Study

Clinical effect of methimazole combined with selenium in the treatment of toxic diffuse goiter in children

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Author contributions: Zhang XH, Yuan GP, and Chen TL designed and performed the study; Zhang XH, Yuan GP, and Chen TL analyzed the data; all authors contributed to the writing and revising of the manuscript.

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

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: No conflict of interest.

Data sharing statement: No additional data are available.

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

Abstract

BACKGROUND

The incidence of toxic diffuse goiter (Graves’ disease) is higher in adolescents and preschool-aged children, with an upward trend. The incidence at 6–13 years of age is approximately 11.0%, and the incidences in men and women are 7.8% and 14.3%, respectively.

AIM

To explore the clinical effect of methimazole combined with selenium in the treatment of toxic diffuse goiter (Graves’ disease) in children and its effect on serum anti-thyroglobulin antibody (TRAb) and anti-thyroid peroxidase antibody (TPOAb).

METHODS

A total of 103 children with Graves’ disease treated in our hospital from January 2018 to June 2021 were divided into a traditional group and a combined group (15-20 mg methimazole orally given to children) and a combined group (50 µg selenium added on the basis of traditional treatment) according to different treatment methods to explore the therapeutic effects of the two methods and to observe the changes in thyroid volume and serum TRAb, TPOAb, free thyroxine (FT4) and inflammatory factor levels before and after treatment. The time taken for FT4 to return to normal was compared between the two groups.

RESULTS

Treatment was significantly more effective in the combined group than in the traditional group (P < 0.05). The thyroid volumes of the children in the two groups were measured before and after treatment. Thyroid volume decreased significantly after treatment in both groups, and the thyroid volume was significantly lower in the combined group than in the traditional group (P < 0.05). The serum levels of interleukin-6 (IL-6), IL-8, TRAb, TPOAb and FT4 in the two groups were detected before and after treatment. The levels of IL-6, IL-8, TRAb,
TPOAb and FT4 were significantly lower in the combined group than in the traditional group ($P < 0.05$). Follow-up of the children in the two groups showed that compared with the traditional group, it took less time for children in the combined group to return to the normal level ($P < 0.05$).

**CONCLUSION**

Methimazole combined with selenium can effectively treat Graves’ disease in children, reduce the expression of TRAb, TPOAb, FT4 and inflammatory factors, and improve the curative effect. Thus, the combined treatment warrants further clinical research.

**Key Words:** Methimazole; Selenium; Children; Antithyroid globulin; Anti-thyroid peroxidase antibody

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**INTRODUCTION**

Toxic diffuse goiter (Graves) is an organ-specific autoimmune disease accompanied by increased secretion of thyroid hormone. It is the most common autoimmune thyroid disease in children. The main clinical symptoms are goiter, pain, and emotional agitation[1]. The enlarged thyroid gland is symmetrical and has a lobulated appearance. The texture of the enlarged gland is as tough as rubber. Some children will have symptoms of hyperthyroidism, and later symptoms of hypothyroidism may seriously affect the child’s physical and mental health. Therefore, timely and effective diagnosis and treatment are important for the child’s condition and prognosis[2,3]. In recent years, methimazole has been widely used in the clinical treatment of Graves. Methimazole is a thyroid disease drug that inhibits the synthesis of thyroxine and improves thyroid function. However, due to children’s physique and drug control problems[4], side effects of methimazole occur frequently in children. Selenium is an essential trace element for the human body. Selenium is closely related to thyroid gland function and can improve the antioxidant capacity of the thyroid gland and curb hypothyroidism. Selenium can inhibit the activity of thyroid hormone receptors, reduce the probability of thyroid hormone binding, reduce the basal metabolic rate, and inhibit the occurrence and development of thyroid diseases[5].

**MATERIALS AND METHODS**

**General information**

A total of 103 children with Graves’ disease who were treated in our hospital from January 2018 to June 2021 were selected and divided into a traditional group and a
combined group according to their different treatment methods. There were 50 children in the traditional group, including 28 males and 22 females, with an average age of 7.85 ± 1.23 years, a course of 2 to 4 years, and an average course of 2.84 ± 0.31 years. There were 53 children in the combined group, including 26 males and 27 females, with an average age of 7.49 ± 1.21 years, a course of 2 to 4 years, and an average course of 2.91 ± 0.35 years. The inclusion criteria were as follows:[7]: (1) Meet the standards in “Internal Medicine. Endocrinology Division”: (a) Clinical manifestations of thyrotoxicosis; (b) B-ultrasound of the thyroid gland suggesting diffuse thyroid enlargement; (c) Thyroid stimulating hormone is reduced, and free triiodothyronine and free thyroxine (FT4) are elevated; (d) Exophthalmos and other infiltrating eye signs; (e) Anterior tibial mucinous edema; and (f) Positive for thyroglobulin antibody (TRAb) or thyroid stimulating antibody. Criteria (a), (b), and (c) are a necessary diagnosis, and criteria (d), (e), and (f) are an auxiliary diagnosis; (2) First treatment; (3) Age 4-13 years; and (4) Complete information. The exclusion criteria were as follows: (1) Thyroid hyperfunctioning adenoma; (2) Toxic nodular goiter; (3) Transient hyperthyroidism such as subacute thyroiditis, Hashimoto’s disease, painless thyroiditis, etc.; (4) Medical history of malignant thyroid tumor; (5) Previous thyroid surgery or 131 iodine therapy; (6) Reduced white blood cells and impaired liver function; and (7) Other autoimmune diseases.

Treatment and testing methods
Children in the traditional group received 15–20 mg of methimazole (Merck Pharmaceuticals (Jiangsu) Co., Ltd., National Medicine Standard: J20171078), 1 time/d, 7 d/course, for 4–5 courses. If the dose calculated based on the weight of the child exceeded the adult level, the adult dose was usually used. After the clinical symptoms of the child were relieved, the dosage of the drug was reduced.

Children in the combined group received methimazole on the same basis as in the traditional group in combination with 50 µg of selenium (Guangzhou Shanyuantang Health Technology Co., Ltd., approval number: Shijianbei 201744000090) orally, 2 times/d, 7 d/course, lasting 4–5 courses.

Blood was collected from all children before and after treatment for 6 mo. Three milliliters of peripheral venous blood was centrifuged in a KH19A centrifuge (Hunan Kaida Scientific Instrument Co., Ltd.) at 4000 r/min with a radius of 5 cm for 10 min, and serum was collected. The chemiluminescence method was used to detect the expression levels of TRAb and anti-thyroid peroxidase antibody (TPOAb) in children using a kit provided by Mingde Biotechnology Co., Ltd., approval number: Shijianbei 201744000090) orally, 2 times/d, 7 d/course, lasting 4–5 courses.

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Evaluation criteria for effects and indicators
The efficacy evaluation criteria were as follows: markedly effective: disappearance of symptoms, weight gain, normal pulse rate, and normal thyroid function; effective: improved symptoms, weight gain, improved pulse rate, and improved thyroid function; invalid: failure to meet the above criteria.

Statistical analysis
Statistical analysis uses SPSS22.0 software, measurement data uses mean ± SD, multi-group comparison uses analysis of variance, pairwise comparison uses LSD-t test; count data comparison uses χ² test. Inspection level = 0.05.

RESULTS
Comparison of the treatment effect of the two groups of children
Comparing the treatment effect of the two groups of children, it was found that the treatment efficiency of the children in the combination group was significantly higher than that of the control group. In the combination group, 25 children had a significant therapeutic effect, 20 children had an effective value, and the total effective rate was 84.9%. In the traditional group, 16 cases were markedly effective, 14 cases were effective, the total effective rate was 60.0%, and the difference was statistically significant (P < 0.05) (Table 1).
### Table 1: Comparison of therapeutic effects between the two groups, \( n(\%) \)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Markedly effective</th>
<th>Efficient</th>
<th>Invalid</th>
<th>Total effective rate</th>
</tr>
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<tbody>
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<td>25</td>
<td>20</td>
<td>8</td>
<td>45 (84.9)</td>
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<tr>
<td>Traditional group</td>
<td>50</td>
<td>16</td>
<td>14</td>
<td>20</td>
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<td>( \chi^2 )</td>
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<td>( P ) value</td>
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</table>

**Comparison of thyroid volume between the two groups of children before and after treatment**

The thyroid volume of the two groups of children before and after treatment showed that the volumes of both groups of children decreased significantly after treatment, and the thyroid volume of the children in the combination group (6.37 ± 1.06) was significantly lower than that of the traditional group (6.92 ± 1.03) \( (P < 0.05) \) (Table 2).

**Comparison of inflammatory indexes between the two groups of children before and after treatment**

The levels of interleukin-6 (IL-6), IL-8 in the serum of the two groups of children were detected before and after treatment, and it was found that the levels of IL-6, IL-8 in the two groups of children were significantly decreased after treatment, and the levels of inflammatory indexes in the serum of the children in the combination group (6.19 ± 1.26 pg/mL, 293.62 ± 20.93 pg/mL) significantly lower than the traditional group (7.61 ± 1.13 pg/mL, 332.78 ± 87.07 pg/mL) \( (P < 0.05) \) (Table 3).

**Comparison of serum TRAb, TPOAb and FT4 before and after treatment in the two groups of children**

The serum levels of serum TRAb, TPOAb, FT4 in the two groups of children before and after treatment were detected. It was found that serum TRAb, TPOAb, FT4 in the two groups were significantly decreased after treatment, and the TRAb, TPOAb, FT4 levels in the combined group (312.77 ± 44.73 μ/mL, 238.42 ± 83.08 μ/mL, 28.39 ± 4.57 pmol/L) were significantly lower the traditional group (617.61 ± 104.05 μ/mL, 332.78 ± 87.07 μ/mL, 24.63 ± 3.96 pmol/L) \( (P < 0.05) \) (Table 4).

**Comparison of the time taken for FT4 to return to normal in the two groups**

Follow-up of the two groups of children found that, compared with the traditional group, it took less time for the FT4 of the combined group to return to the normal level \( (P < 0.05) \) (Table 5).

**DISCUSSION**

The clinical cause of Graves’ disease has not yet been clarified, but recent studies have reported obvious family clustering phenomena\[^8,9\], suggesting genetic or related factors. In addition, children with the disease often have autoimmune diseases such as anemia, diabetes, and reduced adrenal function. Therefore, it is speculated that environmental factors such as infection and excessive intake of iodide in the diet may also be related to the disease\[^10\].

Very young children with this type of thyroiditis have obvious symptoms of hyperthyroidism. Commonly used medications for children include thyroid hormone preparations, antithyroid drugs, and adrenal cortex hormones\[^11,12\]. In the present study, the effect of the combined treatment was significantly better than that of the traditional treatment, indicating that methimazole + selenium regimen is an effective treatment regimen for Graves’ disease. Methimazole is an antithyroid drug that inhibits the expression of peroxidase in the thyroid, thereby blocking the coupling of the iodide oxidant to tyrosine in the gland and ultimately inhibiting the production of thyroxine and triiodothyronine\[^13\]. Selenium is an electron donor for glutathione peroxidase, which can induce the conversion of oxidized glutathione to reduced glutathione. Supplementing selenium can effectively enhance the antioxidant capacity of the thyroid, remove reactive oxygen intermediates, and reduce oxidative damage to thyroid cells, preventing hypothyroidism and playing a balancing role\[^14\].
The addition of selenium can also reduce the amount of hyperthyroidism medication, avoid excessive treatment and cause hypothyroidism.

TRAb is a thyroglobulin-specific antibody synthesized by the human immune system, and TPOAb is an autoantibody mediated by thyroid peroxidase. Abnormal expression of TRAb and TPOAb is closely related to the occurrence and development of autoimmune thyroid diseases. TRAb and TPOAb are commonly used as clinical markers for the detection of immune disorders[15].

### Table 2 Comparison of thyroid volume between the two groups before and after treatment (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Thyroid volume Before treatment</th>
<th>Thyroid volume After treatment</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint group</td>
<td>53</td>
<td>10.25 ± 3.21</td>
<td>6.37 ± 1.06</td>
<td>8.142</td>
<td>0.000</td>
</tr>
<tr>
<td>Traditional group</td>
<td>50</td>
<td>10.87 ± 3.15</td>
<td>6.92 ± 1.03</td>
<td>8.449</td>
<td>0.000</td>
</tr>
</tbody>
</table>

### Table 3 Comparison of inflammatory indexes between the two groups before and after treatment (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>IL-6 (pg/mL) Before treatment</th>
<th>IL-6 (pg/mL) After treatment</th>
<th>IL-8 (pg/mL) Before treatment</th>
<th>IL-8 (pg/mL) After treatment</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint group</td>
<td>53</td>
<td>13.62 ± 3.56</td>
<td>6.19 ± 1.26</td>
<td>351.47 ± 23.89</td>
<td>293.62 ± 20.93</td>
<td>1.03</td>
<td>0.162</td>
</tr>
<tr>
<td>Traditional group</td>
<td>50</td>
<td>12.93 ± 3.17</td>
<td>7.61 ± 1.13</td>
<td>353.69 ± 23.12</td>
<td>332.78 ± 87.07</td>
<td>6.08</td>
<td>0.004</td>
</tr>
</tbody>
</table>

### Table 4 Comparison of Serum anti-thyroglobulin, anti-thyroid peroxidase antibody, free thyroxine between the two groups before and after treatment (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>TRAb (μ/mL) Before treatment</th>
<th>TRAb (μ/mL) After treatment</th>
<th>TPOAb (μ/mL) Before treatment</th>
<th>TPOAb (μ/mL) After treatment</th>
<th>FT4 (pmol/L) Before treatment</th>
<th>FT4 (pmol/L) After treatment</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint group</td>
<td>53</td>
<td>723.62 ± 124.6</td>
<td>312.77 ± 44.73</td>
<td>429.48 ± 93.89</td>
<td>238.42 ± 83.08</td>
<td>56.54 ± 5.56</td>
<td>28.39 ± 4.57</td>
<td>0.028</td>
<td>0.152</td>
</tr>
<tr>
<td>Traditional group</td>
<td>50</td>
<td>722.93 ± 123.2</td>
<td>617.61 ± 104.05</td>
<td>429.74 ± 93.97</td>
<td>332.78 ± 87.07</td>
<td>56.38 ± 5.07</td>
<td>24.63 ± 3.96</td>
<td>19.51</td>
<td>4.451</td>
</tr>
</tbody>
</table>

### Table 5 Comparison of time taken for free thyroxine to return to normal between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Time to return to normal (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint group</td>
<td>53</td>
<td>90.67 ± 8.54</td>
</tr>
<tr>
<td>Traditional group</td>
<td>50</td>
<td>123.5 ± 15.14</td>
</tr>
</tbody>
</table>

*P < 0.05 vs before treatment.

IL-6: Interleukin-6; IL-8: Interleukin-8.
In the present study, serum TRAb and TPOAb levels decreased in both groups of children after treatment but were significantly higher in the combined treatment group than in the traditional treatment group, indicating that the combined regimen is more advantageous in terms of immune balance than methimazole alone. One possible reason is that methimazole has antioxidant and immunoregulatory functions[16]. Animal experiments show that methimazole inhibits the synthesis of antibodies by B lymphocytes and induces the expression of thyroid-stimulating antibodies in the blood, thereby maintaining suppressor T cells. Selenium deficiency inhibits the expression of CD8+ T cells, enhances the function of helper T cells, causes B lymphocytes to synthesize a large number of antithyroid antibodies, promotes the activation of thyroid peroxidase, and ultimately damages thyroid tissue. Selenium supplementation can effectively improve these pathological and physiological changes [17,18]. In addition, selenium supplementation can effectively enhance the antioxidant capacity of the thyroid gland, reduce thyroid cell damage, inhibit the expression of thyroglobulin and thyroid peroxidase, and improve the immune status of children.

FT4 is commonly used as an indicator of thyroid function in *in vitro* tests[19]. In the present study, the time for FT4 to return to normal levels was shorter in the combined group than in the traditional group, indicating that the combined dosing regimen can effectively restore children's thyroid function. Although eye improvement was observed in both groups of children after treatment, eye protrusion was significantly lower in the combined group than in the traditional group, indicating that the combined drug regimen also effectively improved the symptoms of hyperthyroidism in the children. Studies have shown that selenium supplementation plays an important role in the treatment of thyroiditis in children. On this basis, we found that methimazole + selenium has a significantly higher therapeutic effect than simple selenium supplementation in children to restore immune balance, improve the symptoms of hyperthyroidism, and restore thyroid function[20].

**CONCLUSION**

In summary, methimazole combined with selenium can effectively treat Graves' disease, reduce the expression levels of TRAb and TPOAb, and improve thyroid function in children. This regimen warrants further clinical research.

**ARTICLE HIGHLIGHTS**

**Research background**
Thyroglobulin antibody is a common antibody in the serum of children with autoimmune thyroid disease. Anti-thyroid peroxidase antibody (TPOAb) is an indicator closely related to thyroid immune damage.

**Research motivation**
This study explored the therapeutic effects of the two methods, and to detect the changes in serum anti-thyroglobulin antibody (TRAb) and TPOAb levels of the two groups of children before and after treatment.

**Research objectives**
This study aimed to explore the clinical efficacy of methimazole combined with selenium in the treatment of toxic diffuse goiter (Graves’ disease) in children.

**Research methods**
In this study, 103 children with Graves’ disease treated in our hospital were selected and divided into traditional group and combination group according to the treatment method.

**Research results**
The levels of interleukin (IL)-6, IL-8, TRAb, TPOAb and free thyroxine were significantly lower in the combined group than in the traditional group.

**Research conclusions**
The clinical efficacy of combined therapy provides a solid theoretical basis for Graves’
Zhang XH et al. Methimazole combined with selenium in toxic diffuse goiter

clinical diagnosis and treatment.

Research perspectives
This regimen warrants further clinical research.

REFERENCES


5. Jeong SH, Hong HS, Lee JY. The association between thyroid echogenicity and thyroid function in pediatric and adolescent Hashimoto's thyroiditis. Medicine (Baltimore) 2019; 98: e15059 [PMID: 31094635 DOI: 10.1097/MD.0000000000015985]


Retrospective Study

Clinical study on the minimally invasive percutaneous nephrolithotomy treatment of upper urinary calculi

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Author contributions: Xu XJ and Zhang J contributed equally to this study, and are the co-first authors of this article; Xu XJ, Zhang J and Hou JQ designed this retrospective study; Xu XJ and Zhang J wrote the paper; Xu XJ, Zhang J, Li M and Hou JQ were responsible for sorting the data.

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

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

Conflict-of-interest statement: No conflict of interest.

Data sharing statement: No additional data.

Country/Territory of origin: China

Specialty type: Urology and Nephrology

Provenance and peer review: Original Article

Abstract

BACKGROUND

Upper urinary tract stones are very common in my country, with an incidence of 1% to 5% in the North and an even higher incidence of 5% to 10% in the south. The incidence rate in the south is higher than that in the north, mainly due to the water quality, climate and eating habits of the region. From the perspective of sex, incidence is more likely in males than females. In the high-incidence population, young adults are most prone to stones. Men in the age range of 25 to 40 years are more likely to have stones.

AIM

To observe the therapeutic effect of minimally invasive percutaneous nephrolithotomy (mPCNL) on upper urinary tract stones and its influence on the renal function of patients.

METHODS

Patients with upper urinary tract stones who were treated in our hospital from February 2017 to March 2018 were selected as research subjects and were divided into the PCNL group and the mPCNL group according to the random number table method. The general conditions of the two groups of patients were observed during the perioperative period, and the differences in stone clearance, pain, renal function indicators and complication rates were compared between the two groups to determine whether they were statistically significant (P < 0.05).

RESULTS

The operation time of the mPCNL group was longer than that of the PCNL group (t = -34.392, P < 0.001), and the intraoperative blood loss of the mPCNL group was more than that of the PCNL group (t = 34.090, P < 0.001). There was no difference in renal function indices between the two groups of patients before treatment, and there was no difference in the levels of serum creatinine, β2 microglobulin or retinol binding protein in the mPCNL group after treatment. The visual analog...
INTRODUCTION

Urinary calculi formation is a common clinical urinary disease. It currently ranks first in the incidence of urological diseases. In recent years, the incidence of urinary calculi has increased yearly with changes in modern people’s life pressures and diet. Traditional treatments have been the use of medicine to remove the stones, but their effect is moderate, and relapse is common after these types of treatment[1]. In recent years, surgical treatment has played an important role in the treatment of urinary calculi. Traditional percutaneous nephrostomy surgery is invasive, which can easily cause bleeding and cause greater trauma to patients, especially when larger stones are involved. Many limiting factors inhibit the wide application of this method. In recent years, with the development of minimally invasive technology, microchannel technology has reduced damage to the renal cortex by reducing the size of the nephroscope, which not only ensures the effect of the surgical treatment but also reduces harm to the patients[2]. To further analyze the clinical treatment effect of minimally invasive percutaneous nephrolithotomy (mPCNL) on upper urinary tract stones, this study was performed to provide a basis for clinical guidance.

MATERIALS AND METHODS

General information of the patients

Patients with upper urinary tract stones who were treated in our hospital from February 2017 to March 2018 were selected as the research subjects. The inclusion
criteria were as follows: (1) Adults; (2) Those who were diagnosed with upper urinary tract stones; and (3) Those who had no other serious diseases of the urinary system. The exclusion criteria were as follows: (1) Patients with incomplete clinical data; and (2) Patients with urinary system infection. According to the inclusion and exclusion criteria, a total of 80 study subjects were included, including 40 cases in the PCNL group (22 males and 18 females, aged 30-65 years old, with an average age of 39.02 ± 2.68 years) and 40 cases in the mPCNL group (25 males and 15 females, aged 28-64 years old, with an average age of 39.05 ± 3.12 years old). The two groups of patients were comparable with no obvious differences in general information, such as age and sex. The study was reviewed and approved by the hospital ethics committee.

**Method**

Both groups of patients underwent general anesthesia. After satisfactory anesthesia was achieved, the bladder lithotomy position was taken, an F4-6 ureteral catheter was placed, the patient was moved to a prone position, and the puncture area was determined under ultrasound guidance on the patient’s posterior axillary line, 11th intercostal space, under the 12th rib. A 17.5 g renal puncture needle was used to puncture the renal calyces, after which the needle core was removed and physiological saline was injected through the catheter; the renal passage was established, after which a guide wire was inserted for expansion, and then an F16 peeling sheath was inserted.

**PCNL group:** The condition of the ureter was observed, a dilator was used for dilation, and an F24 working sheath was inserted; the ultrasound energy was set to 80% after inserting the nephroscope, after which ultrasound or pneumatic ballistics was used for lithotripsy, and the calculus in the neck of the kidney was clamped and clipped.

**mPCNL group:** A ureteroscope was used to observe the condition in the kidney, and a pneumatic ballistic probe was used to crush the stones; the larger stones were removed with a foreign body forceps, and an infusion pump was used to discharge the smaller stones sequentially. If necessary, dual-channel lithotripsy treatment was carried out.

After stone removal, the ureteral catheter was withdrawn from both groups. If it was difficult to explore the renal pelvis, a zebra guide wire was inserted into the lumen of the ureteral catheter to expose the position of the renal pelvis. An F5-7 double J tube was inserted anteriorly, and an ostomy tube was inserted for urinary catheterization, resulting in more bleeding. The patient was compressed with a clipped fistula tube to stop the bleeding, hemostatic and anti-infective treatments were given after the operation, and the patient was strictly required to stay in bed.

**Evaluation index**

The general condition of the two groups of patients during the perioperative period was observed, and stone clearance, pain, renal function indicators [serum creatinine (Cr), β2 microglobulin (BMG) and retinol binding protein (RBP)], serum inflammation indicators (interleukin-6, tumor necrosis factor-α, C-reactive protein) and differences in the incidence of complications were compared. The evaluation of visual analog scale (VAS) was carried out by the visual analog scoring method. The specific method was as follows: A 10 cm horizontal line was drawn on paper; one end of the horizontal line was 0, indicating no pain, the other end was 10, indicating severe pain, and the midsection indicated different degrees of pain.

**Statistical analysis**

After data entry, SPSS 11.5 software was used for analysis. Counting and measu-
remanent data are expressed as examples and the mean ± SD, respectively. The comparison of general conditions, pain conditions and renal function indices of the two groups of patients during the perioperative period was analyzed by t-test. The comparison of stone clearance and complication rates between the two groups of patients was statistically processed by the chi-square test, which showed statistical significance ($P < 0.05$).

### RESULTS

**Comparison of the general conditions of the two groups of patients during the perioperative period**

The operation time of the mPCNL group is longer than that of the PCNL group ($t = -34.392, P < 0.001$) and that the intraoperative blood loss is greater than that of the PCNL group ($t = 34.090, P < 0.001$) (Table 1).

**Comparison of renal function indices of the two groups of patients before and after treatment**

There is no difference in renal function indices between the two groups of patients before treatment, and after treatment, there is no difference in the levels of Cr, BMG and RBP in the mPCNL group (Table 2).

**Comparison of pain and clearance rate between the two groups**

Table 3 shows that the VAS score of patients in the mPCNL group was lower than that of the PCNL group ($t = 12.191, P < 0.001$) and that there was no significant difference in the stone clearance rate between the two groups ($\chi^2$ value = 1.013, $P = 0.314$).

**Comparison of the incidence of complications between the two groups**

There is no significant difference in the incidence of urine extravasation, dyspnea, and peripheral organ damage between the two groups ($\chi^2 = 1.053, P = 0.305$) (Table 4).

**Comparison of postoperative recovery of the two groups of patients**

One month after treatment and 3 mo after treatment, the quality of life of patients in the mPCNL group is lower than that of the PCNL group, and the Qmax level is higher than that of the PCNL group. The difference is statistically significant ($P < 0.05$) (Table 5).

### DISCUSSION

Kidney stone formation is a common disease in the urinary system. In recent years, its prevalence has shown an increasing trend. Kidney stones generally occur in the renal pelvis and calyces of patients. When the stone diameter is large, the probability of stone removal is reduced. Some patients may have no clinical signs for a long time. When stones cause obstruction of the patient's urinary system, they cause kidney function damage, which results in long-term renal insufficiency, and thus treatment should be carried out as soon as possible[3,4]. Studies have shown that the factors affecting the formation of stones are relatively large and are related to many factors, such as environment, diet, age, and genetics. On one hand, the stone-forming substances in the urine are in a state of supersaturation, and the substances that promote the formation of stones have increased; on the other hand, renal tubule damage to the epithelial cells leads to stone formation[5]. At present, surgical treatment has become an important method for the treatment of kidney stones. Traditional open surgery is more traumatic for patients and has a slow postoperative recovery. Therefore, with the rapid development of minimally invasive techniques, more options are provided for the treatment of kidney stones[6]. Percutaneous nephrolithotomy is widely carried out in clinical practice, but the blood supply of the human renal cortex is abundant, while the blood supply of the renal medulla is lower. The outer diameter of the traditional standard channel is larger, and kidney damage is serious, so bleeding easily occurs. During this process, the patient’s tolerance is reduced due to prolonged surgery, and the damaged renal parenchyma has greater bleeding. Surgery will cause expansion of the damage, the formation of small blood clots in the bleeding, and changes in renal hemodynamics, which may easily cause the
Table 2 Comparison of renal function indexes of the two groups of patients before and after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Cr (μmol/L) Before therapy</th>
<th>Cr (μmol/L) After treatment</th>
<th>BMG (ng/L) Before therapy</th>
<th>BMG (ng/L) After treatment</th>
<th>RBP (mg/L) Before therapy</th>
<th>RBP (mg/L) After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>124.35 ± 8.11</td>
<td>124.36 ± 7.42</td>
<td>3.16 ± 1.01</td>
<td>3.15 ± 0.22</td>
<td>55.34 ± 5.68</td>
<td>55.38 ± 6.03</td>
</tr>
<tr>
<td>PCNL group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mPCNL group</td>
<td>124.33 ± 7.45</td>
<td>124.37 ± 5.88</td>
<td>3.15 ± 0.98</td>
<td>3.17 ± 0.38</td>
<td>55.32 ± 4.97</td>
<td>55.35 ± 7.49</td>
</tr>
<tr>
<td>t value</td>
<td>0.011</td>
<td>-0.007</td>
<td>0.045</td>
<td>-0.288</td>
<td>0.017</td>
<td>0.020</td>
</tr>
<tr>
<td>P value</td>
<td>0.495</td>
<td>0.497</td>
<td>0.482</td>
<td>0.387</td>
<td>0.493</td>
<td>0.492</td>
</tr>
</tbody>
</table>

mPCNL: Minimally invasive percutaneous nephrolithotomy; Cr: Serum creatinine; BMG: β2 microglobulin; RBP: retinol binding protein.

Table 3 Comparison of pain and clearance rate between the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Case</th>
<th>VAS</th>
<th>Clearance rate, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCNL group</td>
<td>40</td>
<td>3.52 ± 0.61</td>
<td>40 (100.00)</td>
</tr>
<tr>
<td>mPCNL group</td>
<td>40</td>
<td>2.27 ± 0.22</td>
<td>39 (97.50)</td>
</tr>
<tr>
<td>t/χ² value</td>
<td></td>
<td>12.191</td>
<td>1.013</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>&lt; 0.001</td>
<td>0.314</td>
</tr>
</tbody>
</table>

mPCNL: Minimally invasive percutaneous nephrolithotomy; VAS: Visual analog scale.

Table 4 Comparison of the incidence of complications between the two groups of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Case</th>
<th>Urine extravasation</th>
<th>Difficulty breathing</th>
<th>Damage to surrounding organs</th>
<th>Total incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCNL group</td>
<td>40</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>mPCNL group</td>
<td>40</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>χ² value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.053</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.305</td>
</tr>
</tbody>
</table>

mPCNL: Minimally invasive percutaneous nephrolithotomy.

Table 5 Comparison of postoperative recovery of the two groups of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>QOL</th>
<th>Qmax</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mo after treatment</td>
<td>3 mo after treatment</td>
</tr>
<tr>
<td>PCNL group</td>
<td>1.95 ± 0.34</td>
<td>1.76 ± 0.24</td>
</tr>
<tr>
<td>mPCNL group</td>
<td>1.68 ± 0.52</td>
<td>1.55 ± 0.31</td>
</tr>
<tr>
<td>t value</td>
<td>2.749</td>
<td>3.388</td>
</tr>
<tr>
<td>P value</td>
<td>0.007</td>
<td>0.001</td>
</tr>
</tbody>
</table>

mPCNL: Minimally invasive percutaneous nephrolithotomy; QOL: Quality of life.

perfusion fluid to return. The flow causes infectious stones and bacteria to enter the bloodstream, aggravating the damage to the kidneys[7,8].

In this study, a microchannel percutaneous nephrolithotomy was used to treat kidney stones. This method improved the traditional standard channel nephrolithotomy. The expansion channel used in the microchannel was an F14-18, and a ureteroscope was used instead of the nephroscope to allow for the full flexibility of the ureteroscope. Due to the small diameter of the scope, it can enter the renal pelvis and calyces through the fistula, especially for partial renal calyx stenosis, and can pass...
smoothly[9,10]. Microchannel percutaneous nephrolithotomy uses ultrasound guidance to observe the structure of the puncture channel in real time and distinguish the collection system, the renal calyx, and the location of kidney stones, which helps the physician grasp the position of the puncture needle, the puncture angle and the depth and avoid the puncture. This route prevents damage to the nearby pleura and spleen [11-15]. The establishment of an ideal percutaneous renal channel is an important factor for successful stone removal. Clinically, a path with a relatively thin renal cortex and fewer blood vessels should be selected according to the location, size and outflow tract of the stone to establish a puncture channel as long as possible to reach the junction of the target renal calyx, renal pelvis and ureter. It is convenient to maximize the operating angle and facilitate the placement of the double J tube anteriorly[16-18]. Microchannel percutaneous nephrolithotomy can also use an ultrasonic lithotripsy probe to quickly suck the stone fragments and the perfusate out of the body while directly looking at the ultrasonic lithotripsy through the working channel, accelerating the outflow of the perfusate, and effectively reducing the pressure in the renal pelvis. There is no need to repeatedly clamp and remove the stone. By reducing the puncture caliber, reducing the loss of renal cortex and reducing the pressure in the renal pelvis, the stone removal rate is greatly improved[19]. To prevent iatrogenic kidney laceration from causing hemorrhage due to excessive expansion of the mPCNL operation, the needle should be punctured at a suitable position under ultrasound guidance to avoid overextension of the puncture. At the same time, the anesthesiologist can cooperate to maintain the kidney to fix the kidney. Pulmonary inflation allows the kidney to move down and fix it in place, which effectively reduces the difficulty of puncture. At the same time, it can preventively reduce the mucosal congestion and edema caused by stones due to the administration of antibacterial drugs before surgery. At the same time, attention should be given to monitoring the coagulation factors[20].

This study showed that patients in the mPCNL group had a longer operation time than those in the PCNL group and had more intraoperative blood loss than those in the PCNL group, indicating that mPCNL treatment for urinary calculi is more complicated and that blood loss during the operation is greater. After treatment, there was no difference in the levels of Cr, BMG and RBP in the mPCNL group, indicating that the two surgical methods do not have a significant impact on the renal function of patients with urinary calculi. The VAS score of patients in the mPCNL group was lower than that in the PCNL group. There was no significant difference in the stone removal rate between the two groups, indicating that mPCNL can reduce pain in the treatment of urinary calculi. Both methods can effectively remove stones. There was no significant difference in the incidence of urinary extravasation, dyspnea, and peripheral organ damage between the two groups of patients, indicating that the application of mPCNL for the treatment of urinary calculi will not increase the occurrence of complications and is safe to use. The advantage of this study lies in the analysis of the clinical efficacy of the two surgical methods applied to urinary calculi, which provides a basis for further clarifying the choice of treatment options for urinary calculi. The clinical features of the patient’s calculi and the economic situation should be considered for a reasonable selection of surgical options. This study included a limited number of patients, and long-term follow-up observation was not possible. Therefore, further multicenter, large-sample, randomized controlled trials are needed for in-depth demonstration.

CONCLUSION

In summary, mPCNL has a good therapeutic effect on upper urinary tract stones. The stone removal rate is high, and this method will not cause kidney damage or increase the incidence of complications. Thus, it has a good application value.

ARTICLE HIGHLIGHTS

Research background

Upper urinary tract stones are very common in China. However, there are few clinical reports on the impact of minimally invasive percutaneous nephrolithotomy (mPCNL) on patients with inflammatory factors, and because of the different levels of technology, some minimally invasive surgeries have frequent postoperative complications.
**Research motivation**
The authors studied the mPCNL on upper urinary tract stones and its influence on the renal function of patients.

**Research objectives**
This study aimed to observe the therapeutic effect of mPCNL on upper urinary tract stones.

**Research methods**
The authors selected patients as research subjects and were divided into the PCNL group and the mPCNL group.

**Research results**
The Qmax level of the mPCNL group was higher than that of the PCNL group.

**Research conclusions**
mPCNL has a good therapeutic effect on upper urinary tract stones.

**Research perspectives**
The purpose of this study was to further confirm the therapeutic effect of mPCNL in upper urinary calculi.

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**REFERENCES**


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**Xu XJ et al. Minimally invasive percutaneous nephrolithotomy treatment of upper urinary calculi**
Xu XJ et al. Minimally invasive percutaneous nephrolithotomy treatment of upper urinary calculi


Observational Study

Comparison of diagnostic validity of two autism rating scales for suspected autism in a large Chinese sample

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Author contributions: Li Y contributed to conceptualization; Chu JH contributed to draft writing; Li YL, Bian F and Yan RY contributed to data collection; Cui YH contributed to supervision; Cui YH and Li Y contributed equally to this study; all authors have read and agreed to the published version of the manuscript.

Institutional review board statement: Written informed consent will be obtained from the participant and/or their guardian before they were included in this study. The ethics committees of Capital Medical University and Beijing Children's Hospital authorized the protocols used in the present study. The Institutional Review Board (IRB) number is 2019-k-396.

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

Abstract

BACKGROUND
Autism is the most common clinical developmental disorder in children. The childhood autism rating scale (CARS) and autistic autism behavior checklist (ABC) are the most commonly used assessment scales for diagnosing autism. However, the diagnostic validations and the corresponding cutoffs for CARS and ABC in individuals with suspected autism spectrum disorder (ASD) remain unclear. Furthermore, for suspected ASD in China, it remains unclear whether CARS is a better diagnostic tool than ABC. Also unclear is whether the current cutoff points for ABC and CARS are suitable for the accurate diagnosis of ASD.

AIM
To investigate the diagnostic validity of CARS and ABC based on a large Chinese sample.

METHODS
A total of 591 outpatient children from the ASD Unit at Beijing Children’s Hospital between June and November 2019 were identified. First, the Clancy autism behavior scale (CABS) was used to screen out suspected autism from these children. Then, each suspected ASD was evaluated by CARS and ABC. Receiver operating characteristic (ROC) curve analysis was used to compare diagnostic validations. We also calculated the area under the curve (AUC) for both CARS and ABC.

RESULTS
We found that the Cronbach alpha coefficients of CARS and ABC were 0.772 and 0.426, respectively. Therefore, the reliability of the CARS was higher than that of the ABC. In addition, we found that the correlation between CARS and CABS was 0.732. Next, we performed ROC curve analysis for CARS and ABC, which yielded AUC values of 0.846 and 0.768, respectively. The cutoff value, which is associated with the maximum Youden index, is usually applied as a decision threshold. We found that the cutoff values of CARS and ABC were 34 and 67, respectively.
Autism is a neurodevelopmental disorder that occurs in early childhood and results in stereotypical interests, communication deficits, social deficits and repetitive behaviors [1]. Autism spectrum disorder (ASD) has received increasing attention in recent years [2]. Moreover, early diagnosis and intervention play a critical role in the treatment of ASD patients[3]. However, early diagnosis lacks specific biological markers. The diagnosis of ASD was based on a detailed developmental history, parents’ report, observed behavior, and validated screening tools or criteria of the diagnostic and statistical manual of mental disorders, fifth edition (DSM-5)[4,5]. Therefore, clinical assessments are important for diagnosing ASD[4,6,7]. The scales most commonly used to diagnose ASD in children are the autism behavior checklist (ABC) and childhood autism rating scale (CARS).

There are numerous suspected ASD cases (showing one or more symptoms of ASD but no final diagnosis) that originate from community health-service centers and preschools in China, most of whom are initially screened via the Clancy autism behavior scale (CABS)[8]. The cutoff point of 14 for CABS is always used as the criterion for suspected ASD in China. When a suspected ASD case was identified, his or her parents received suggestions to go to a hospital for a final diagnosis. When they reach hospitals for final diagnoses, most of them might undergo further assessments, such as ABC or CARS. According to previous studies on various assessments of ASD, CARS exhibits better diagnostic validation than ABC[9]. However, the diagnostic validations and the corresponding cutoff for CARS and ABC in individuals with suspected ASD remain unclear[4]. Notably, it remains unclear whether CARS is a better diagnostic tool than ABC for suspected ASD in China. Furthermore, it is unclear whether the current cutoff points for ABC and CARS are suitable for the accurate diagnosis of ASD.

Therefore, the purpose of this study was to compare the diagnostic validities of CARS and ABC for suspected ASD, as well as to obtain more updated and appropriate cutoff scores for each assessment scale. For the definition of suspected ASD, we used the CABS as a screening tool with a cutoff score of 14[8]. A receiver operating characteristic curve was used to compare the diagnostic validities of CARS and ABC, as well as the corresponding cutoff determinations. Our present findings provide insights into the usage of optimal assessment scales for suspected ASD in Chinese mental health hospitals.

CONCLUSION
This result indicated that CARS is superior to ABC in the Chinese population with suspected ASD.

Key Words: Suspected autism spectrum disorder; Children; Childhood autism rating scale; Autism behavior checklist; Receiver operating characteristic curve; Cutoff value

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INTRODUCTION
Autism spectrum disorder (ASD) has received increasing attention in recent years [2]. Moreover, early diagnosis and intervention play a critical role in the treatment of ASD[3]. However, early diagnosis lacks specific biological markers. The diagnosis of ASD was based on a detailed developmental history, parents’ report, observed behavior, and validated screening tools or criteria of the diagnostic and statistical manual of mental disorders, fifth edition (DSM-5)[4,5]. Therefore, clinical assessments are important for diagnosing ASD[4,6,7]. The scales most commonly used to diagnose ASD in children are the autism behavior checklist (ABC) and childhood autism rating scale (CARS).

There are numerous suspected ASD cases (showing one or more symptoms of ASD but no final diagnosis) that originate from community health-service centers and preschools in China, most of whom are initially screened via the Clancy autism behavior scale (CABS)[8]. The cutoff point of 14 for CABS is always used as the criterion for suspected ASD in China. When a suspected ASD case was identified, his or her parents received suggestions to go to a hospital for a final diagnosis. When they reach hospitals for final diagnoses, most of them might undergo further assessments, such as ABC or CARS. According to previous studies on various assessments of ASD, CARS exhibits better diagnostic validation than ABC[9]. However, the diagnostic validations and the corresponding cutoff for CARS and ABC in individuals with suspected ASD remain unclear[4]. Notably, it remains unclear whether CARS is a better diagnostic tool than ABC for suspected ASD in China. Furthermore, it is unclear whether the current cutoff points for ABC and CARS are suitable for the accurate diagnosis of ASD.

Therefore, the purpose of this study was to compare the diagnostic validities of CARS and ABC for suspected ASD, as well as to obtain more updated and appropriate cutoff scores for each assessment scale. For the definition of suspected ASD, we used the CABS as a screening tool with a cutoff score of 14[8]. A receiver operating characteristic curve was used to compare the diagnostic validities of CARS and ABC, as well as the corresponding cutoff determinations. Our present findings provide insights into the usage of optimal assessment scales for suspected ASD in Chinese mental health hospitals.
MATERIALS AND METHODS

Participants
A total of 591 outpatient children from the ASD Unit at Beijing Children’s Hospital between June and November 2019 were identified. First, they were initially screened with CABS. The cutoff point of 14 for CABS was always used as the criterion for suspected ASD. Based on these criteria, a total of 117 outpatient children were excluded and 474 were identified as suspected ASD. The total sample size included 407 boys and 67 girls, aged between 18 mo and 14 years (4.1 ± 1.93). Then, each suspected ASD was evaluated by CARS and ABC. Parents filled in the ABC scale. After filling in all of them, the specialist gave the due load score for the items that were answered “yes” according to the provisions of the scale. Then, CARS was assessed by two specialists. Prior to the study, two specialists conducted studies and consistency training on evaluation. Second, the DSM-5 was used to confirm the diagnosis of ASD via more than two attending physicians. They diagnosed or excluded autism based on the parents’ detailed description of the child’s development history, observed behavior, and the DSM-5 criteria for diagnosing autism in children. A total of 399 children were diagnosed with ASD (Figure 1) (a total of 75 suspected ASDs did not meet the DSM-5 criteria).

Assessment scales
The CARS is one of the most widely used autism assessment scales[10]. Several studies assessed the internal consistency of the CARS by measuring Cronbach’s alpha, which resulted in a range of 0.82 to 0.95[11]. Park and Kim[12] investigated the construct validity of the CARS in the context of DSM-5 criteria and found that the two-factor model had good fit indices. It is suitable for children over 18 mo old and exhibits good reliability and validity. The CARS is a clinician-rated questionnaire with four frequency levels from 1 to 4 based on observations of individuals and their corresponding information, such as teacher and/or parents reports[13]. The CARS is a behavioral rating scale, consisting of 15 items, that is invariably used to quantitatively describe the severity of suspected ASD symptoms[14]. According to the CARS manual, ASD is defined as a CARS score of ≥ 30 points. A score of 30 or more strongly indicates the existence of ASD. A score of 30-36 suggests mild symptoms, whereas a score of 37 or above suggests moderate to severe ASD[15].

ABC is a well-established assessment scale for screening and diagnosing ASD, and been successfully used in the differential diagnosis of ASD. There was a preliminary study on the validity of the ABC in 2005. The results showed that ABC was effective in differentiating children with autism from children with language disorders and those without complaints[16]. In addition, Yousefi et al[17] evaluated the psychometric features of the Persian version of ABC and found that the internal consistency was 0.73; they also verified the instrument’s concurrent validity with the Gilliam Autism Rating Scale and the correlation between total scores was 0.94. The ABC scale contains 57 items segmented into five categories: Social and self-help, body and object use, relating, language, and sensory features[18]. Based on the degree of association with pathological behavior, each item is rated four frequency levels from 1 to 4. Calculation of the scores for each of the five domains yields the partial and overall scores for each domain[19]. Based on the sum of these scores, severe behavioral characteristics can then be analyzed. Higher scores indicate more autistic behavioral symptoms. In the present study, we used 68 as the ABC cutoff score since this value has been previously recommended[20].

In addition, there were some studies on the application of CABS[4,21-24]. The results all showed that CABS was highly sensitive to screening autism and autism tendencies. Therefore, CABS is the most commonly used screening tool on the Chinese mainland[24]. For this assessment scale, parents completed the Chinese version of the CABS, which is based on its first edition in 1969[24]. A total of 14 items are included, each of which has three frequency levels: “Never” (score of 0), “Occasionally” (score of 1), and “Frequently” (score of 2)[8]. In the present study, any participant with a total CABS score ≥ 14 was identified as a suspected ASD case.

Procedure
Given that the ABC and CARS were developed in English, we needed to translate these two scales. First, permission to translate and evaluate the psychometric features of the CARS and ABC was obtained from the publisher of the instrument. The original version of the profile was translated into Chinese according to the International Quality of Life Assessment approach. First, the two scales were translated into the
Figure 1 Flowchart of the recruitment of participants in the present study. ASD: Autism spectrum disorder; CABS: Clancy autism behavior scale; ABC: Autism behavior checklist; CARS: Childhood autism rating scale; DSM-5: Diagnostic and statistical manual of mental disorders, fifth edition.

Chinese language by two independent Chinese professionals familiar with special education. The forward translations were compared and discussed in a group meeting of the two translators and two of the authors. Differences were discussed until consensus was reached about the final Chinese version. Then, to examine the equivalence of this translated version with the original version, back-translation to English was performed by a Chinese-English bilingual professional. Third, a committee of 10 professionals including six speech and language pathologists and four child psychiatrists were asked to confirm the validity of the translation and revise the Chinese version.

Statistical analysis
The present study used the statistical package, MedCalc 19.0, for all statistical analyses. We primarily used receiver operating characteristic (ROC)[25] curve analysis to determine the best cutoff values for CARS and ABC and to evaluate the sensitivities, specificities, and accuracies of CARS and ABC[10]. ROC curve analysis was also used to compare diagnostic validations. We also calculated the area under the curve (AUC) for both CARS and ABC. Larger AUCs were indicative of improved prediction efficacies. Each cutoff point and its corresponding sensitivity and specificity were also calculated. A P value < 0.05 was considered to be statistically significant.

Ethical approval
The ethics committees of Capital Medical University and Beijing Children's Hospital authorized the protocols used in the present study. The institutional review board number is 2019-k-396. All of the guardians of the participants offered written informed consent.
RESULTS

Table 1 presents our assessments of ABC and CARS for suspected ASD. The mean and standard deviation (SD) of CARS total scores were 35.72 and 4.10, respectively, while the mean and SD of ABC total scores were 70.05 and 1.19, respectively. According to the results of t tests (both \( P > 0.05 \)), there were no significant differences in CARS or ABC scores between male and female participants. The skewness coefficient and kurtosis coefficient of CARS were 0.99 and 1.39, respectively. In contrast, the skewness coefficient and kurtosis coefficient of ABC were -0.04 and 0.39, respectively.

The most commonly applied measure of scale reliability is the Cronbach’s alpha coefficient (\( \alpha \)), originally developed by Cronbach (1951), which is used for estimating internal consistency[26]. For this coefficient, larger \( \alpha \) values (namely those greater than 0.7) are indicative of higher reliability. We found that the Cronbach alpha coefficients of CARS and ABC were 0.772 and 0.426, respectively (Table 1). Therefore, the reliability of the CARS was higher than that of the ABC. In addition, we found that the correlation between CARS and CABS was 0.732.

Next, we performed ROC curve analysis for CARS and ABC, which yielded AUC values of 0.846 and 0.768, respectively (Figure 2). Notably, ROC curves (AUCs) represent the most commonly applied global index of diagnostic accuracy. The diagnostic capacity of an assessment tool is usually not evaluated by a single number but is instead usually assessed via two or more diagnostic procedures[27]. Diagnosis is generally based on a cutoff or threshold value[28]. It is often recommended that the Youden index be used to define the best cutoff point. The cutoff value, which is associated with the maximum of the Youden index, is usually applied as a decision threshold[29]. Table 2 shows the cutoff scores for ABC and CARS with their corresponding sensitivity and specificity values. The results showed that the differences in AUC values and specificities between CARS and ABC were statistically significant (\( P < 0.05 \)). The false-positive rate (1-specificity) was indicative of a lower misdiagnosis rate[27]. We found that the cutoff values of CARS and ABC were 34 and 67, respectively. For more details see Table 2 and Figure 2.

The negative predictive values (NPVs) and positive predictive values (PPVs) of CARS and ABC are shown in Table 3. The PPV for ASD of a screening test is defined as the proportion of children screened as positive who received an ASD diagnosis divided by the total number of screen-positive cases. PPVs and NPVs are affected by the specificity and sensitivity of the screening tool, as well as by the baseline prevalence of ASD in the population being screened[3]. Moreover, we performed a chi-square test on the PPV and NPV values of ABC and CARS, which revealed that there was no significant difference identified between CARS and ABC.

Based on these results, we suggest the diagnostic procedures for suspected ASD was as follow Figure 3.

DISCUSSION

In this study, we found that the AUC of CARS was larger than that of ABC. This finding suggests that the CARS is better than the ABC in terms of its diagnostic validity for suspected ASD. We also found that the cutoff scores of the CARS and ABC for suspected ASD were 34 and 67, respectively. Sensitivity and specificity values included in criterion-validity measures are known to be particularly helpful in clinical settings[26]. The results of a t test on the specificities between these two assessments also revealed a significant difference, indicating that the specificity of the CARS was higher than that of ABC. Furthermore, we verified that the Cronbach alpha coefficient of CARS was 0.772, while that of ABC was 0.426. This finding suggests that the CARS may be more suitable for diagnosing suspected ASD.

Early diagnosis of ASD plays an important role in the intervention and rehabilitation. However, as the etiology of ASD is not clear, it is difficult to make diagnosis based on biochemical indicators at present. The CARS is one of the most important tools for the assessment of ASD, such that both clinical and research practices often use it[31]. Recently, CARS-2 was exploited based on the original edition of the CARS[32]. CARS-2 (normalized form) is the same as original the CARS, whereas CARS-2-HF (high-functioning form) is a newly developed optional diagnostic for evaluating ASD in children over a certain age and with intelligence quotient (IQ) scores above 80[11]. In this study, we revisited the validation of the CARS and found that it functioned as a better diagnostic than ABC. We also identified an updated cut-off score of the CARS for its further usage in diagnosing suspected ASD.
Table 1 The description of autism behavior checklist and childhood autism rating scale

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean</th>
<th>SD</th>
<th>Kurtosis</th>
<th>Skewness</th>
<th>Cronbach’s α</th>
<th>AUC</th>
<th>AUC (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>70.05</td>
<td>1.19</td>
<td>0.39</td>
<td>-0.04</td>
<td>0.426</td>
<td>0.768</td>
<td>0.727-0.805</td>
</tr>
<tr>
<td>CARS</td>
<td>35.72</td>
<td>4.10</td>
<td>1.39</td>
<td>0.99</td>
<td>0.772</td>
<td>0.846</td>
<td>0.810-0.877</td>
</tr>
</tbody>
</table>

SD: Standard deviation; ABC: Autism behavior checklist; CARS: Childhood autism rating scale; AUC: Area under curve; CI: Confidence interval.

Table 2 The cutoff points and corresponding sensitivity and specificity of autism behavior checklist and childhood autism rating scale

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Sensitivity</th>
<th>95%CI</th>
<th>Specificity</th>
<th>95%CI</th>
<th>+LR</th>
<th>-LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 62</td>
<td>80.45</td>
<td>76.2-84.2</td>
<td>58.67</td>
<td>46.7-69.9</td>
<td>1.95</td>
<td>0.33</td>
</tr>
<tr>
<td>&gt; 63</td>
<td>77.94</td>
<td>73.6-81.9</td>
<td>61.33</td>
<td>49.4-72.4</td>
<td>2.02</td>
<td>0.36</td>
</tr>
<tr>
<td>&gt; 64</td>
<td>76.19</td>
<td>71.7-80.3</td>
<td>65.33</td>
<td>53.5-76.0</td>
<td>2.2</td>
<td>0.36</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>73.68</td>
<td>69.1-77.9</td>
<td>68</td>
<td>56.2-78.3</td>
<td>2.3</td>
<td>0.39</td>
</tr>
<tr>
<td>&gt; 66</td>
<td>72.18</td>
<td>67.5-76.5</td>
<td>69.33</td>
<td>57.6-79.5</td>
<td>2.35</td>
<td>0.4</td>
</tr>
<tr>
<td>&gt; 67</td>
<td>68.17</td>
<td>63.4-72.7</td>
<td>76</td>
<td>64.7-85.1</td>
<td>2.84</td>
<td>0.42</td>
</tr>
<tr>
<td>&gt; 68</td>
<td>63.41</td>
<td>58.5-68.1</td>
<td>80</td>
<td>69.2-88.4</td>
<td>3.17</td>
<td>0.46</td>
</tr>
<tr>
<td>&gt; 69</td>
<td>58.9</td>
<td>53.9-63.8</td>
<td>82.67</td>
<td>72.2-90.4</td>
<td>3.4</td>
<td>0.5</td>
</tr>
<tr>
<td>&gt; 72</td>
<td>48.12</td>
<td>43.1-53.1</td>
<td>82.67</td>
<td>72.2-90.4</td>
<td>2.78</td>
<td>0.63</td>
</tr>
<tr>
<td>&gt; 73</td>
<td>44.36</td>
<td>39.4-49.4</td>
<td>84</td>
<td>73.7-91.4</td>
<td>2.77</td>
<td>0.66</td>
</tr>
<tr>
<td>&gt; 74</td>
<td>41.1</td>
<td>36.2-46.1</td>
<td>85.33</td>
<td>75.3-92.4</td>
<td>2.8</td>
<td>0.69</td>
</tr>
<tr>
<td>CARS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>92.98</td>
<td>90.0-95.3</td>
<td>40</td>
<td>28.9-52.0</td>
<td>1.55</td>
<td>0.18</td>
</tr>
<tr>
<td>&gt; 31</td>
<td>85.46</td>
<td>81.6-88.8</td>
<td>60</td>
<td>48.0-71.1</td>
<td>2.14</td>
<td>0.24</td>
</tr>
<tr>
<td>&gt; 32</td>
<td>78.7</td>
<td>74.3-82.6</td>
<td>76</td>
<td>64.7-85.1</td>
<td>3.28</td>
<td>0.28</td>
</tr>
<tr>
<td>&gt; 33</td>
<td>68.42</td>
<td>63.6-73.0</td>
<td>90.67</td>
<td>81.7-96.2</td>
<td>7.33</td>
<td>0.35</td>
</tr>
<tr>
<td>&gt; 34</td>
<td>57.64</td>
<td>52.6-62.5</td>
<td>94.67</td>
<td>86.9-98.5</td>
<td>10.81</td>
<td>0.45</td>
</tr>
<tr>
<td>&gt; 35</td>
<td>33.33</td>
<td>28.7-38.2</td>
<td>97.33</td>
<td>90.7-99.7</td>
<td>12.5</td>
<td>0.68</td>
</tr>
<tr>
<td>&gt; 36</td>
<td>29.07</td>
<td>24.7-33.8</td>
<td>98.67</td>
<td>92.8-100.0</td>
<td>21.8</td>
<td>0.72</td>
</tr>
<tr>
<td>&gt; 37</td>
<td>1</td>
<td>0.3-2.5</td>
<td>98.67</td>
<td>92.8-100.0</td>
<td>0.75</td>
<td>1</td>
</tr>
</tbody>
</table>

ABC: Autism behavior checklist; CARS: Childhood autism rating scale; CI: Confidence interval; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio.

Table 3 The positive predictive value and negative predictive value for autism behavior checklist and childhood autism rating scale

<table>
<thead>
<tr>
<th>Variables</th>
<th>ABC</th>
<th>CARS</th>
<th>Chi² value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV</td>
<td>93%</td>
<td>95%</td>
<td>1.048</td>
<td>0.306</td>
</tr>
<tr>
<td>NPV</td>
<td>32%</td>
<td>40%</td>
<td>2.243</td>
<td>0.134</td>
</tr>
</tbody>
</table>

ABC: Autism behavior checklist; CARS: Childhood autism rating scale; PPV: Positive predictive value; NPV: Negative predictive value.

One of the advantages of our study is the introduction of the concept of suspected ASD, which differs from concepts offered in previous studies. In China, there is an increasing number of suspected ASDs that have been identified at community health-service centers and preschools [24]. It has been reported that early diagnosis plays a
Figure 2 Receiver operating characteristic curves of autism behavior checklist and childhood autism rating scale. ABC: Autism behavior checklist; CARS: Childhood autism rating scale.

Figure 3 The suggested diagnostic procedures of suspected autism spectrum disorder. ABC: Autism behavior checklist; CABS: Clancy autism behavior scale; CARS: Childhood autism rating scale; ASD: Autism spectrum disorder; DSM-5: Diagnostic and statistical manual of mental disorders, fifth edition.

critical role in improving the outcomes of ASD[33]. In this context, preliminary screening tools are a critical step for the timely diagnosis and intervention of ASD[34]. As a preliminary screening tool, CABS can help childcare physicians, teachers, and parents to quickly screen children with suspected autism[8].

Moreover, most children with suspected ASD require further assessments, such as via ABC and/or the CARS. Based on the results of our present study, we suggest that the CARS may be sufficient for further assessment of suspected ASD. Previous studies have suggested that the cutoff scores of the CARS and ABC for distinguishing autism and non autism are 30 and 68, respectively[17]. However, for patients with suspected ASD, it has been suggested that these previously proposed cutoff values may no longer be accurate. Based on the results of the present study, we suggest a new cutoff value of the CARS (namely, a score of 34) for the diagnosis of suspected ASD. Based on our present findings, we suggest that children with suspected ASD be initially screened via CABS and that any suspected cases be further confirmed via CARS.

Based on clinically suspected children with ASD in the present study, we found that the diagnostic validation of CRAS was better than that of ABC. Although previous studies have confirmed the strength of the CARS, the sample sizes have been limited [8]. In the present study, we confirmed that the CARS may be more suitable than ABC for diagnosing ASD in China, especially for suspected ASD[12]. However, there are few qualified physicians after receiving training in this examination method in China. We need a scale that is relatively simple and easy to operate to quickly screen suspected autistic patients.
It should be noted that the only available means of ASD diagnosis are behavioral assessments rather than blood tests or noninvasive assessments\[35\]. Furthermore, to conduct the most comprehensive evaluation of ASD, different measurement tools are required in different assessment environments. The CARS is a valid and reliable assessment tool that is used for the diagnosis and screening of ASD in a number of countries\[5\]. As mentioned above, the main purpose of this study was to explore the diagnostic validation of the CARS in a large Chinese sample. Our results further confirmed that the CARS can effectively and efficiently diagnose patients with suspected ASD. Therefore, to comprehensively evaluate ASD, we recommend the combined use of the CABS and CARS, which might improve the efficiency of clinical work in hospitals.

Three specific limitations needed to be addressed. First, the adult ASD group was not included in this study, and future studies should clarify the diagnostic validation of ABC and CARS in different age groups. Second, although a total of 474 outpatients were included in this study, the sample was still small. A large sample of ASD is needed to confirm these results in future studies. Third, CARS-2 has been well developed\[36\], but there is currently no Chinese version of CARS-2. More new tools for the assessments of ASD in China are needed, especially the original tools designed by a Chinese researcher in a Chinese setting.

**CONCLUSION**

This study demonstrated that the CARS was superior to the ABC in terms of its diagnostic validity in assessing suspected ASD cases in children. In the clinical evaluation for suspected ASD, our findings suggest that the cutoff values of CARS and ABC were 34 and 67, respectively. Based on our results, we recommend that the CARS could be used for assessments of suspected ASD cases in Chinese hospitals.

**ARTICLE HIGHLIGHTS**

**Research background**

Autism is the most common clinical developmental disorder in children. The childhood autism rating scale (CARS) and autism behavior checklist (ABC) are the most commonly used assessment scales for diagnosing autism. However, the diagnostic validations and the corresponding cutoffs for CARS and ABC in individuals with suspected autism spectrum disorder (ASD) remain unclear. Furthermore, for suspected ASD in China, it remains unclear whether CARS is a better diagnostic tool than ABC. Also unclear is whether the current cutoff points for ABC and CARS are suitable for the accurate diagnosis of ASD.

**Research motivation**

According to previous studies on various assessments of ASD, CARS exhibits better diagnostic validation than ABC. However, the diagnostic validations and the corresponding cutoff values for CARS and ABC on individuals with suspected ASD remain unclear. Furthermore, for suspected ASD in China, it remains unclear whether CARS is a better diagnostic tool than ABC. Furthermore, it is unclear whether the current cutoff points for ABC and CARS are suitable for the accurate diagnosis of ASD.

**Research objectives**

The purpose of this study was to compare the diagnostic validities of CARS and ABC for suspected ASD, as well as to obtain more updated and appropriate cutoff scores for each assessment scale. Our present findings provide insights into the usage of optimal assessment scales for suspected ASD in Chinese mental health hospitals.

**Research methods**

A total of 591 outpatient children from the ASD Unit at Beijing Children’s Hospital between June and November of 2019 were identified. First, the CABS was used to screen out suspected autism from these children. Then, each suspected ASD was evaluated by CARS and ABC. Receiver operating characteristic curve analysis was used to compare diagnostic validations. We also calculated the area under the curve for both CARS and ABC.
Research results
In this study, we found that the CARS is better than the ABC in terms of its diagnostic validity for suspected ASD. Furthermore, we verified that the diagnostic reliability of the CARS is better than the ABC in terms of the Cronbach alpha coefficient for suspected ASD. We also found that the cutoff scores of the CARS and ABC for suspected ASD were 34 and 67, respectively. These findings suggest that the CARS may be more suitable for diagnosing suspected ASD. However, there are three specific limitations were need to be addressed. First, the adult ASD group was not included in this study, and future studies should clarify the diagnostic validation of ABC and CARS in different age groups. Second, although a total of 474 outpatients were included in this study, the sample was still small. A large sample of ASD is needed to confirm these results in future studies. Third, CARS-2 has been well developed, but there is currently no Chinese version of CARS-2. More new tools for the assessments of ASD in China are needed, especially the original tools which designed by Chinese researcher in a Chinese setting.

Research conclusions
This study demonstrated that the CARS was superior to the ABC in terms of its diagnostic validity in assessing suspected ASD cases in children. In the clinical evaluation for suspected ASD, our findings suggest that the cutoff values of CARS and ABC were 34 and 67, respectively. Based on our results, we recommend that the CARS could be used for assessments of suspected ASD cases in Chinese hospitals.

Research perspectives
First, future studies should clarify the diagnostic validation of ABC and CARS in different age groups as the adult ASD group was not included in this study. Furthermore, CARS-2 (normalized form) is the same as the original CARS, whereas CARS-2-HF (high-functioning form) is a newly developed optional diagnostic for evaluating ASD in children over a certain age and with IQ scores above 80. We can introduce and verify the reliability and validity of CARS-2 for its further usage in diagnosing suspected ASD in China. More new tools for the assessments of ASD in China are needed, especially the original tools which designed by Chinese researcher in a Chinese setting.

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**Observational Study**

**Doctor-led intensive diet education on health-related quality of life in patients with chronic renal failure and hyperphosphatemia**

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**Author contributions:** Feng XD and Tang GZ design the experiment; Xie X drafted the work, Li F and He R collected the data; Feng XD, Li F and He R analysed and interpreted data, Feng XD and Tang GZ wrote the article.

**Institutional review board statement:** This study was approved by the Chengdu Second People’s Hospital Ethics Committee.

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

**Conflict-of-interest statement:** The authors declared that there is no conflict of interest between them.

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

**Country/Territory of origin:** China

**Specialty type:** Urology and Nephrology

**Provenance and peer review:**

**Abstract**

**BACKGROUND**

Secondary hyperparathyroidism, renal osteodystrophy, and cardiovascular adverse events can occur if long-term hyperphosphatemia is not corrected, leading to the adverse prognosis of patients with chronic renal failure. Besides the use of phosphorus binders, clinical control measures for hyperphosphatemia in these patients should also incorporate diet control.

**AIM**

To observe doctor-led intensive diet education effects on health-related quality of life in patients with chronic renal failure and hyperphosphatemia.

**METHODS**

We assessed 120 patients with hyperphosphatemia and chronic renal failure on hemodialysis admitted to our hospital (July 2018 to March 2020). The control group (n = 60) was given routine nursing guidance, and the observation group (n = 60) was given doctor-led intensive diet education. The changes in EQ-5D-3L scores, disease-related knowledge, and compliance scores before intervention and 3 and 6 mo after intervention in the two groups were recorded. The levels of serum parathyroid hormone (iPTH), calcium (Ca), phosphorus (P), calcium-phosphorus product (Ca × P), serum creatinine (Scr), and blood urea nitrogen (BUN) before intervention and 3 and 6 mo after intervention in the two groups were assessed along with patient satisfaction.

**RESULTS**
There was no significant difference in blood iPTH, Ca, P, Ca × P, Scr, or BUN levels between the groups before intervention. After 3 and 6 mo of intervention, the blood iPTH, Ca, P, and Ca × P levels in the two groups decreased gradually (P < 0.05), but there were no significant differences in Scr or BUN. The blood iPTH, Ca, P, and Ca × P levels in the observation group were lower than those in the control group (P < 0.05). The satisfaction rate in the observation group after 3 mo was 93.33% and after 6, 90.00%, which was high compared with the 80.00% and 71.67%, respectively, in the control group (P < 0.05). There was no significant difference in EQ-5D-3L score between the two groups before intervention. After 3 and 6 mo of intervention, the visual analogue scale score of the two groups increased gradually (P < 0.05); and the scores of action ability, self-care, daily activities, pain and discomfort, and anxiety and depression decreased gradually (P < 0.05). The overall EQ-5D-3L score in the observation group was better than that in the control group (P < 0.05). There was no significant difference in disease-related knowledge or compliance scores between the groups before intervention. After 3 and 6 mo of intervention, the scores of disease, diet, and medication knowledge and compliance in the two groups increased gradually (P < 0.05). The scores of disease-related knowledge and compliance were higher in the observation group than in the control group (P < 0.05).

CONCLUSION
Doctor-led intensive diet education can improve patient satisfaction and the quality of life in patients with chronic renal failure and hyperphosphatemia and promote low-phosphorus diet behavior.

Key Words: Dietary education; Chronic renal failure; Hemodialysis; Hyperphosphatemia; Quality of life; Satisfaction

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Core Tip: Clinical control of hyperphosphatemia in patients with chronic renal failure can be improved with innovative diet interventions. Compared with conventional nursing interventions, doctor-led intensive diet education can better promote patients' mastery of and compliance with health knowledge, and thereby, aid in effective regulation of the balance of calcium and phosphorus in patients' bodies and further improve the quality of patients' lives.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i4.1217

INTRODUCTION
Chronic renal failure is the final stage of kidney disease wherein renal function in patients is almost lost. Therefore, maintenance hemodialysis is needed for renal replacement therapy. Hyperphosphatemia, which is related to renal dysfunction and endocrine changes, is a common complication during treatment[1-4]. The lack of knowledge about hyperphosphatemia in patients with chronic renal failure on hemodialysis affects their rational diet and medication according to doctor’s advice, which directly causes the continuous increase of blood phosphorus levels. Therefore, health education during treatment is necessary[5]. At present, the nursing staff is mostly responsible for the health education of patients. Communication and interaction between doctors and patients is limited, and the content of health education may be poorly remembered. Doctor-led health education can improve the interactions between doctors, nurses, and patients and has a good intervention effect on multiple lifestyle-related diseases[6]. This study observed the effect of doctor-led
intensive diet education on health-related quality of life in patients with chronic renal failure and hyperphosphatemia.

MATERIALS AND METHODS

Baseline data
A total of 120 patients with chronic renal failure and hyperphosphatemia on hemodialysis who were admitted to our hospital between July 2018 and March 2020 were selected as the research subjects. There were 67 male and 53 female patients; their ages ranged from 42 to 70 years, with an average age of 60.25 ± 7.85 years. According to the treatment method, patients were divided into two groups with 60 patients each. As shown in Table 1, no significant difference (P > 0.05) was reported for the general data comparison.

Inclusion and exclusion criteria
Inclusion criteria for our study were defined as follows. (1) In line with the standard of chronic renal failure[7]; (2) Blood phosphorus was ≥ 1.78 mmol/L while phosphate binders were taken; (3) Age was ≥ 18 years but ≤ 70 years; (4) Expected survival period was > 6 mo, the disease was relatively stable, and patient’s understanding ability was good (i.e., the ability to cooperate with the treatment and curative effect evaluation); (5) Hemodialysis treatment was for ≥ 6 mo; and (6) Complete clinical data was available.

Patients were excluded if they had: (1) Chronic renal failure combined with heart failure, severe infection, malignant tumor, or other serious complications; (2) Central nervous system diseases, infectious diseases, or severe depression and anxiety; or (3) A history of diseases that could affect calcium (Ca), phosphorus (P), and parathyroid hormone (iPTH) metabolism.

Methods
The control group was given routine health guidance and publicity materials, such as the Handbook of Health Education for Dialysis Patients. The educational topics reviewed with patients included the causes of hyperphosphatemia in patients on hemodialysis, its clinical manifestations, hazards, treatment drugs, medication precautions, common phosphorus-rich foods, methods to reduce phosphorus intake in the diet, and common food phosphorus/protein ratios. Nursing staff carried out oral education during hemodialysis.

The observation group was given doctor-led intensive diet education on the basis of the control group, and the intensive health instructors included bed doctors and responsible nurses. Doctors gave lectures regularly and organized patients to carry out centralized education, consistent with the Handbook of Health Education for Dialysis Patients. Doctors used common pictures of high phosphorus foods in the form of slides and oral lectures to enhance the understanding and memory of patients and their families. Doctors described ways to reduce phosphorus intake in patients’ daily diets and guidelines for cooking. Types of common phosphate binders, methods of intake, and associated precautions were also introduced. According to the patients’ conditions, examination results, complications, etc., personalized diet guidance was given to encourage patients to ask questions and to answer patients’ questions in detail. A Diet Diary was issued, and patients were asked to record the type and quantity of food consumed for 3 consecutive days. In accordance with their entries, the problems existing in patients’ diets were understood and corrected.

Indices
The changes in EQ-5D-3L scores, disease-related knowledge, and compliance scores before intervention and 3 and 6 mo after intervention in the two groups were recorded. The levels of serum iPTH, Ca, P, calcium-phosphorus product (Ca × P), serum creatinine (Scr), and blood urea nitrogen (BUN) before intervention and 3 and 6 mo after intervention in the two groups were detected, and the satisfaction of the two groups was statistically analyzed.

Detection method
The venous blood of patients under a fasting state and before dialysis was collected before intervention and 3 and 6 mo after intervention. The blood was centrifuged at 3500 r/min for 10 min. Serum was used to detect iPTH with a chemiluminescence
immunoassay analyzer (Roche, E601). The blood Ca, P, Scr, and BUN levels were detected using the 7600 automatic biochemical analyzer and its supporting reagents from Hitachi, Japan. Serum Ca × P levels were subsequently calculated.

### Evaluation standard

EQ-5D-3L scores\(^8\) included the health description system and visual analogue scale (VAS) scores. The health description system included five dimensions: action ability, self-care, daily activities, pain and discomfort, and anxiety and depression. The higher the score, the lower the quality of life in patients. The VAS score was assessed on a 100-point scale. The higher the score, the better the patient’s health status. Disease-related knowledge scores were determined using self-administered questionnaires that covered disease, diet, and medication knowledge of three methods. Each of these aspects was assessed on a 100-point scale. The higher the score, the richer the patient’s disease-related knowledge.

Patients’ compliance scores were assigned based on a self-administered questionnaire and evaluated on a 100-point scale. The higher the score, the better the patient’s compliance. Similarly, patient satisfaction was determined using the self-administered questionnaire and evaluated on a 100-point scale. A total score of 90 was indicative of a rating of “very satisfactory”. The total score was 70-90. A total score < 70 indicated a patient rating of “not satisfactory”.

### Statistical analysis

SPSS Statistics 19.0 software was used to process the data. Measurement indicators were described by mean ± SD. Independent sample \(t\)-test was used to compare data between groups, paired \(t\)-test was used to compare data within groups, and the \(\chi^2\) test was used to compare count data. A \(P\) value of less than 0.05 was statistically significant.

### RESULTS

#### Comparison of blood iPTH, Ca, P, and Ca × P levels between the two groups

There was no significant difference in blood iPTH, Ca, P, or Ca × P levels between the two groups before intervention \((P > 0.05)\). After 3 and 6 mo of intervention, the blood iPTH, Ca, P, and Ca × P levels in the two groups decreased gradually \((P < 0.05)\). Further comparison showed that the blood iPTH, Ca, P, and Ca × P levels in the observation group were lower than those in the control group \((P < 0.05)\) (Table 2).

#### Comparison of renal function indices between the two groups

Before and 3 and 6 mo after intervention, there were no significant differences in Scr or BUN between the two groups \((P > 0.05)\). Further comparison between the observation and control groups showed that there were still no significant differences in Scr and BUN \((P > 0.05)\) (Table 3).
Table 2 Comparison of blood parathyroid hormone, calcium, phosphorus, and calcium-phosphorus product levels between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of examples</th>
<th>Time</th>
<th>Blood, iPTH (pg/mL)</th>
<th>Blood-based Ca (mmol/L)</th>
<th>Blood-P (mmol/L)</th>
<th>Ca × P (mmol²/L²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>60</td>
<td>Before the intervention</td>
<td>379.63 ± 43.25</td>
<td>2.30 ± 0.25</td>
<td>2.15 ± 0.36</td>
<td>4.82 ± 0.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention for 3 mo</td>
<td>312.36 ± 36.21</td>
<td>2.19 ± 0.22</td>
<td>2.02 ± 0.29</td>
<td>4.61 ± 0.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention for 6 mo</td>
<td>295.69 ± 21.44</td>
<td>2.11 ± 0.26</td>
<td>2.05 ± 0.25</td>
<td>4.55 ± 0.56</td>
</tr>
<tr>
<td>Observation group</td>
<td>60</td>
<td>Before the intervention</td>
<td>383.45 ± 42.96</td>
<td>2.28 ± 0.26</td>
<td>2.19 ± 0.33</td>
<td>1.78 ± 0.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention for 3 mo</td>
<td>296.88 ± 28.02</td>
<td>2.11 ± 0.21</td>
<td>1.73 ± 0.31</td>
<td>4.15 ± 0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention for 6 mo</td>
<td>249.63 ± 23.44</td>
<td>2.08 ± 0.26</td>
<td>1.70 ± 0.26</td>
<td>4.08 ± 0.49</td>
</tr>
</tbody>
</table>

*P < 0.05 vs those before intervention in this group.
*dP < 0.05 vs the control group.

iPTH: Serum parathyroid hormone; Ca: Calcium; P: Phosphorus; Ca × P: calcium-phosphorus product.

Table 3 Comparison of renal function indicators between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of examples</th>
<th>Time</th>
<th>Scr (μmol/L)</th>
<th>BUN (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>60</td>
<td>Before the intervention</td>
<td>1120.36 ± 241.36</td>
<td>36.85 ± 10.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention for 3 mo</td>
<td>1055.89 ± 269.33</td>
<td>35.84 ± 9.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention for 6 mo</td>
<td>1078.96 ± 271.54</td>
<td>37.11 ± 12.45</td>
</tr>
<tr>
<td>Observation group</td>
<td>60</td>
<td>Before the intervention</td>
<td>1098.36 ± 269.33</td>
<td>37.32 ± 9.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention for 3 mo</td>
<td>1102.42 ± 301.02</td>
<td>40.02 ± 10.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention for 6 mo</td>
<td>1083.67 ± 274.25</td>
<td>38.96 ± 9.02</td>
</tr>
</tbody>
</table>

*P < 0.05 vs those before intervention in this group.
*dP < 0.05 vs the control group.

Scr: Serum creatinine; BUN: Blood urea nitrogen.

Comparison of satisfaction between the two groups

The satisfaction rate in the observation group after 3 mo of intervention was 93.33% and after 6 mo, 90.00%, which was high compared with the 80.00% and 71.67%, respectively, in the control group (*P < 0.05*) (Table 4).

Comparison of EQ-5D-3L score between the two groups

There was no significant difference in EQ-5D-3L scores between the two groups before intervention (*P > 0.05*). After 3 and 6 mo of intervention, the VAS scores of the two groups increased gradually (*P < 0.05*), and the scores of action ability, self-care, daily activities, pain and discomfort, and anxiety and depression decreased gradually (*P < 0.05*). Further comparison revealed that the overall EQ-5D-3L score of the observation group was better than that of the control group (*P < 0.05*) (Table 5).

Comparison of disease-related knowledge and compliance scores between two groups

There was no significant difference in disease-related knowledge or compliance scores between the two groups before intervention (*P > 0.05*). After 3 and 6 mo of intervention, the scores of disease, diet, and medication knowledge and compliance in the two groups increased gradually (*P < 0.05*). Further comparison revealed that the scores of disease-related knowledge and compliance in the observation group were higher than those in the control group (*P < 0.05*) (Table 6).
<table>
<thead>
<tr>
<th>Group</th>
<th>Number of examples</th>
<th>Time</th>
<th>Very satisfied</th>
<th>Satisfaction</th>
<th>Not satisfied</th>
<th>Satisfaction level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>60</td>
<td>Three months</td>
<td>28 (46.67)</td>
<td>20 (33.33)</td>
<td>12 (20.00)</td>
<td>48 (80.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Six months</td>
<td>34 (56.67)</td>
<td>22 (36.67)</td>
<td>4 (6.67)</td>
<td>56 (93.33)</td>
</tr>
<tr>
<td>Observation group</td>
<td>60</td>
<td>Three months</td>
<td>22 (36.67)</td>
<td>21 (35.00)</td>
<td>17 (28.33)</td>
<td>43 (71.67)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Six months</td>
<td>30 (50.00)</td>
<td>24 (40.00)</td>
<td>6 (10.00)</td>
<td>54 (90.00)*</td>
</tr>
</tbody>
</table>

*P < 0.05 vs the control group.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of examples</th>
<th>Time</th>
<th>Action ability</th>
<th>Self-care</th>
<th>Daily activities</th>
<th>Pain and discomfort</th>
<th>Anxiety and frustration</th>
<th>VAS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>60</td>
<td>Before the intervention</td>
<td>2.03 ± 0.44</td>
<td>2.12 ± 0.51</td>
<td>1.78 ± 0.62</td>
<td>2.16 ± 0.41</td>
<td>2.03 ± 0.52</td>
<td>58.25 ± 12.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention for 3 mo</td>
<td>1.54 ± 0.32*</td>
<td>1.43 ± 0.43b</td>
<td>1.21 ± 0.32*</td>
<td>1.46 ± 0.37a</td>
<td>1.50 ± 0.46a</td>
<td>69.36 ± 7.14a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention for 6 mo</td>
<td>1.56 ± 0.41a</td>
<td>1.42 ± 0.32a</td>
<td>1.26 ± 0.25a</td>
<td>1.38 ± 0.26a</td>
<td>1.44 ± 0.51a</td>
<td>68.23 ± 8.27a</td>
</tr>
<tr>
<td>Observation group</td>
<td>60</td>
<td>Before the intervention</td>
<td>2.01 ± 0.42</td>
<td>2.14 ± 0.47</td>
<td>1.75 ± 0.56</td>
<td>2.12 ± 0.43</td>
<td>2.06 ± 0.47</td>
<td>57.44 ± 12.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention for 3 mo</td>
<td>1.32 ± 0.25d</td>
<td>1.26 ± 0.37c</td>
<td>1.09 ± 0.26d</td>
<td>1.24 ± 0.33c</td>
<td>1.34 ± 0.39c</td>
<td>75.89 ± 6.98c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention for 6 mo</td>
<td>1.33 ± 0.21d</td>
<td>1.22 ± 0.32d</td>
<td>1.05 ± 0.24d</td>
<td>1.25 ± 0.29d</td>
<td>1.29 ± 0.27d</td>
<td>77.02 ± 8.45d</td>
</tr>
</tbody>
</table>

*P < 0.05 vs those before intervention in this group.

\(^b\)P < 0.05 vs the control group.

VAS: Visual analogue scale.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of examples</th>
<th>Time</th>
<th>Disease knowledge</th>
<th>Diet knowledge</th>
<th>Drug-taking knowledge</th>
<th>Compliance</th>
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<tbody>
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<td>60</td>
<td>Before the intervention</td>
<td>52.14 ± 6.14</td>
<td>61.14 ± 5.85</td>
<td>46.96 ± 5.25</td>
<td>58.23 ± 10.02</td>
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<tr>
<td></td>
<td></td>
<td>Intervention for 3 mo</td>
<td>68.96 ± 5.44*</td>
<td>75.36 ± 6.02*</td>
<td>68.11 ± 6.36*</td>
<td>74.01 ± 6.59*</td>
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<td></td>
<td></td>
<td>Intervention for 6 mo</td>
<td>69.23 ± 6.01*</td>
<td>71.45 ± 5.22*</td>
<td>64.25 ± 5.23*</td>
<td>72.85 ± 6.98*</td>
</tr>
<tr>
<td>Observation group</td>
<td>60</td>
<td>Before the intervention</td>
<td>51.92 ± 8.98</td>
<td>60.88 ± 7.23</td>
<td>48.02 ± 6.32</td>
<td>57.96 ± 8.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention for 3 mo</td>
<td>87.12 ± 6.55*</td>
<td>84.96 ± 8.02*</td>
<td>82.55 ± 7.65*</td>
<td>87.55 ± 7.14*</td>
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<tr>
<td></td>
<td></td>
<td>Intervention for 6 mo</td>
<td>86.25 ± 7.12*</td>
<td>84.98 ± 7.96*</td>
<td>85.02 ± 6.44*</td>
<td>86.96 ± 8.05*</td>
</tr>
</tbody>
</table>

*P < 0.05 vs those before intervention in this group.

\(^d\)P < 0.05 vs the control group.

**DISCUSSION**

Hyperphosphatemia is a common metabolic comorbidity in patients on hemodialysis that can stimulate iPTH secretion, aggravate mineral metabolism disorders, cause renal bone disease and skin itching (pruritus), and increase the risk of cardiovascular disease[9]. At present, the clinical treatment of hyperphosphatemia in patients with chronic renal failure mainly proceeds from hemodialysis, the use of intestinal
phosphorus binders, and restriction of dietary phosphorus intake[10].

Blood phosphorus mainly comes from food and is absorbed through the small intestine. Patients on hemodialysis need a high-protein diet due to excessive protein consumption. The high phosphorus content of protein leads to an increase in phosphorus intake. In patients with chronic renal failure, glomerular filtration function decreases, as does the ability to excrete phosphorus. Thus, it is vital to instruct patients to follow a reasonable diet to achieve a balance between protein intake and phosphorus intake.

Although increasing the frequency and duration of dialysis and taking intestinal phosphorus binders can reduce the amount of phosphorus in the blood to a certain extent, such activities still may not work to maintain blood phosphorus within the normal range. Correct diet control is of great importance to reduce blood phosphorus levels[11]. However, most patients lack the knowledge of diet control and cannot achieve satisfactory self-management results. Under conventional intervention methods, the nursing staff is mostly responsible for health education, and measures such as the distribution of publicity materials and oral education between diagnosis and treatment are adopted. However, because of the differences in patients’ understanding capability and educational level, the effect of health education is not ideal[12].

Doctor-led intensive diet education is based on regular health education with doctor interventions, regular lectures, and face-to-face health education with patients via a combination of slides, oral lectures, and pictures to strengthen patients’ disease-related knowledge. This approach can also offer personalized dietary guidance according to the specificities of patients’ situations. Patients can be instructed to make a Diet Diary, based on which problems can be found and corrected. Doctor-led intensive dietary education can enable patients to grasp disease-related knowledge and control their diets[13,14].

In this study, the blood iPTH, Ca, P, and Ca×P levels of those who received doctor-led intensive diet education interventions for 3 and 6 mo were lower than those of patients who received conventional nursing interventions; patient satisfaction of the former group was also higher. However, the levels of Scr and BUN in the two groups were similar. This result suggests that doctor-led intensive diet education can ameliorate the state of Ca and P metabolism disorders in patients with chronic renal failure and hyperphosphatemia and boost patient satisfaction. However, doctor-led intensive diet education does not affect renal function. This result is essentially consistent with the conclusions of the extant research[15-18] and can be explained by the notions that patients often have better compliance with doctors’ requirements, and doctors provide patients with more comprehensive knowledge of dietary phosphorus limits, through more intuitive and specific education models.

The EQ-5D-3L questionnaire is commonly used in clinical settings to evaluate the quality of life in patients with chronic renal failure with good reliability and efficacy[19,20]. This study found that, compared with conventional nursing interventions, doctor-led intensive diet education interventions resulted in patients having VAS scores that were higher for mobility, self-care, and daily activities and lower for pain and discomfort and anxiety and depression, and in higher scores of disease-related knowledge and compliance. These results suggest that doctor-led intensive diet education can advance the quality of life in patients with chronic renal failure and hyperphosphatemia and strengthen disease-related knowledge and compliance.

Chronic renal failure with hyperphosphatemia is unfavorable to the prognosis of patients, and a reduction in blood phosphorus should be emphasized in clinical work. Restricting the intake of phosphorus in patients’ diets is an important way to reduce blood phosphorus. However, the status quo of patients’ knowledge of a reasonable diet with chronic renal failure and the effect of routine health education are not ideal. In this study, doctor-led intensive diet education was used in comparison with routine nursing education; the former can promote patients’ mastery of and compliance with health knowledge and has certain advantages in regulating the balance of Ca and phosphorus in patients’ bodies and improving the quality of patients’ lives. Thus, doctor-led intensive diet education should be popularized and applied.

**CONCLUSION**

Doctor-led intensive diet education can improve the quality of life in patients with chronic renal failure and hyperphosphatemia, promote low-phosphorus diet behavior, and boost patient satisfaction.
ARTICLE HIGHLIGHTS

Research background
Secondary hyperparathyroidism, renal osteodystrophy, and cardiovascular adverse events can occur if long-term hyperphosphatemia is not corrected, leading to the adverse prognosis of patients with chronic renal failure. The clinical control measures for hyperphosphatemia in these patients include diet control.

Research motivation
Provide reference for the treatment of patients with chronic renal failure and hyperphosphatemia.

Research objectives
This study aimed to observe doctor-led intensive diet education effects on health-related quality of life, in patients with chronic renal failure and hyperphosphatemia.

Research methods
We assessed 120 patients with chronic renal failure hemodialysis and hyperphosphatemia admitted to our hospital (July 2018–March 2020). The levels of serum parathyroid hormone (iPTH), calcium (Ca), phosphorus (P), calcium-phosphorus product (Ca × P), serum creatinine (Scr), and blood urea nitrogen (BUN) before intervention and 3 and 6 mo after intervention in the groups were assessed.

Research results
After 3 mo and 6 mo of intervention, the blood iPTH, Ca, P and Ca × P in the two groups decreased gradually, but there was no significant difference in Scr and BUN. The blood iPTH, Ca, P and Ca × P in the observation group were lower than those in the control group. The overall EQ-5D-3L score of the observation group was better than that of the control group. The scores of disease-related knowledge and compliance were higher in the observation group than in the control group.

Research conclusions
Doctor-led intensive diet education can improve the quality of life of patients with chronic renal failure and hyperphosphatemia, promote low-phosphorus diet behavior, and improve patient satisfaction.

Research perspectives
Exploring treatment approaches for patients with chronic renal failure and hyperphosphatemia can provide references for clinical work in the future.

REFERENCES


What are the self-management experiences of the elderly with diabetes? A systematic review of qualitative research

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Abstract

BACKGROUND
The number of elderly individuals with diabetes is dramatically increasing. Diabetes is a long-term condition and a noncommunicable disease and requires intensive daily self-management. Understanding of self-management from the patients’ perspectives is important to nurses, healthcare providers, and researchers and benefits people by improving their self-management skills.

AIM
To examine and synthesize qualitative studies that explore the experiences of elderly people in self-managing diabetes.

METHODS
Electronic databases were searched, including MEDLINE, CINAH, PsycINFO, PubMed, CNKI, and WANFADATA. Relevant research was identified by manually searching reference lists and gray literature. Only English and Chinese publications were included. The Critical Appraisal Skills Program was used to assess the quality of the research. The Confidence in the Evidence from Reviews of Qualitative research approach was used to assess the confidence of the findings.

RESULTS
A total of 10 qualitative studies were included, and content analysis was...
performed. Five themes were identified: The need for knowledge about diabetes care, support systems, functional decline, attitudes toward diabetes, and healthy lifestyle challenges.

**CONCLUSION**

This present review provides a deep and broad understanding of the experiences in the self-management of diabetes and can be valuable to nursing practice and provide recommendations for future research.

**Key Words:** The elderly; Self-management; Diabetes; Experience; Systematic review

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**Core Tip:** In the establishment of strategies that enable the elderly to self-manage diabetes, the particularities of this group need to be addressed. The self-management experiences of the elderly refer to information, social support, physical, attitude, and lifestyle dimensions. To identify the facilitators and barriers of self-management, nurses, healthcare providers, and researchers can develop self-management and education programs for this population.

**Citation:** Li TJ, Zhou J, Ma JJ, Luo HY, Ye XM. What are the self-management experiences of the elderly with diabetes? A systematic review of qualitative research. World J Clin Cases 2022; 10(4): 1226-1241

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i4/1226.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i4.1226

**INTRODUCTION**

Diabetes is a common and long-term disease. The International Diabetes Federation[1] reported that 463 million people have diabetes worldwide. Diabetes is a serious threat to global and individual health. People with diabetes are at risk of developing many serious and life-threatening complications, which can reduce their quality of life, increase the need for medical care, and exacerbate the stress on families[1]. Owing to improvements in medicine, technologies, and healthcare delivery in recent years, the human life span has been extended dramatically[2] and the number of older adults is significantly increasing around the world. By 2050, the number of people who are 60 or older are expected to reach 2 billion[2]. Global aging has imposed a great burden to healthcare[3].

Aging is an important driver of diabetes prevalence because of increased life expectancy and progressively urban lifestyles, making type 2 diabetes a disease associated with old age[4-6]. Diabetes has no known cure and is considered one of this century’s most serious health challenges[7]. Diabetes can cause short- and long-term complications, such as diabetic ketoacidosis, hypoglycemia, cardiovascular diseases, retinopathy, nephropathy, vascular nephropathy, foot complications, and diabetes-related complications of pregnancy[1], placing a heavy burden on social and health services and economies[8]. Owing to the aging process, the situation of complications in elderly people with diabetes can be complex. The American Diabetes Association[9] reported that elderly people with diabetes present higher rates of functional disability, premature death, coexisting illness, accelerated muscle loss, coronary heart disease, stroke, and hypertension than people without diabetes. A study showed that diabetes complications can be more complex to affect elderly individuals than other age groups, with increased functional disability and premature mortality[10]. To delay or prevent the development of diabetes-related complications, effective diabetes self-management and improvements in socio-psychological functions are needed[11], including medical care and personal care behaviors, such as healthy diet, suitable physical activity, self-monitoring of blood glucose levels, engagement with prescribed medication regimens, and self-foot checks[12]. Sub-optimal diabetes self-management can lead to long-term and detrimental multi-system complications such as vascular disorders and neuropathies, disabilities, diabetes-related distress, depression, and mortality[9].
Therefore, self-management and structured education is essential to patients with diabetes. Meanwhile, self-management is considered a greater challenge for elderly people with diabetes, and providing high-quality care to an increasing number of elderly people with diabetes is a significant challenge for health professionals[13]. Previous studies showed that self-efficacy, knowledge, social support, self-regulation, and outcome expectations can affect self-management in elderly people with diabetes [5,14], who are more likely to be affected by geriatric syndromes such as polypharmacy, falls, cognitive impairment, depression, and incontinence, than those without diabetes. This situation further complicates care of elderly people with diabetes[9]. Therefore, self-management can be an essential and challenging issue for elderly individuals with diabetes.

Elderly people with diabetes need special care[15] because they are more likely than younger people to have comorbid chronic conditions that are difficult to manage[16]. A large number of studies have been conducted on the self-management of diabetes, but few focused on the elderly individuals with diabetes. Understanding the experiences regarding the self-management of diabetes is essential. The purpose of the review is to explain the experiences of self-management among the elderly people with diabetes on the basis of current findings.

MATERIALS AND METHODS

This systematic review was registered in PROSPERO (Regd. No. CRD42020135516). The enhancing transparency in reporting the synthesis of qualitative research guidelines (ENTREQ) were used in guiding the current systematic review[17]. The Critical Appraisal Skills Program (CASP) was used in appraising the quality of the included publications[18]. The Confidence in the Evidence from Reviews of Qualitative research (CERQual) approach was used in assessing the confidence of the findings in this review[19]. It is a structured approach to appraisal that requires reviewer judgment and interpretation throughout the approach and was developed by the Cochrane Methods Group. CERQual consists of four components: Methodological limitations, relevance, coherence, and adequacy of the data. For each finding, the confidence was evaluated as high, moderate, low, or very low. The CASP was used in assessing the methodological limitations.

Search strategies

The main citation search involved several key health-related databases: MEDLINE, CINAHL, PsycINFO, PubMed, CNKI, and WANFADATA. All of the databases were accessed on September 20, 2021. We included keyword and subject heading searches. Four search strings were included in the current interview: (Aged OR The elderly OR Geriatric OR Older adult OR Old age OR Senior OR Elderly) AND (Diabetes OR Diabetic) AND (Self-management OR Self-care OR Self-monitoring OR Self-regulation) AND (Qualitative research OR Qualitative study OR Focus group OR Field study OR Grounded theory OR Narrative OR Hermeneutic OR Phenomenological research OR Experience OR Interview). Reference chaining and hand searching for relevant empirical articles were conducted when electronic searches were completed. We searched for gray literature from Google, Google Scholar Electronic These Online Services, INVOLVE, Index to Theses, conference proceedings, and government sites. Owing to language restriction, only English and Chinese publications were included.

Inclusion criteria

All qualitative papers about the experiences and needs of elderly people with diabetes and their perspectives and attitudes toward self-management of diabetes were included. No limitation in the type of qualitative research was placed. The participants had been diagnosed with diabetes, and the focus was on self-management or self-care in individuals aged over 60.

Exclusion criteria

The following papers were excluded: papers that were not qualitative methodologies, primary empirical papers that had not focused on the experience, perception, perspective and attitudes toward self-management of older people with diabetes, papers with secondary evidence (any type of review), papers where the participants do not have diabetes and finally papers not focusing on self-management or self-care in individuals aged over 60.
Study selection
The potential literature then underwent a two-stage screening. First, we screened the titles and abstracts of all the relevant articles. We discussed the results to resolve any disagreement. If disagreements persisted, the publications were included in the full-text review.

Second, the full texts of all the articles selected from the first stage were reviewed by two independent reviewers. Any discrepancy was discussed, and discrepancies that were not resolved by the two reviewers were resolved by a third reviewer. The selection process was summarized with the PRISMA flow chart below[20] (Figure 1).

RESULTS
A total of 10 qualitative studies met the inclusion criteria and were included in the current systematic review. Five were conducted in the United States, one each in China, Brazil, Korea, Singapore, and Australia. Nine of them were published in English, and one in Chinese. The included publications differed in stated focus and aims, but all of them investigated the experiences of elderly people with diabetes with regard to self-management. A total of 170 participants were included. The number of participants for each study ranged from 10 to 31. The target population in each included publication was the elderly, and the age range was 60–85 years. All the participants had been diagnosed with diabetes. For data collection, four studies used focus group interview, four used individual interviews, one used sociopoetics, and one used both focus group and individual interviews. A range of qualitative methods were used, including thematic analysis (n = 5), descriptive methods (n = 1), phenomenology analysis (n = 2), interpretive methods (n = 1), and content-based analysis (n = 1). A summary of the included studies is provided in Table 1.

Quality appraisal
In this systematic review, CASP was used in appraising the quality of the included publications. However, CASP cannot be used in scoring the studies. According to previous research[21], a scoring system was designed. When an answer for a certain item was YES, a score of 1 was given. When the answer was CAN’T TELL, a score of 0.5 was given. When the answer was NO, a score of 0 was given in Table 2.

Many methods are used in managing studies in a systematic review. Some articles may be excluded according to the quality of the research[21-23], or all studies may be included[24,25]. All included publications can be used, and the contributions of the final findings to the review are weighted[26]. In the present review, all papers were used in synthesizing the final findings and further assessing the impact of research quality.

Data extraction and synthesis
In the current systematic review, thematic analysis techniques were used in synthesizing included data and finding key concepts. The thematic analysis process was previously outlined[25]. Three steps were included.

Step 1: Coding the text: We coded the findings from the citations, translated codes and concepts between citations, and put the codes into a code-book line by line.

Step 2: Developing descriptive themes: We examined and analyzed the meaning of the codes and reorganized the codes into related categories.

Step 3: Generating analytical themes: We examined and compared the categories, found the differences and similarities, and merged similar categories into higher-level constructs and themes.

Findings
The main findings for this systematic review were synthesized according to the following themes: Need for knowledge about diabetes care, support system, functional decline, attitudes toward diabetes, and healthy lifestyle challenges.

Eight of the included studies mentioned the need for knowledge. With regard to the interventions, participants stated that the lack of understanding of diabetes self-management remained a major barrier[27]. Some participants had difficulty understanding diabetes care and gaining knowledge about it[28]. Consequently, the participants barely knew how to engage in diabetes self-management[29]. Some participants even unwittingly engaged in high-risk behaviors because of lack of knowledge and because they believed that they should choose their diabetes regimen.
Li TJ et al. Self-management experiences of the elderly with diabetes

| Table 1 Summary of studies and reported study results |
|---------------------------------|-----------------|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Ref.**                         | **Purpose**                                             | **Method**                      | **Study population/setting** | **Data collection** | **Data analysis** | **Major findings** |
| Pamungkas *et al* [35], 2017, Brazil | Identify categories of self-care among older adults with diabetes, considering their physical, mental and spiritual dimensions | Qualitative n = 13; Aged ≥ 60; With diabetes | Method | Difficulties of self-control while living with diabetes; Self-care in living with diabetes and raising self-esteem; Optimism and perseverance in diabetes care; Living peacefully with diabetes; The burden of diabetes in life; Self-care always to live longer and better; Understanding the importance of coexistence with the family; Self-care with the body and the mind; Conscious carelessness; Living happily all of the time |
| Joo and Lee [32], 2016, United States | Explore barriers to and facilitators of diabetes Self-management among first-generation Korean–American elderly immigrants with type 2 diabetes | Qualitative n = 18; Aged ≥ 65; 12 males; 11 females; Diagnosed with type 2 diabetes for at least a year | (1) Focus group interview; and (2) Individual interview | Content-based analysis | High cost of type 2 diabetes care; Language issues; Loss of self-control; Memory loss; Limited access to healthcare resources; Time; Seeking information; Family and peer support |
| Song *et al* [31], 2010, Korea | Identify barriers to and facilitators of self-management Adherence in Korean older adults with type 2 diabetes mellitus | Qualitative n = 24; Aged ≥ 65; 10 males; 14 females; Had been diagnosed with diabetes 12.8 yr before | Focus group interview | Interpretive methodology | Aging-related physical and psychological changes; Restrictions related to specific cultural factors; Lack of self-discipline; Poor understanding of self-management; Knowing the benefits of self-management and having a system to reinforce it; Being the master of oneself by reshaping historical life habits and family support |
| Li *et al* [27], 2013, Singapore | Describe, through qualitative methods, the experiences and ways of coping of older Singaporean Chinese women with type 2 diabetes | Qualitative n = 10; Aged 60–69; 10 females diagnosed with type 2 diabetes | Semi-structured interviews | Thematic analysis | Living with diabetes; Coping with diabetes; Caring for self |
| Bustillos and Sharkey [36], 2020, United States | To study the experiences and challenges of type 2 diabetesSelf-management among homebound older adults who regularly receive home-delivered meals and services | Qualitative n = 31; Aged ≥ 65; Eight males; 23 females; Diagnosed with type 2 diabetes | Semi-structured interviews | Thematic analysis | Perceived seriousness of diabetes relative to other health problems; Perceived self-management; Perceived barriers to self-management; Physical activity; Perceived barriers to self-management: Economic |
| Beverly *et al* [28], 2014, United States | Explore older adults’ values and preferences regarding type 2 diabetes care | Qualitative n = 25; Aged ≥ 60; 11 males; 14 females diagnosed with type 2 diabetes by a doctor at least 1 yr before the study | Focus groups interview | Thematic analysis | Respect and responsiveness to individual values and preferences can foster collaboration in physician–patient treatment relationship and help older adults feel confident that their treatment matches the values and preferences they deem important |
| George and Thomas [30], 2010, United States | Elucidate experiences and perceptions of individuals with diabetes with regard to self-management, as narrated by older people diagnosed with insulin-dependent diabetes living in a rural area | Qualitative n = 10; Aged = 65–85; Diagnosed with type 2 diabetes | Unstructured interviews | Phenomenology analysis | Your body will let you know; I thought I was fine, but I wasn’t; The only way out is to die; You just go on |
| Washington and Wang-Letzkus [37], 2009, United States | Identify risk factors related to lifestyle, attitudes, and health | Qualitative n = 13; Aged ≥ 65; Seven males; Six females; | Focus group interview | Thematic analysis | Positive perceptions and optimistic attitudes will optimise diabetes self-care outcomes |
beliefs, and the influence to self-care practices of Chinese American immigrants

Carolan-Olah and Cassar\cite{33}, 2018
Experience of living with diabetes and factors that facilitated or inhibited access to diabetes services
Qualitative
Diagnosed with type 2 diabetes at least one year before the study
Focus group interview
The value of health; The impact of diabetes; Making changes; Managing diabetes; Access to information and services

Tang et al\cite{29}, 2015, China
To understand the self-management ability of elderly people with diabetes in the rural areas of Jí’ān
Qualitative
n = 13; Eight males; Five females; Aged ≥ 60; Diagnosed with type 2 diabetes
Semi-structured interviews
Lack of related knowledge of diabetes; Unable to change habits; Influence of family social support and health condition

Support system

Two sub-themes were related to support system: Support from the healthcare system and support from social care. Three studies mentioned support from healthcare\cite{28,29,32}. Owing to limited healthcare conditions, participants faced difficulties when accessing healthcare resources, especially in rural areas\cite{24,25,28}. An effective physician–patient relationship was emphasized. The participants were more willing to follow treatment recommendations when they had good relationships with healthcare providers\cite{28}.

Social support associated with diabetes includes diabetes group consultation, peer support, family and friends’ support, and social groups\cite{34}. Support from family was emphasized in the included studies\cite{29,31,32,35}. Support from family is essential to elderly people with diabetes given that they suffer from memory loss and decreased physical activities. It is also a major facilitator of self-management for elderly people, especially when their family members participate in the self-management activities together with them, or help remind them about activities. For example, family members can provide reminders about eating a healthy diet, engaging in physical activity, and taking prescribed medications and also provide financial and emotional support; thus, the participants appreciated support from their families\cite{31,32}. Another study mentioned that some participants felt helpless without the help of their families\cite{29}. The study also mentioned that the elderly with diabetes require additional assistance in daily life, particularly in cooking, transportation, cleaning, and finances, because of their decline in physical health\cite{29,32,36}. This theme shows moderate confidence according to the CERQual assessment and details are presented in Table 3 below.
**Table 2 Critical appraisal skills program score and GRADE-confidence in the evidence from reviews of qualitative research relevance ratings**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>1-Was there a clear statement of the aims of the research?</th>
<th>2-Is a qualitative methodology appropriate?</th>
<th>3-Was the research design appropriate to the aims of the research?</th>
<th>4-Was the recruitment strategy appropriate to the aims of the research?</th>
<th>5-Were data collected in a way that addresses the research issue?</th>
<th>6-Was the relationship between researcher and participants been considered?</th>
<th>7-Were ethical issues considered?</th>
<th>8-Was the data analysis sufficiently rigorous?</th>
<th>9-Was the statement of findings clear?</th>
<th>10-How valuable is the research?</th>
<th>Score</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamungkas et al[35], 2017</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>8.5</td>
<td>I</td>
</tr>
<tr>
<td>Joo and Lee [32], 2016</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>9</td>
<td>R</td>
</tr>
<tr>
<td>Song et al[31], 2010</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>9</td>
<td>R</td>
</tr>
<tr>
<td>Li et al[27], 2013</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>9.5</td>
<td>P</td>
</tr>
<tr>
<td>Bustillos and Sharkey[38], 2020</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>9</td>
<td>R</td>
</tr>
<tr>
<td>Beverly et al [28], 2014</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<td>7</td>
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</tr>
<tr>
<td>George and Thomas[30], 2010</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>9</td>
<td>R</td>
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<tr>
<td>Washington and Wang-Letzkus[37], 2009</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>No</td>
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<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>6.5</td>
<td>P</td>
</tr>
<tr>
<td>Carolan-Olah and Cassar [33], 2018</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Tang et al[29], 2015</td>
<td>Yes</td>
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<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>7.5</td>
<td>R</td>
</tr>
</tbody>
</table>

GRADE-confidence in the evidence from reviews of qualitative research relevance component: I: Indirect relevance; P: Partial relevance; R: Relevant; U: Uncertain relevance.

**Functional decline**

Seven of ten papers mentioned functional decline[27,30-33,36,37], discussing aging-related symptoms, memory loss, joint pain, deterioration of vision, peripheral nerve damage, and weakness, which made self-management challenging for the participants.
<table>
<thead>
<tr>
<th>Summary of review findings</th>
<th>Studies contributing to the review findings</th>
<th>Methodological limitations</th>
<th>Relevance</th>
<th>Coherence</th>
<th>Adequacy</th>
<th>Assessment of confidence in the evidence</th>
<th>Explanation of CERQual assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for knowledge about diabetes care</td>
<td>Eight Studies[27,29-33,35,36]</td>
<td>Minor methodological limitations (six no concerns; two minor concerns)</td>
<td>Minor concerns (one indirect; two partial; five relevant)</td>
<td>Very minor concerns (data very consistent within and across studies)</td>
<td>No concerns (eight studies that offered rich data)</td>
<td>High confidence</td>
<td>Finding graded as high because of the range of studies, richness of data, and relative consistency of the finding in relation to the review question</td>
</tr>
<tr>
<td>Support system</td>
<td>Eight studies[27-29, 31-33,35,36]</td>
<td>Minor methodological limitations (six no concerns; two minor concerns)</td>
<td>Minor concerns (one indirect, three partial, four relevant)</td>
<td>Minor concerns (data very consistent within and across studies)</td>
<td>Minor concerns (Eight studies that together offered data to the two sub-themes)</td>
<td>Moderate confidence</td>
<td>Finding graded as high because of the range of studies, the richness of the data and the relative consistency of the finding in relation to the review question</td>
</tr>
<tr>
<td>Function decline</td>
<td>Seven studies[27,30-33,35,36]</td>
<td>Minor methodological limitations (six no concerns; one moderate concerns)</td>
<td>Minor concerns (three partial; four relevant)</td>
<td>Minor concerns (data consistent within and across studies)</td>
<td>Minor concerns (seven studies that offered moderately rich data)</td>
<td>Moderate confidence</td>
<td>This finding was graded as moderate confidence because of minor concerns regarding methodological limitations, relevance, coherence, and adequacy</td>
</tr>
<tr>
<td>Attitudes toward diabetes</td>
<td>Six Studies[27,30,31,35-37]</td>
<td>Minor methodological limitations (five no concerns; one with moderate concerns)</td>
<td>Moderate concerns (one indirect; two partial; three relevant)</td>
<td>Minor concerns (data consistent within and across studies)</td>
<td>Minor concerns (six studies that offered moderately rich data)</td>
<td>Moderate confidence</td>
<td>This finding was graded as moderate confidence because of moderate methodological limitations and minor concerns regarding relevance, coherence, and adequacy</td>
</tr>
<tr>
<td>Healthy lifestyle challenges</td>
<td>Ten studies[27-37]</td>
<td>Minor methodological limitations (seven with no concerns; two minor concerns; one with moderate concerns)</td>
<td>Minor concerns (one indirect; four partial; five relevant)</td>
<td>Minor concerns (data consistent within and across studies)</td>
<td>No concerns (eight studies that offered rich data)</td>
<td>High confidence</td>
<td>This finding was graded as moderate confidence because of moderate methodological limitations and minor concerns regarding relevance and coherence</td>
</tr>
</tbody>
</table>

CERQual: Confidence in the Evidence from Reviews of Qualitative research.

Owing to memory loss, the participants sometimes forgot to take their prescribed medicines, or were unable to remember whether or not they had taken their prescribed medicines. Some of the participants forgot to take their medicines when they were outdoors, and some forgot to take their medicines altogether. In some instance, they forgot to check their blood glucose levels[32].

Regular exercise is important to people with diabetes; however, owing to frailty, pain, physical limitations, and less self-discipline, participants lack exercise[27,31-33,36]. Moreover, trying to maintain physical activity can increase depressive symptoms because of the pain and difficulty associated with their declining health conditions[33]. Only one study indicated that the included participants were willing to participate in an exercise program[37]. This theme shows moderate confidence according to the CERQual assessment and details are presented in Table 3 below.
Attitudes toward diabetes

Six studies mentioned attitudes toward diabetes\cite{27,30,31,35-37}. Some participants tried to stay happy, optimistic, and peaceful with diabetes. Positive emotions can benefit diabetes self-management\cite{27,35-37}. However, some participants experienced somber thoughts, anxiety, and helplessness, which led to loss of hope and motivation. They knew the risk of diabetes-related complications caused by sub-optimally controlled diabetes. However, they lost control of their lives and their willingness to accept consequences\cite{27,30}. This theme shows low confidence according to the CERQual assessment and details are presented in Table 3 below.

Healthy lifestyle challenges

All of the included studies mentioned healthy lifestyle challenges\cite{27-37}. Some of the participants faced difficulties in making lifestyle changes in their daily lives. In particular, diet and weight control were emphasized. In eight studies, participants indicated that they experienced difficulties in following healthy eating patterns\cite{27,29,31-37}. Their discipline was not high enough to restrict the amount of food they ate\cite{32}. Dietary control is influenced by food cultures\cite{36,37}, but some traditional foods are not healthy choices as they contain high levels of saturated fats, sodium, carbohydrates, and sugars. Three of the included studies mentioned weight issues\cite{31,32,35}. Participants faced difficulties in managing their weight issues, and some indicated that quality of life is important to lifestyle changes\cite{28,30,37}. The participants preferred to maintain traditions, peace, and independence in their lives\cite{28}. This theme shows high confidence according to the CERQual assessment and details are presented in Table 3 below.

DISCUSSION

Ten studies were included in the present review. Five themes related to the experience of self-management of elderly people with diabetes emerged.
First, the need for knowledge about diabetes was a common issue among the elderly with diabetes. Knowledge about diabetes has been considered one of the key determinants of engagement in diabetes self-management practices. Patients who have more knowledge about diabetes are more likely to comprehend their illness, and they are more willing to exhibit self-management behaviors, such as exercise, eating a healthy diet, and testing their blood glucose levels[38]. Another study mentioned that knowledge about diabetes affects the self-management practices of people living with diabetes[39]. The researchers emphasized the importance of diabetes knowledge in self-management practices. They found that patients with more knowledge about diabetes were more likely to control their glucose levels and were less likely to smoke. Researchers speculated that knowledge may be necessary before action is taken[40].

Elderly people with diabetes were more likely to experience cognitive impairment and memory decline when they have suboptimal understanding of diabetes self-management[41,42]. Elderly people with diabetes have difficulty in understanding information from reading resources, formal diabetes self-management education, or other resources; this issue often causes confusion and creates overwhelming feelings and frustration[43,44]. Providing ongoing self-management support to people with diabetes, particularly appropriate support for the elderly, is crucial[45,46].

Second, the support system was considered important. The participants indicated that support from the healthcare system and social care can influence their diabetes self-management. The participants preferred obtaining support from the healthcare system. A person-centered care team with trust-based relationships, shared decision making, and good healthcare provider–patient communication can improve treatment engagement and patient’s satisfaction and ultimately lead to good overall outcome[9,46]. For people with diabetes, healthcare professionals and unpaid informal supporters, such as friends and families, play an essential role in supporting diabetes self-management[47].

Social support can be important to many elderly individuals. For people with diabetes, a high level of social support improves glycemic outcomes and clinical outcomes and reduces HbA1c levels[34,48]. Social support, which includes diabetes group consultations, peer support, family and friends’ support, and social groups, is associated with improved self-care behaviors and knowledge among people with diabetes[34].

Support from family members is a major facilitator of diabetes self-management[49,50]. However, negative forms of communication from family members, particularly nagging, criticizing, and arguing, are associated with worsening glycemic control and low engagement with diabetes self-management[51,52]. Involving family members in diabetes care can be harmful[53,54]. Family members may undermine or sabotage patients’ self-care efforts by questioning the need for medication or by providing unhealthy foods[54]. Therefore, positive support from family is particularly important to self-management of elderly people with diabetes.

Third, the experience of functional decline was mentioned. All the participants were older than 60, which could lead to the physical influence on their diabetes self-management. Compared with young people with diabetes, old patients are at a higher risk of developing physical or cognitive dysfunction or multimorbidity[55]. Furthermore, old patients can face more challenges beyond traditional diabetes-related issues that overlap with the aging process because of age-related diseases. The elderly can experience cognitive dysfunction, which incorporates many domains, such as learning, memory, mental flexibility, executive function, and attention[56]. These behaviors are important when patients are required to do complex tasks, such as recognizing and treating hypoglycemia appropriately, predicting the impact of physical activity on blood glucose levels, and even matching their insulin level with the carbohydrate content of food[56].

Fourth, attitudes toward diabetes are important. Healthcare professionals have to recognize that long-term behaviors are difficult to change or adjust; therefore, healthcare professionals need to understand the factors that are associated with diabetes self-management behaviors[40]. Understanding patients’ attitudes toward their problems requires knowledge about their attitudes that influence reactive behaviors[57].

For people with diabetes, attitudes can play an important role in their emotional responses and affect their efforts in the self-management of diabetes in daily life[40]. People with positive attitudes toward the self-management of diabetes are more likely to adjust their management behaviors and achieve a high level of healthcare; by contrast, people with negative attitudes can inhibit self-management behaviors[57,58]. For instance, attitudes significantly affect dietary choices, and people with a high level of positive attitude show increasing level of self-management in terms of healthy
eating. Positive attitudes also influence the frequency of blood glucose testing\cite{40}. Therefore, creating a high level of positivity to self-manage diabetes is essential because it can lead to effective diabetes self-management and improve quality of life.

Fifth, healthy lifestyle challenges were mentioned. Diabetes has no cure, and it must be controlled with medications and a healthy lifestyle\cite{59}. Healthy lifestyle behaviors include a healthy diet, physical activity, and weight control\cite{60,61}. For people with all types of diabetes and of all ages, achieving an active, healthy lifestyle is an important part of diabetes management\cite{62}. However, changing well-established habits may be difficult for some people with diabetes\cite{63}. Elderly people may have much more difficulty in changing their established lifestyles\cite{64}.

Elderly people with diabetes need to have access to appropriate nutrition and physical activity engagement opportunities\cite{65,66}. Appropriate nutrition behaviors are considered effective approaches for glycemic control\cite{67}. An appropriate diet includes reducing energy intake, increasing fiber intake, lowering carbohydrate intake, eating regular meals, and reducing alcohol consumption\cite{59}. For elderly people with diabetes, nutrition has been highlighted\cite{68}. Muscle mass reduces with age, so elderly people often have reduced energy needs; however, micronutrient and protein needs remain the same, thereby increasing the risk of malnutrition\cite{5}. Therefore, people with diabetes should take a food-based and individualized dietary approach\cite{68}.

Diabetes and increasing age are important independent predictors of loss of independence and disability\cite{69-71}. As age increases, physical activity levels can decline, and such decline increases the risk of ill health, decreases physical function, and increases the risk of falls\cite{72}. However, physical activity is a key strategy for preventing and managing diabetes\cite{2}. Weight loss is important to people with diabetes and can reduce the risk of macro- and microvascular complications and remittent hyperglycemia\cite{73,74}.

**Limitations**

The current review has some limitations. First, it only included studies published in English and Chinese, and thus some relevant articles written in other languages might have been overlooked. Second, the first-hand patient experience was not examined. The authors of qualitative studies may have reported themes they deemed pivotal. Third, the included studies were limited to six countries and few ethnicities, and thus the generalizability of the findings to other countries or cultures is limited.

**CONCLUSION**

The present systematic review aims to improve our understanding of the experiences of elderly people with diabetes with regard to self-management. Nurses are in a prime position to provide support to the elderly with diabetes who are self-managing. The current review found that patients lack knowledge about diabetes. Ongoing support involving the assessment of the knowledge and understanding of diabetes self-management is necessary. We suggest that nurses assess patients’ knowledge and provide diabetes education. Furthermore, the elderly have difficulty in changing well-established habits; therefore, nurses should assess their lifestyles and help them maintain a healthy lifestyle. Considering the unique challenges that may be encountered by elderly individuals, particularly age-related physical changes, cognitive impairment, memory loss, and functional decline is important, and strategies for diabetes self-management improvement should address individual and organizational levels, especially for the elderly with well-established habits. Patients’ attitudes, support from the healthcare system, and social care can have a negative or positive influence on diabetes self-management. Innovative approaches for enabling patients to maintain independence while conducting effective self-management and receiving additional support from the healthcare system, family, and social care with diabetes regimens may be necessary. Nurses, healthcare providers, and researchers should consider adopting interventions when designing diabetes intervention programs for the elderly with diabetes on the basis of the following dimensions: Information, healthcare and social support, physical well-being, attitude, and lifestyle.
**ARTICLE HIGHLIGHTS**

**Research background**
Aging is an important driver of diabetes prevalence worldwide, and the number of elderly individuals with diabetes may reach over 252.8 million by 2035. Compared with other groups, the elderly presents the highest rate of diabetes-related complications. Hence, synthesizing qualitative evidence about experiences in self-management is critical to strategies for elderly individuals with diabetes.

**Research motivation**
Understanding the experiences, expectations, needs, and barriers associated with the self-management of diabetes is essential to the planning and implementation of effective interventions. Compared with young people, elderly people are more likely to develop complications, which are complex and difficult to manage. Many studies on the self-management of diabetes have been conducted, but few focused on the elderly. This review addressed this gap, aiming to examine the self-management experiences of elderly people with diabetes.

**Research objectives**
The current review aimed to (1) Explore the self-management experiences of elderly individuals with diabetes; (2) Provide recommendations for future nursing practice; and (3) Provide recommendations for future research.

**Research methods**
The framework of population, context, and outcome was used in developing the review question. We performed a comprehensive and systematic electronic literature search, using search terms relevant to the self-management experiences of elderly individuals with diabetes. The inclusion and exclusion criteria were based on population, context, outcome, design, and language. Ten studies were included after selection by two independent reviewers. Finally, thematic analysis techniques were used in synthesizing the included studies’ data, and key concepts were identified from the included research.

**Research results**
Five common themes emerged: The need for knowledge about diabetes care, support systems, functional decline, attitudes toward diabetes, and healthy lifestyle challenges.

**Research conclusions**
The current review recommends that healthcare professionals should improve self-management intervention programs for elderly individuals with diabetes and provide person-centered care considering the following dimensions: Information, social support, physical condition, attitude, and lifestyle.

**Research perspectives**
The current review focuses on the experiences of the elderly. Further qualitative studies are needed to explore the experiences of families and healthcare providers given that they are essential to the elderly’s self-management practice. This review highlights the need for high-quality research including different culture settings and ethnic minorities and considering multimorbidity.

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Comparison of the clinical performance of i-gel and Ambu laryngeal masks in anaesthetised paediatric patients: A meta-analysis

Di Bao, Yun Yu, Wei Xiong, Ya-Xin Wang, Yi Liang, Lu Li, Bin Liu, Xu Jin

Abstract

BACKGROUND
Paediatric supraglottic airway devices (SGAs) are widely used in routine anaesthesia and serve as primary or back-up devices for difficult airway management. The inflatable Ambu laryngeal masks and non-inflatable i-gel are two improvements of SGAs based on classic laryngeal masks. The clinical performance and safety of these two devices in paediatric patients are still unclear and warrant further investigation.

AIM
To perform a systematic review and meta-analysis on the clinical performance and safety of Ambu laryngeal masks and i-gel in anaesthetised paediatric patients.

METHODS
MEDLINE, Embase, Web of Science and Cochrane Central Register of Controlled Trials were searched from inception dates to April 2020. We identified published randomised controlled trials (RCTs) in which the intervention involved the use of Ambu laryngeal masks and i-gel in anaesthetised paediatric patients (age < 18 years). We assessed the oropharyngeal leak pressure (OLP) as the primary outcome. The secondary outcomes were insertion time, success rate of insertion, and incidence of adverse events.

RESULTS
After searching for all relevant trials published up to April 2020, data from seven RCTs with a total of 667 paediatric patients (323 and 344 participants in the i-gel and Ambu groups, respectively) were evaluated. The mean OLP in anaesthetised paediatric patients was lower in the Ambu group \[21.82 \text{ cmH}_2\text{O for Ambu} \text{ vs } 23.98 \text{ cmH}_2\text{O for i-gel}, P = 0.003, 95\% \text{ confidence interval (CI): -3.58 to -0.75, } I^2 = 68\%, \text{ Mantel-Haenszel random model}]$. We did not find any clear evidence of differences between the devices in terms of insertion time, success rate of insertion, and incidence of adverse events except for blood staining (risk ratio 5.86, 95\%CI: 1.76 to 19.46, $P = 0.004, F = 0$, fixed-effect model).
CONCLUSION
The i-gel airway may provide a better seal and is therefore probably more suitable than the Ambu laryngeal mask airway in anaesthetised paediatric patients. However, the evidence is insufficient to allow making firm conclusions or to guide clinical practice, owing to the small number of relevant published studies.

Key Words: i-gel; Ambu laryngeal masks; Pediatric; Clinical performance

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Core Tip: The inflatable Ambu laryngeal masks and non-inflatable i-gel are two improvements of supraglottic airway devices based on classic laryngeal masks. The clinical performance and safety of these two devices in paediatric patients are still unclear and warrant further investigation. We performed a systematic review and meta-analysis on the clinical performance and safety of Ambu laryngeal masks and i-gel in anaesthetised paediatric patients. The results of this study showed that the i-gel airway may provide a better seal with a lower risk of adverse events and is therefore probably more suitable than the Ambu laryngeal mask airway in anaesthetised paediatric patients.

INTRODUCTION
Supraglottic airway devices (SGAs) have gained widespread acceptance for use in routine anaesthesia and emergency airway management in children since the 1980s, owing to advantages such as easy insertion, decreased use of neuromuscular blocking agents, hemodynamic stability, and low risk of postoperative airway complications compared with tracheal intubation[1-3]. To solve the deficiencies of classic laryngeal masks, including airway leak, gastric insufflation, and risk of aspiration with positive pressure ventilation[4,5], the design of the perfect paediatric SGA has undergone a long and productive evolution leading to i-gel and Ambu laryngeal masks, which are two improvements based on classic laryngeal masks.

The i-gel airway (Intersurgical Ltd., Wokingham, United Kingdom), a representative disposable second-generation SGA, has been available in small sizes since 2010. Made from a soft medical-grade thermoplastic elastomer with a non-inflatable cuff, i-gel was designed to create an anatomical seal of the pharyngeal, laryngeal, and peri-laryngeal structures while avoiding compression trauma. Moreover, its built-in drainage channel allows for gastric catheter placement to facilitate the efflux of gastric fluids. Studies in children have reported its easy insertion, high oropharyngeal leak pressure (OLP), and few postoperative adverse effects[6,7]. However, as some studies have shown that its straighter design makes it prone to sliding out and becoming displaced, it should be cautiously used especially in very small children[8,9].

Compared with the non-inflatable mask i-gel, the inflatable mask Ambu Aura (Ambu A/S, Ballerup, Denmark) family of SGAs has a variety of types, such as AuraGain, AuraOnce (single use, preformed shaft), Aura40 (preformed shaft, reusable), AuraStraight (straight shaft), AuraFlex (flexible shaft), and Aura-i[10]. AuraGain is a newly developed disposable SGA with an inflatable cuff and a curved body. Its wide airway tube allows for a conduit for tracheal intubation. In addition, it has a second port providing gastric access for draining gastric content and air. AuraOnce is constructed from a single-piece polyvinyl chloride mould with the cuff and tube forming a 90° angle, which is designed to approximate the airway anatomy and is thus difficult to displace. The clinical safety and efficacy of both Ambu AuraOnce and Ambu AuraGain in paediatric and adult use have already been demonstrated[10-13].
Several studies have compared the efficacy and safety of i-gel and Ambu laryngeal masks in paediatric patients[14-18]; however, the results have been inconsistent. To our knowledge, no previous systematic review has been sufficiently comprehensive to draw a clinically meaningful conclusion about the use of the two devices in paediatric patients[19]. To address this deficiency, we conducted an updated systematic review and meta-analysis to compare the clinical performance and safety of the non-inflatable mask i-gel and the inflatable mask Ambu Aura.

MATERIALS AND METHODS

This meta-analysis was performed following the recommendations in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement[20]. The meta-analysis was registered at PROSPERO (registration No. CRD42020168555).

Literature search
Two reviewers (Li L and Xiong W) independently searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (PubMed), Web of Science, and Embase to evaluate all potentially eligible studies using the Medical Subject Headings and text words related to ‘Ambu’, ‘Aura’, ‘i-gel’, and ‘paediatric’, from the inception dates to April 20, 2020. The reference lists of the retrieved full texts were also tracked. Furthermore, original randomised controlled trials (RCTs) included in relevant systematic reviews or meta-analyses, as well as ongoing studies in ClinicalTrials.gov, metaRegister of Controlled Trials, and other national trial registries were also identified. Any disagreement was resolved with the corresponding author of the study (Jin X) through a discussion and consensus process (see Supplementary material).

Eligibility criteria
Published RCTs in which the intervention involved the use of Ambu laryngeal masks and i-gel in anaesthetised paediatric patients (age < 18 years) were included. We excluded manikin studies and animal studies, which are susceptible to bias. We also excluded trials that compared the two devices in cases of difficult intubation, tracheostomy procedures, or cardiopulmonary resuscitation. We did not impose language restrictions.

Data extraction and outcome measures
Two reviewers (Wang YX and Liang Y) independently extracted the following data: lead author, publication year, type of surgery, airway size, participant characteristics (age, weight, sample size), risk of bias, and outcome indicators. The primary outcome of our study was OLP, which is the most commonly used quantitative indicator of seal in SGAs. We extracted the data recorded 10 min after SGA insertion to ensure consistency in the pooled analysis. The secondary outcomes included insertion time and success rate of insertion on the first attempt, which are important potential advantages of SGAs. We also aimed to assess adverse events that may reflect irritation to the vocal cords, such as coughing or laryngospasm.

Risk of bias assessment
Two reviewers (Bao D and Xang YX) used the Cochrane method to assess the quality of data reporting according to Review Manager software (version 5.1; The Cochrane Collaboration, Oxford, United Kingdom), considering seven different criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), selective outcome reporting, and other biases. The methodology of each trial was independently assessed by two authors and graded as having ‘high’, ‘low’, or ‘unclear’ risk of bias. Any disagreements were resolved with the corresponding author of the study (Jin X) through a discussion and consensus process.

Statistical analyses
The pooled risk ratio (RR) or the mean difference (MD) and the corresponding 95% confidence interval (CI) were calculated for each outcome using Review Manager software (version 5.3, The Cochrane Collaboration). We assessed the heterogeneity of the included studies based on both clinical diversity (e.g., measurement methods) and methodological diversity (risk of bias assessment). We considered an I² statistic value of > 50% to indicate considerable heterogeneity, mandating further subgroup analyses.
according to mean age and Ambu subtype. We also performed sensitivity analyses to evaluate the effect of a single study on the overall estimate by sequentially excluding each study. A funnel plot analysis was performed to qualitatively report bias or assess publication bias when > 10 studies were included[21].

RESULTS

Study selection
The database search identified 25 potentially relevant records after excluding 46 duplicates. On the basis of the titles, abstracts, and full texts, 18 records were removed, of which 5 were found to be comments, overview, manikin studies, and conference summary, and 1 article compared two devices in the setting of difficult intubation. Finally, seven eligible trials involving 667 paediatric patients in total (323 patients in the Ambu group and 344 patients in the i-gel group) were included in this meta-analysis[9,13-18]. A flowchart for identification is shown in Figure 1.

Characteristics of the included studies
The seven included RCTs were published between 2011 and 2019 and were conducted in five different countries (China, Japan, Republic of Korea, Sweden, and Saudi Arabia). The sample size of the included trials ranged from 59 to 208. The patients in six studies underwent elective surgery, and three-dimensional magnetic resonance imaging of the head and neck was performed in one study. None of the studies administered neuromuscular blocking agents before laryngeal mask insertion, except for one trial[14]. Among the seven included RCTs, two studies did not report any funding sources[9,22]; one was not funded[13]; and the other four were sponsored by King Saud University[17,18], Asan Medical Center[15], or Seoul National University Hospital[14]. Further descriptions of the included trials are presented in Table 1.

Risk of bias within studies
Six of the seven studies mentioned the specific methods used for random sequence generation, and four studies[9,13-15] performed allocation concealment using sealed or opaque envelopes. The assessment of postoperative adverse events in three studies was performed by a blinded investigator[13,17] or investigators who were not involved in the clinical procedure[9]. One study did not set blinding[15]. One study did not evaluate blinding[18]. The other two studies did not mention the specific method of blinding[14,22]. Three studies[9,13,15] used objective methods (manometric stability) of obtaining the OLP. However, it was obviously not possible in any study to blind the operator involved in airway management or the assessors of leak pressure. Funding sources were not stated in three studies[15,16,18], and it was not apparent whether any commercial sponsors were involved. The other studies had no obvious commercial involvements. The risk of bias is summarised in Figure 2. Aqil et al[18] reported randomisation, but did not describe the methods of allocation concealment and participant blinding. A sensitivity analysis was performed to determine the impact of their study on the results.

Synthesis of results
OLP, insertion time, success rate of insertion on the first attempt, and adverse events with the Ambu laryngeal mask and i-gel in anaesthetised paediatric patients were evaluated in this review.

Primary outcome: All seven studies assessed the OLP of the two devices. The intracuff pressures were maintained at 20-40 cmH2O[13-15,22] or 60 cmH2O[9,17,18], and a fresh gas flow of 3 L/min was maintained to determine the OLP. The methods used to quantify OLP included audible noise detection[17,18], stethoscopic noise[14], and manometric stability[9,13,15]; however, one study did not describe the methodological details[22]. Excluding two studies[14,18], five studies individually showed higher mean leak pressures in the i-gel group. Overall, the combined results of all seven studies revealed that the mean leak pressure was higher in the i-gel group than in the Ambu group, with substantial heterogeneity (21.82 cmH2O for Ambu vs 23.98 cmH2O for i-gel, P = 0.003, 95% CI: -3.58 to -0.75, I2 = 68%, Mantel-Haenszel random model) (Figure 3). A subgroup analysis according to the mean age of the study participants (Figure 4) was performed to assess the impact of age, and the combined OLP from studies with participants whose mean age was < 3 years was significantly higher for i-gel (MD -3.53 cmH2O, 95% CI: -4.58 to -2.49, P < 0.00001, I2 = 0%). Pooled analysis from
**Table 1 Description of the included trials comparing Ambu and i-gel values are presented as numbers, mean ± SD, or median (interquartile range)**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Airway (intervention)</th>
<th>n</th>
<th>Airway size</th>
<th>Age (yr or mo)</th>
<th>Weight (kg)</th>
<th>OLP measurement method</th>
<th>Type of surgery</th>
<th>Ventilation</th>
<th>NBD</th>
<th>Depth of anesthesia for laryngeal mask placement and the proficiency of anesthesiologists</th>
<th>Primary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theiler et al [9] (2011)</td>
<td>Aura once</td>
<td>102</td>
<td>Size 1.5 (5-9.9 kg); Size 2 (10-18.9 kg); Size 2.5 (20-29.9 kg); Size 3 (30-50 kg)</td>
<td>6.2 ± 4.0 yr</td>
<td>24.7 ± 11.6</td>
<td>Manometric stability</td>
<td>Elective day surgery under general anaesthesia (urology, orthopaedics, visceral, dermatology)</td>
<td>Mechanical</td>
<td>No</td>
<td>Absence of motor and cardiovascular responses to the jaw thrust maneuver; anesthesiology staff at the University Hospital Bern</td>
<td>OLP</td>
</tr>
<tr>
<td></td>
<td>I-gel</td>
<td>106</td>
<td>Size 1.5 (5-9.9 kg); Size 2 (10-24.9 kg); Size 2.5 (25-34.9 kg); Size 3 (35-50 kg)</td>
<td>6.3 ± 3.7 yr</td>
<td>24.7 ± 11.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gu et al [22] (2016)</td>
<td>Aura Once</td>
<td>32</td>
<td>Size 2</td>
<td>29.28 ± 11.32 mo</td>
<td>13.78 ± 2.55</td>
<td>NR</td>
<td>Elective hypospadias repair surgery</td>
<td>Mechanical</td>
<td>No</td>
<td>After the eyelash reflex disappeared and the mandibular joint loosened; NR</td>
<td>OLP and respiratory dynamic data</td>
</tr>
<tr>
<td></td>
<td>I-gel</td>
<td>32</td>
<td></td>
<td>26.72 ± 12.16 mo</td>
<td>13.95 ± 2.87</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzahem et al [17] (2017)</td>
<td>Auraonce</td>
<td>48</td>
<td>NR</td>
<td>32.3 ± 38 mo</td>
<td>13.2 ± 8.3</td>
<td>Noise detection</td>
<td>Elective surgery</td>
<td>Mechanical</td>
<td>No</td>
<td>Lack of a motor response to jaw thrust; had more than 20 years' experience in the specialty and more than 1000 successful insertions of these SGADs</td>
<td>OLP</td>
</tr>
<tr>
<td></td>
<td>I-gel</td>
<td>64</td>
<td></td>
<td>30.6 ± 37.4 mo</td>
<td>12.7 ± 8.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aqil et al [18] (2017)</td>
<td>Auraonce</td>
<td>30</td>
<td>Size 1.5/2/2.5/3</td>
<td>4.62 ± 2.85 yr</td>
<td>18.28 ± 7.23</td>
<td>Noisedetection</td>
<td>3D-MRI of the head and neck</td>
<td>Spontaneous breathing</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I-gel</td>
<td>29</td>
<td></td>
<td>4.76 ± 3.18 yr</td>
<td>17.66 ± 7.47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al [14] (2019)</td>
<td>Auragain</td>
<td>29</td>
<td>Size 1.5 (5-10 kg); Size 2 (10-20 kg); Size 2.5 (20-30 kg)</td>
<td>1.5 (0.75-5) yr</td>
<td>12.2 (9.4-21.8)</td>
<td>Stethoscopic noise</td>
<td>Elective surgery</td>
<td>Mechanical</td>
<td>Yes</td>
<td>Muscle relaxation with rocuronium and mask ventilation for 90 s; experienced anaesthesiologists</td>
<td>Safety margin</td>
</tr>
<tr>
<td></td>
<td>I-gel</td>
<td>30</td>
<td>Size 1.5 (5-12 kg); Size 2 (10-25 kg); Size 2.5 (25-35 kg)</td>
<td>3 (0.75-6) yr</td>
<td>13.9 (10.2-23.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al [15] (2019)</td>
<td>Auragain</td>
<td>34</td>
<td>Size 1.5 (5-9.9 kg); Size 2 (10-20 kg)</td>
<td>23.5 ± 17.8 mo</td>
<td>11.6 ± 3.3</td>
<td>Manometric stability</td>
<td>Upper-/lower-extremity surgery under general anaesthesia</td>
<td>Mechanical</td>
<td>No</td>
<td>Absence of motor and cardiovascular responses to the jaw thrust maneuver; skilled and vastly experienced at inserting supraglottic airway devices</td>
<td>Requirement for additional airway manoeuvres</td>
</tr>
<tr>
<td></td>
<td>I-gel</td>
<td>33</td>
<td></td>
<td>15.6 ± 11.5 mo</td>
<td>10.5 ± 2.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Bao D et al. The clinical performance of two laryngeal masks

<table>
<thead>
<tr>
<th>Mihara et al.[19] (2019)</th>
<th>Auragain</th>
<th>48</th>
<th>Size</th>
<th>1.5/2.0/2.5 mo</th>
<th>14.4 ± 5.0 cmH2O</th>
<th>Manometric stability</th>
<th>Elective surgery with an expected surgery time of &lt; 2 h</th>
<th>Mechanical No</th>
<th>Lack of a motor response to jaw thrust; had experience of SGA insertion of more than 20 times</th>
<th>OLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-gel</td>
<td>50</td>
<td>42</td>
<td>14-66 mo</td>
<td>13.7 ± 5.4 cmH2O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MRI: Magnetic resonance imaging; OLP: Oropharyngeal leak pressure; SGADs: Supraglottic airway devices; NBD: Neuromuscular blocking agent; NR: Not reported.

Figure 1 PRISMA flowchart.

the other four studies in which the mean age was ≥ 3 years showed no significance between the two devices (MD -0.45 cmH2O, 95%CI: -3.12 to -2.23, P = 0.74, I2 = 77%). Another subgroup analysis according to the Ambu subtype was performed, and the pooled results revealed significant differences with a still high heterogeneity (AuraGain: MD -4.03 cmH2O, 95%CI: -7.37 to -0.72, P = 0.02, I2 = 77%; AmbuOnce: MD -2.24 cmH2O, 95%CI: -4.03 to -0.45, P = 0.02, I2 = 75%). The sensitivity analysis (Figure 5) suggested that the results were relatively stable, except when Aqil et al.\[18\]'s study was excluded, which resulted in a lower heterogeneity (from 68% to 44%).

**Insertion time:** Data on insertion time were obtained from four trials\[9,15,17,19\] including 485 patients, and no clear evidence of differences was seen between the two devices (i-gel: 18.052 s vs Ambu: 18.602 s, P = 0.70, 95%CI: -2.28 to 3.38, I2 = 83%, Mantel-Haenszel random model) (Figure 6A). The most common depth of anesthesia for laryngeal mask placement was the lack of a motor response to jaw thrust\[9,15,17,19\] while one study did not describe it\[18\], and one described it as “muscle relaxation with rocuronium and mask ventilation for 90 s”\[14\]. The proficiency of anesthesiologists in these four studies is significantly different, from “who had experience of SGA insertion of more than 20 times”\[19\] to “who had more than 20 years' experience in the specialty and more than 1000 successful insertions of these SGADs”\[17\]. Insertion time was defined as the time from the moment the mask was removed and the SGA was picked up to the moment that stable capnography was traced on the monitor\[13,15,17\] or the achievement of sufficient ventilation\[9\]. We performed subgroup analysis to assess the effect of the Ambu type and patient age; however, the results were not altered and a large heterogeneity was still observed.

**Success of insertion on first attempt:** Five studies (n = 544; 262 in the Ambu group and 282 in the i-gel group)\[9,15,17,19\] reported successful insertion on the first
attempt. One study[18] reported no instances of failed airway insertion for the two devices, whereas the average success rates in the other four studies were 94.5% for Ambu and 91.2% for i-gel. Although all four studies individually found that the success rate with i-gel was lower than that with Ambu, there was no evidence for differences in the success rate on the first attempt (RR 1.03, 95%CI: 0.99 to 1.07, P = 0.12, I² = 0%) (Figure 6B).

**Adverse events**

**Blood staining on the removed device:** Four studies[9,13,15,22] that included 421 patients compared the incidence of blood staining on the removed device. Overall,
8.1.2 Mean age < 3

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ambu Mean (SD)</th>
<th>i-gel Mean (SD)</th>
<th>Mean difference</th>
<th>Mean difference IV, Random, 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheim AM et al(2017)</td>
<td>22.5 (3.9)</td>
<td>48 (25.4)</td>
<td>25.4 (4.1)</td>
<td>64</td>
</tr>
<tr>
<td>Ha-Jung Kim et al(2019)</td>
<td>18.9 (3.5)</td>
<td>34 (23.3)</td>
<td>4 (33)</td>
<td>17.0%</td>
</tr>
<tr>
<td>Zhirong Gu et al(2016)</td>
<td>20.72 (4.56)</td>
<td>32 (24.38)</td>
<td>5.89 (32)</td>
<td>13.1%</td>
</tr>
<tr>
<td>Subtotal (95%CI)</td>
<td>114</td>
<td>129</td>
<td>48.7%</td>
<td>-3.53 [-4.58, -2.49]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.59, df = 2 (P = 0.45; I²=0%
Test for overall effect: Z = 6.60 (P < 0.00001)

8.1.3 Mean age > 3

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ambu Mean (SD)</th>
<th>i-gel Mean (SD)</th>
<th>Mean difference</th>
<th>Mean difference IV, Random, 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqil M et al(2016)</td>
<td>26.23 (6.46)</td>
<td>30 (23.41)</td>
<td>7.41 (29)</td>
<td>9.4%</td>
</tr>
<tr>
<td>Je-Hyun Lee et al(2019)</td>
<td>29 (7.2)</td>
<td>29 (27.9)</td>
<td>7.6 (30)</td>
<td>8.8%</td>
</tr>
<tr>
<td>Takahiro Mihara et al(2019)</td>
<td>21.9 (6)</td>
<td>46 (23.1)</td>
<td>7.3 (50)</td>
<td>12.9%</td>
</tr>
<tr>
<td>Theiler LG et al(2011)</td>
<td>19 (3)</td>
<td>100 (22)</td>
<td>5 (99)</td>
<td>20.3%</td>
</tr>
<tr>
<td>Subtotal (95%CI)</td>
<td>207</td>
<td>208</td>
<td>51.3%</td>
<td>-0.45 [-3.13, -2.23]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 5.45; Chi² = 12.93, df = 3 (P = 0.005; I²=77%
Test for overall effect: Z = 0.33 (P < 0.74)

Total (95%CI)

<table>
<thead>
<tr>
<th>Mean difference IV, Random, 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2.17 [-3.58, -0.75]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 2.22; Chi² = 18.68, df = 6 (P = 0.005; I²=68%
Test for overall effect: Z = 3.00 (P = 0.003)
Test for subgroup differences: Chi² = 4.41, df = 1 (P = 0.04), F=77.3%

Figure 4 Forest plot of subgroup analysis of oropharyngeal leak pressure according to the mean age of the study population: Ambu vs i-gel. The combined oropharyngeal leak pressure from studies with participants whose mean age was < 3 years was significantly higher for i-gel (mean difference -3.53 cmH₂O, 95% confidence interval: -4.58 to -2.49, P < 0.00001, I²=0%) while pooled analysis from the other four studies showed no significance between the two devices. CI: Confidence interval.

Blood staining: In 17 participants (7.9%) in the Ambu group and 2 participants (0.96%) in the i-gel group. A statistically significant reduction was found with i-gel (RR 5.86, 95%CI: 1.76 to 19.46, P = 0.004) (Figure 6C). The heterogeneity was low (P = 0%).

Desaturation: Among five studies evaluating the occurrence of desaturation, four studies[9,13,17,22] assessed desaturation as pulse oximetry saturation (SpO₂) < 90% and one study did not specify a quantitative standard[15]. No evidence for a difference in desaturation between the two devices was found (RR 0.89, 95%CI: 0.31 to 2.57, P = 0.83, I² = 2%) (Figure 6D).

Bronchospasm: Of the five studies[9,13,15,17,22] that evaluated bronchospasm, two studies[9,15] reported its occurrence. The overall incidence was 5.6% (12 of 214 participants) in the Ambu group and 4.3% (9 of 207 participants) in the i-gel group, and no clinically important differences were found between the two devices (RR 1.03, 95%CI: 0.18 to 5.85, P = 0.97, F = 69%) (Figure 6E). Notably, the incidence of laryngospasm significantly varied across the studies, from 0%[13,17,22] to 10%[15]. Three studies reported extubation under anaesthesia[13] or deep anaesthesia[9,17]. In the study by Kim et al[15], extubation was performed when the airway reflexes were restored. Extubation was not mentioned in Theiler et al[9]’s study.
Bao D et al. The clinical performance of two laryngeal masks

### Figure 6 Forest plot of Ambu versus i-gel.

<table>
<thead>
<tr>
<th>A</th>
<th>Study or Subgroup</th>
<th>Ambu</th>
<th>I-gel</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Alahmadi AH et al. (2019)</td>
<td>16.1</td>
<td>6.5</td>
<td>48</td>
<td>15.5</td>
<td>7</td>
</tr>
<tr>
<td>Ha-Jung Kim et al. (2019)</td>
<td>13.3</td>
<td>3.7</td>
<td>34</td>
<td>13.1</td>
<td>4.9</td>
</tr>
<tr>
<td>Takahiro Mihrara et al. (2019)</td>
<td>21.3</td>
<td>6.5</td>
<td>48</td>
<td>17.1</td>
<td>4.5</td>
</tr>
<tr>
<td>Thalier LG et al. (2011)</td>
<td>24</td>
<td>8</td>
<td>100</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>232</td>
<td>253</td>
<td>100.0%</td>
<td>0.55 [-2.28, 3.38]</td>
<td>0.55 [-2.28, 3.38]</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 6.99; \chi^2 = 17.49; \text{df} = 3 (P = 0.0066); f = 63.3%$

Test for overall effect: $Z = 0.30 (P = 0.70)$

<table>
<thead>
<tr>
<th>B</th>
<th>Study or Subgroup</th>
<th>Ambu</th>
<th>I-gel</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>Weight</td>
<td>M-H, Fixed, 95%CI</td>
<td>M-H, Fixed, 95%CI</td>
</tr>
<tr>
<td>Alahmadi AH et al. (2019)</td>
<td>48</td>
<td>48</td>
<td>62</td>
<td>64</td>
<td>29.8%</td>
</tr>
<tr>
<td>Ha-Jung Kim et al. (2019)</td>
<td>39</td>
<td>30</td>
<td>29</td>
<td>29</td>
<td>32.7%</td>
</tr>
<tr>
<td>Takahiro Mihrara et al. (2019)</td>
<td>84</td>
<td>34</td>
<td>32</td>
<td>33</td>
<td>23.9%</td>
</tr>
<tr>
<td>Thalier LG et al. (2011)</td>
<td>46</td>
<td>48</td>
<td>45</td>
<td>50</td>
<td>17.3%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>262</td>
<td>282</td>
<td>100.0%</td>
<td>1.03 [-0.69, 1.07]</td>
<td>1.03 [-0.69, 1.07]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 1.21; \text{df} = 4 (P = 0.87)$; $I^2 = 0$

Test for overall effect: $Z = 1.55 (P = 0.12)$

### Figure 6 Forest plot of Ambu versus i-gel.

- A: Insertion time;
- B: The success of insertion on the first attempt;
- C: The incidence of blood staining on the removed device;
- D: The incidence of desaturation;
- E: The incidence of bronchospasm;
- F: The incidence of coughing.

CI: Confidence interval.
Coughing

Three studies\cite{9,13,22} reported this outcome. Overall, coughing occurred in 16 participants (8.89\%) in the Ambu group and in 7 participants (4.02\%) in the i-gel group. The total incidence of coughing was 4.87\% higher in the Ambu group; however, whether the difference is reasonable or not is uncertain (RR 2.21, 95\%CI: 0.93 to 5.24, \(P = 0.07, I^2 = 0\%\)) (Figure 6F).

No cases of aspiration of gastric fluid were reported in any of the studies.

DISCUSSION

The principal finding of our meta-analysis was that i-gel provides a higher OLP than Ambu laryngeal masks with a low incidence of adverse events in anaesthetised paediatric patients, and we considered that i-gel may be superior to the Ambu laryngeal masks; however, the generalizability of the overall results is limited owing to the small number of published studies.

Primary outcome

OLP is the most commonly used quantitative indicator of seal in SGAs. It indicates the degree of airway protection, successful SGA placement, and the feasibility of positive pressure ventilation\cite{23}. Seven studies with 658 participants revealed a statistically higher (by 2.17 cm) OLP with i-gel. It showed that although i-gel laryngeal mask does not contain cuffs and cannot adjust the cuff pressure to achieve the purpose of sealing the airway as Ambu, the gel material of its cover achieve small amplitude shaping based on the children’s oropharyngeal structure to achieve better sealing effects. Higher oropharyngeal leak pressure results in better sealing of the hypopharynx, which may be beneficial in clinical settings requiring increased airway pressure and important for patients with aspiration and reflux risks. However, moderate to high heterogeneity (\(I^2 = 68\%\)) was suspected when we pooled the results, which was probably due to the clinical diversity of the OLP measurements. When exploring the heterogeneity, the hypotheses that the mean patient age and the subtype of Ambu were the causes of heterogeneity were not supported by the subgroup analyses, whereas there was a significant reduction in heterogeneity after sensitivity testing. The reasons for the high heterogeneity generated by Aqil et al\cite{18}’s study may include the following two aspects: first, the risk of bias in this study was set from ‘unclear’ to ‘high’ at least once, indicating that the overall quality of evidence was very low, which resulted in potential methodological sources of heterogeneity among the evaluated studies. Second, spontaneous breathing mode was applied in Aqil et al\cite{18}’s trial, whereas mechanical ventilation was required for elective surgery in the other trials, resulting in greater clinical heterogeneity. We downgraded this outcome from high quality to moderate quality because of the risk of bias with imprecision (small sample size). Previous meta-analyses yielded similar results, showing that the OLP with i-gel was higher than that with other laryngeal mask airways in children\cite{22}. Although it cannot be sealed by cuff inflation, its shape, contour, and softness precisely fit with the anatomy and account for a better sealing effect of the pharyngeal, laryngeal, and peri-laryngeal structures.

Insertion time and success of insertion on first attempt

A high rate of insertion success on the first attempt was reported in our meta analysis, and that insertion of the devices takes only about 18 s for both devices, demonstrating their effectiveness in anaesthetised paediatric patients and especially in emergency situations such as failure to intubate and ventilate. Although the non-inflatable cuff of i-gel can help save time, the final time was similar because additional airway intervention is required during i-gel insertion whereas the curved airway tube of Ambu may facilitate its insertion. The different definitions of insertion time, the use of muscle relaxants, the depth of anesthesia and the experience level of the anesthesiologist who inserted the laryngeal mask may be the sources of high heterogeneity. Notably, Theiler et al\cite{9}’s study showed that the pediatric i-gel has a straighter ventilating tube than the adult model, which correlates with the tendency for the device to slide out. Kim et al\cite{15}’s study also point out that the large-sized mask of i-gel is a disadvantage with respect to dislodgement. Therefore, it is necessary to choose the appropriately size and secure it with tape when applying i-gel in small children.
Adverse events
Most adverse events were infrequent and did not differ between the two devices, except for the higher incidence of blood staining on Ambu with significant differences. The significantly lower incidence of blood staining on i-gel in our results indicated a lower incidence of oral or pharyngeal mucosal injuries during the insertion or removal of the device. This factor might become the dominant advantages of i-gel laryngeal mask in pediatric anesthesia and indicated that awareness of compression damage of the throat induced by Ambu should be concerned. Previous comparative analyses [19, 24] revealed that the risk of blood staining on i-gel was significantly lower than that on other SGAs. This may be because of its unique soft gel-like cuff and certain shape, which allow it to function in harmony with the anatomy, thus reducing compression and displacement trauma. In addition, the cuffs of Ambu is made of poly vinyl chloride, which are more likely to induce sore throat in pediatric patients. However, the study by Mihara et al [13] showed that there was no direct relationship with postoperative sore throat, and the clinical impact was unclear.

Insufficient differences were observed between the two devices in terms of the incidence of laryngospasm. However, as the depth of anaesthesia at extubation was different for each trial, the validity of combining different studies within this outcome is unquestionable. Both devices are efficient in protecting the airway from aspiration, and no cases of aspiration of gastric fluid were reported in any study.

This review had several limitations. First, although subgroup and sensitivity analyses were performed, there are many potential clinical and methodological sources of heterogeneity among the evaluated studies, including different methods of measurement of outcomes, use of neuromuscular blocking agents, proficiency of practitioners, different ventilation methods, and depth of anaesthesia. Second, publication bias could not be visually assessed using a funnel plot because the number of studies was too few to obtain valid results. Consequently, it is not yet possible to draw firm conclusions based on single-centre studies with limited available data.

CONCLUSION
In conclusion, we compared the clinical performance and safety of two types of SGAs in paediatric patients, and performed subgroup and sensitivity analyses to identify the sources of heterogeneity, including quality assessment. Both devices are suitable for airway management during general anaesthesia, with sufficient OLP, ease of insertion, and few adverse events. The results of the current meta-analysis suggest that i-gel is a better SGA in terms of superior OLP with a low risk of adverse events, which provided clinical evidence for the application of laryngeal mask in anaesthetised paediatric patients. However, it should be used with caution in paediatric patients. Further high-quality clinical studies are required to confirm our results.

ARTICLE HIGHLIGHTS
Research background
The inflatable Ambu laryngeal masks and non-inflatable i-gel are two widely used paediatric supraglottic airway devices (SGAs) in routine anaesthesia and served as primary or back-up devices for difficult airway management. However, the clinical performance and safety of the two devices in paediatric patients are still unclear and warrant further investigation.

Research motivation
In this study, we aimed to perform a systematic review and meta-analysis on the clinical performance and safety of Ambu laryngeal masks and i-gel in anaesthetised paediatric patients. The results of this study may provide clinical evidence for the application of laryngeal mask in anaesthetised paediatric patients.

Research objectives
To perform a systematic review and meta-analysis on the clinical performance and safety of Ambu laryngeal masks and i-gel in anaesthetised paediatric patients.
Research methods
We identified published randomised controlled trials (RCTs) in which the intervention involved the use of Ambu laryngeal masks and i-gel in anaesthetised paediatric patients (age < 18 years) in MEDLINE, Embase, Web of Science, Cochrane Central Register of Controlled Trials from the inception dates to April 20, 2020. We assessed the oropharyngeal leak pressure (OLP) as the primary outcome. The secondary outcomes were insertion time, success rate of insertion on the first attempt, and incidence of adverse events.

Research results
Data from seven RCTs with a total of 667 paediatric patients were evaluated and showed that the mean OLP and the incidence of adverse events was lower in the non-inflatable i-gel group in anaesthetised paediatric patients.

Research conclusions
The non-inflatable i-gel airway may provide a better seal with a low risk of adverse events and is therefore probably more suitable than the inflatable Ambu laryngeal mask airway in anaesthetised paediatric patients. However, the evidence is insufficient to allow making firm conclusions or to guide clinical practice, owing to the small number of relevant published studies.

Research perspectives
Further high-quality clinical studies of the application of laryngeal masks in anaesthetised paediatric patients are required to confirm our results.

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15 Kim HJ, Park HS, Kim SY, Ro YJ, Yang HS, Koh WU. A Randomized Controlled Trial Comparing Ambu AuraGain and i-gel in Young Pediatric Patients. *J Clin Med* 2019; 8 [PMID: 31426378 DOI: 10.3390/jcm80801235]


Autogenous iliotibial band enhancement combined with tendon lengthening plasty to treat patella baja: A case report

De-Zhou Tang, Qian Liu, Jian-Kang Pan, Yue-Ming Chen, Wei-Hong Zhu

BACKGROUND
Patella baja is a severe complication after knee injury or surgery, resulting in pain and impaired movement. This disorder is also a substantial challenge for orthopaedic surgeons. Currently, no consensus exists regarding the gold standard management of patella baja. If not appropriately treated, significant dysfunction of the knee joint will occur.

CASE SUMMARY
A 46-year-old man with a left patellar fracture was treated with tension band fixation at a local hospital. He had undergone a second operation at the same hospital because of limited knee flexion 6 mo after surgery. Unfortunately, the patellar tendon was ruptured. The patellar tendon was subsequently repaired using an ipsilateral semitendinosus tendon. Two years later, the patient presented to our department with knee pain and loss of range of motion. Autogenous iliotibial band (ITB) enhancement combined with sagittal tendon lengthening plasty was used to improve the symptoms of the knee joint. The patient was followed up for 2 years. The knee joint function of the patient returned to the normal level.

CONCLUSION
We successfully treated patella baja using autogenous ITB enhancement combined with sagittal tendon lengthening plasty.

Key Words: Patella baja; Tendon lengthening; Iliotibial band; Patellar fracture; Case report

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Core tip: Patella baja combined with knee dysfunction can be observed in patients with patellar trauma. If not properly managed, joint stiffness and patellofemoral arthritis will occur, seriously affecting quality of life. Various therapeutic approaches are available, but no consensus exists regarding which is the best surgical approach. In this case report, we used our approach to treat patella baja using autogenous iliotibial band enhancement combined with tendon lengthening plasty to restore knee function with remarkable results.

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INTRODUCTION

Patella baja is a condition in which the patella is positioned abnormally low relative to the femoral trochlea. Patella baja is normally classified into three types: congenital acquired and mixed[1]. Although the exact pathological mechanism of acquired patella baja remains unclear, several contributing factors have been reported, such as cicatricial hyperplasia of the patellar tendon after total knee arthroplasty, complete resection of the infrapatellar fat pad, chronic injury of the femoral quadriceps, and long-term immobilization after knee surgery[2-4].

Knee pain and dysfunction are the main clinical manifestations of acquired patella baja. If not addressed properly, joint stiffness and patellofemoral arthritis will occur, significantly affecting quality of life[5]. In contrast to conservative treatments, timely and effective surgical interventions play a key role in improving knee function. Although many surgical procedures have been attempted to manage this pathology[6-10], no consensus exists regarding which is the best option. In this case report, we used our method to treat patella baja using autogenous iliotibial band (ITB) enhancement combined with tendon lengthening plasty.

CASE PRESENTATION

Chief complaints
A 46-year-old man was admitted to our hospital because of left knee pain and loss of range of motion (ROM) for 2 years.

History of present illness
The patient had a left patellar fracture and was treated with tension band fixation at a local hospital 2 years prior. He had undergone a second operation at the same hospital because of limited knee flexion 6 mo after the surgery. The surgeon removed the internal fixation and performed manipulation under anaesthesia. Unfortunately, the patellar tendon was ruptured. The patellar tendon was subsequently repaired using an ipsilateral semitendinosus tendon.

History of past illness
No remarkable personal and family history.

Personal and family history
No special personal and family history.

Physical examination
Physical examination on admission revealed a longitudinal surgical scar of approximately 15 cm in length on the left knee joint, without obvious skin damage or ulceration. The patient presented with a lameness gait and pain in the knee, left quadriceps atrophy, and knee flexion limited by 45°. The Lysholm score and Interna-
Tang DZ et al. Surgical treatment of patella baja

Functional Knee Documentation Committee (IKDC) score were 50 and 40, respectively.

**Laboratory examinations**
The laboratory findings were normal.

**Imaging examinations**
The patient was diagnosed with patella baja using a lateral-view radiograph of his left knee (Figure 1A–1C). Magnetic resonance imaging (MRI) further demonstrated that the patellar tendon was contracted and thickened (Figure 1C).

**FINAL DIAGNOSIS**
The final diagnosis was left patella baja and post-traumatic knee dysfunction.

**TREATMENT**
We used our method to treat patella baja using autogenous ITB enhancement combined with tendon lengthening plasty.

**Surgical procedures and methods**
A tourniquet was placed on the left thigh, with the patient in the supine position. Manipulation under anaesthesia was performed. Arthroscopic examination found a large amount of scar tissue and synovial hyperplasia in the joint. Although extensive arthrolysis was then performed by debriding fibrotic scar tissue in the suprapatellar bursa, medial recess, lateral recess, and intercondylar fossa, the ROM of the knee joint was 0°–65° (Figure 2A), and the patellar mobility was not significantly improved. Therefore, open surgery to lengthen the patellar tendon was conducted.

The approach was made along the original incision extending from 5 cm above the superior pole of the patella to the tibial tubercle (Figure 2B). After removing scar tissue surrounding the patella and patellar tendon, a minor increase in ROM was observed. The patellar tendon was subsequently freed and prepared for lengthening.

The length of the patellar tendon was approximately 35 mm (Figure 3A). The medial patellar insertion and lateral tibial insertion of the patellar tendon were carefully preserved when splitting along the midline (Figure 3B). Next, the patella was overturned upwards with the knee in 90° of flexion to assess the tendon length. The distance to be prolonged for the patient was approximately 60 mm, and the overlapping distance of the two free tendon ends was approximately 10 mm (Figure 3B). An ultrabraid suture (#2; Smith & Nephew, Andover, FL, USA) was used to overlap the tendon ends in a whipstitch fashion. To enhance the reconstructed patellar tendon, a 60 mm ITB graft was harvested (Figure 4A). The ITB graft was first fixed at the proximal and distal insertion of the patellar tendon by two TWINFIX Ti 3.5 mm suture anchors (Smith & Nephew) (Figure 3C), and then the graft and patellar tendon were sutured together using ultrabraid sutures. The length of the graft was calculated to avoid excess. Three MB66 polyester sutures (#5; Ethicon) were passed through the tibial and patellar bone tunnels as cerclage to avoid high tension when flexing the knee (Figure 4B). The ROM of the knee improved to 100°. Intraoperative fluoroscopy showed that the height of the patella was significantly recovered, with a Carton index of 1.0. After rinsing the wound thoroughly, it was closed normally, and drainage was left.

**OUTCOME AND FOLLOW-UP**
The patient was allowed partial weight-bearing using crutches with hinged knee brace protection on postoperative day 1. Straight-leg raises, ankle pump exercise and continuous passive motion were started within the first week after surgery. The initial ROM was limited between 0° and 15° for the first week after the procedure. An increment of 15° was allowed every week, and the ROM was increased to 90° by 6 wk. Full weight-bearing and unrestricted ROM were allowed after 2 mo, and the brace was discontinued after 3 mo.
Tang DZ et al. Surgical treatment of patella baja

Figure 1 Preoperative lateral radiograph of the left knee and measurement of the patellar height. A: Before the second operation, the fracture healed, and the Caton–Deschamps index was 0.38; B: Before the third operation. The ratio of the red dotted line and yellow dotted line indicates that the Caton–Deschamps index was 0.12, and the ratio of the white dotted line to the blue dotted line indicated that the Insall–Salvati index was 0.42; C: The contracted patellar tendon is approximately 35.0 mm in length and 11.3 mm in thickness.

Figure 2 Arthroscopic release measurements were followed by range of motion (ROM) measurements and open surgery. A: ROM of the knee joint after arthroscopic release was slightly improved compared with the preoperative ROM. B: The approach was made from 5 cm above the superior pole of the patella to the tibial tubercle. A periosteal elevator (black arrow) was used to mobilize the contracted patellar tendon (white star) and identify its medial and lateral margins.

Figure 3 Schematic diagram of the lengthening method. A: The patellar tendon was longitudinally split along the midline while preserving the medial patellar insertion and the lateral tibial insertion of the patellar tendon (red line); B: Ultrasound sutures were used to overlap the two tendon-free ends in a whipstitch fashion (blue line); C: The reconstructed patellar tendon was further strengthened using an iliotibial band graft (yellow area), which was fixed with two suture anchors (black circles), and suture cerclage was used to decrease tension (light blue line).

The postoperative radiograph showed that the patellar height was almost normal (Figure 5). The patient was followed up for 2 years. At the final follow-up, the ROM of his knee was 0° to 120° (Figure 6). Additionally, the Lysholm score and IKDC score improved to 92 and 86, respectively.
DISCUSSION

Patella baja is a severe complication after knee injury or surgery, resulting in pain and impaired movement. The specific aetiology of this disorder remains unknown. Currently, no consensus exists regarding the gold standard management of patella baja. We have successfully treated patients with a history of multiple knee surgeries.
Tang DZ et al. Surgical treatment of patella baja

Notably, our case had severe scar hyperplasia in the knee and contracture of the patellar tendon, which was of poor quality. The combination of patellar tendon lengthening and ITB enhancement to treat patella baja was suitable for this patient. Additionally, this treatment does not cause additional surgical trauma. Previous studies have attempted various methods to treat patella baja. In et al[8] used the classic Ilizarov technique to prolong the patellar tendon. Although the symptoms of the patient were considerably improved, the affected limb must be fixed for 3 mo, increasing the risk of joint stiffness. The modified Z-shaped plasty used by Guido et al [10] was a successful technique, but these patients did not have rupture of the patellar tendon and did not undergo patellar tendon surgery; thus, the patellar tendon was of relatively good quality. Modified Z-plasty would not be suitable for these patients. Bruhin et al[7] connected the patellar tendon with the quadriceps femoris surface using a transplanted tendon. Although this method does not affect tendon stress distribution and blood supply, it may cause certain restrictions on the quadriceps femoris. Additionally, transposition of the tibial tuberosity is a common technique to address patella baja[6,9]. However, complications were observed such as avulsion of the tibial tubercle and rupture of the patellar tendon. Judet’s quadriceps muscle is the modality applied to describe a surgical procedure of the quadriceps muscle to improve knee flexion in severely ankylosed knees[11,12]. Although Judet’s technique of disinsertion and muscle sliding is a useful technique in fixed knee extension contracture, it has an obvious disadvantage of a long incision and major invasiveness. Here, we reported a complex case of patella baja. A detailed and individualised surgical plan was customised preoperatively: arthroscopic arthrolysis, extensive resection of hyperplastic scar tissue, sagittal Z-plasty for patellar tendon lengthening, autogenous ITB transplantation for enhancement, and suture cerclage for decreased tension.

Arthroscopic surgery to treat knee stiffness has been reported with satisfactory results [13,14]. At the beginning of the operation, we performed arthrolysis on the patient’s knee joint under arthroscopy. However, the ROM was not obviously promoted after arthroscopic release; thus, we converted to open surgery. After thoroughly debriding the scar tissue around the patella and patellar tendon, the patellar tendon was equally split and overlapped to ensure a sufficient length when flexing the knee at 90°. To use the contracted patellar tendon more accurately, before surgery, the patellar tendon was evaluated and measured on MRI. After thorough debridement during the operation, the patellar tendon was measured again and compared with the preoperative measurements. Notably, the insertions of the patellar tendon at the patella and tibial tuberosity were well preserved, benefiting the mechanical properties and blood supply of the tendon. Furthermore, we used an autogenous ITB graft to strengthen the lengthened patellar tendon. Autogenous graft transplantation can not only provide mechanical enhancement but may also promote tendon healing[15-17]. Intraoperatively, ITB is used for patellar tendon enhancement, which will not cause additional surgical trauma. Additionally, considering that high-performance suture materials provide better stability[18], we passed three MB66 sutures as cerclage in the bone tunnels to reduce the tension. This suture cerclage may decrease the risk of rupture after surgery.

We analysed the possible reasons for patella baja of our patient. First, the local orthopaedic surgeon left a relatively long end of the K-wire at the index operation. The long end of the K-wire might irritate the patellar tendon and quadriceps tendon, making rehabilitation challenging[19,20]. Second, it is a common phenomenon that patients who were treated at county-level hospitals did not have a systematic rehabilitation protocol in China. Presently, our government is strengthening the construction of a community rehabilitation medical centre. Finally, the patellar tendon ruptured when performing manipulation under anaesthesia during the second surgery. This may be related to the insufficient release of intra-articular adhesion.

This case had several limitations. First, the harvested ITB may cause pain in the graft harvest site, which depends on the intraoperative condition and surgeon’s experience. Second, more cases are needed to verify the effectiveness of our method. Third, the follow-up was short.

Importantly, much knowledge was gained from the patient’s prior surgery. We reviewed the patient’s medical records and radiological data, which helped to plan the detailed surgical procedures and avoid possible intraoperative pitfalls.

**CONCLUSION**

We successfully treated patella baja using autogenous ITB enhancement combined...
with sagittal tendon lengthening plasty. The repair and enhancement of the patellar tendon were achieved effectively and is a worthwhile approach for patients who have had multiple knee surgeries.

ACKNOWLEDGMENTS

We thank our patient for consenting to have his case presented and published.

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Sintilimab-induced autoimmune diabetes: A case report and review of the literature

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Author contributions: Yang J contributed to data curation; Tong XM and Wang Y contributed to project administration and resources; Yang J wrote the first draft; Tong XM reviewed and edited the manuscript.

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

Conflict-of-interest statement: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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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Country/Territory of origin: China

Abstract

BACKGROUND
With the widespread application of immune checkpoint inhibitor (ICI) therapy, the number of immune-related adverse effects (irAEs) has increased over the years. Autoimmune diabetes mellitus (DM) is a rare irAEs of ICIs and can be troublesome and life threatening.

CASE SUMMARY
We report a 78-year-old woman with no history of diabetes who presented with hyperglycemia up to 23.4 mmol/L (random blood glucose level) after 14 courses of sintilimab. Hemoglobin A1c was 8.2%, fasting insulin was 0.29 mIU/mL, and fasting C-peptide was decreased to a level with negative autoantibodies. Combining her medical history and laboratory examination, she was diagnosed with programmed cell death (PD)-1-inhibitor-induced, new-onset autoimmune DM. After controlling her blood glucose, she was treated with daily insulin by subcutaneous injection. She was allowed to continue anti-PD-1 therapy and she still obtained some therapeutic efficacy. We also reviewed some published cases (n = 36) of PD-1/PD-ligand 1 (PD-L1) inhibitor-induced DM. We also discuss potential pathogenic mechanisms, clinical features, prognostic markers (β cell antibodies, human leukocyte antigen type, PD-L1 Level) of this rare adverse effect.

CONCLUSION
It is important for all clinicians to be aware of DM as an irAEs of ICIs.

Key Words: Sintilimab; Immune related adverse effects; Small cell lung cancer; Autoim-
**INTRODUCTION**

Immune checkpoint inhibitors (ICIs) have been used widely in the treatment of various advanced malignancies. Programmed cell death (PD)-1 (also known as CD279) is one of the best-known ICs, and is expressed on T cells, B cells, activated monocytes, dendritic cells (DCs) and natural killer cells[1]. Its ligand PD-L1 (B7-H1, CD274) is expressed on antigen-presenting cells, macrophagocytes, nonhematopoietic cells and parenchymatous organs such as heart, lungs, placenta and liver. When PD-1 binds to PD-L1 (B7-H1, CD274)/PD-L2 (B7-DC, CD273), a signal that inhibits the proinflammatory ability of T cells and attenuates the function of cytotoxic T cells is delivered. T cell tolerance protects human tissues from immune-mediated tissue damage[2]. However, PD-1 and PD-L1 pathways are also seized by tumors, which impairs tumor immunity and facilitates tumor survival. PD-1/PD-L1 inhibitors remove the inhibitory signals of T cells, enhance cytotoxicity and increase cytokine production. Thus, ICIs can enhance the antitumor effect, but they also increase the chance of inflammatory injury (Figure 1).

According to recent research, ICIs induce immune-related adverse events (irAEs) that involve the whole body, including skin (46%–62%), gastrointestinal tract (22%–48%), autoimmune hepatitis (7%–33%), endocrine system (12%–34%), respiratory system (3%–8%) and urinary system (1%–7%)[3]. PD-1/PD-L1-inhibitor-associated autoimmune diabetes mellitus (DM) is rare, with an incidence rate of 0.1% in clinical trials[4]. ICI-induced DM (ICI-DM) is an irreversible event that can be life-threatening if not promptly recognized. Its incidence has increased with the widespread use of immunotherapy. Therefore, it is important for clinicians to fully understand the pathogenic mechanisms of these treatments and their potential irAEs.

Sintilimab is a PD-1 inhibitor that was newly approved in China for treatment of relapsed or refractory Hodgkin’s lymphoma in February 2019[5], and it is now also a feasible treatment for a variety of solid tumors, including non-small cell lung cancer and esophageal cancer. Small cell lung cancer (SCLC) is a malignant tumor with rapid metastasis and poor prognosis. Treatment of SCLC with sintilimab alone or combined with other chemotherapeutic drugs is rare and there are no reports published to describe its clinical effects. Here, we present the first case of new-onset autoimmune DM in a patient with SCLC during treatment with sintilimab, along with marked antitumor efficacy. We also provide a review of case reports of ICI-DM.

This study was conducted according to the advice of the Ethics Center of Zhejiang Provincial People’s Hospital. The patient’s written informed consent was obtained for publication of this case and any images or information that may identify the patient.

**CASE PRESENTATION**

**Chief complaints**

A 78-year-old Chinese woman was diagnosed with SCLC 1 year ago with no history of DM who presented with hyperglycemia up to 23.4 mmol/L (random blood glucose...
level) after 14 courses of sintilimab. The plasma glucose line shown in Figure 2.

History of present illness
The patient initially developed polyuria and polydipsia and her blood glucose level showed a mild increase after 12 cycles of sintilimab, but the treatment was continued. Two months later, the patient presented with hyperglycemia up to 23.4 mmol/L (random blood glucose level) with strong positive uric sugar (++++) and hemoglobin A1c of 8.2%.

History of past illness
The patient was diagnosed with SCLC on October 29, 2019 in the First Affiliated Hospital of Zhejiang University. She underwent endobronchial ultrasound-guided transbronchial needle aspiration, and the results were suggestive of poorly differentiated cell carcinoma, considered to be SCLC. Immunohistochemical staining demonstrated CKpan(+), P40(+), P63(+), Ki67 (50%+), TTF-1(+), CgA(+), Syn(+), CD56(+) and CD45(). The patient immediately underwent concurrent chemotherapy and immunotherapy for SCLC (extensive). She received her first treatment, etoposide 82 mg, days 1–3; cisplatin 20 mg, days 1–3; and sintilimab 200 mg, day 1; EP plan) on October 30, 2019. The patient came to our hospital to continue treatment. After we assessed her condition, she continued the EP treatment plan, but we reformulated the doses as follows: etoposide 240 mg, days 1–3; cisplatin 250 mg, days 1–3; and sintilimab 200 mg, day 1. This therapy did control her disease well, with decreased tumor markers and no metastases found on imaging. In the following days, she came to our hospital monthly for evaluation. Her blood glucose level was normal after treatment. After five cycles with the EP plan, we changed to sintilimab 200 mg and anlotinib 8 mg q.d. because of severe gastrointestinal adverse reactions. After three cycles of the new treatment, the patient developed lower urinary tract infection, such as urinary frequency, difficulty urinating, pain with urination, and hematuria. Therefore, we had to stop anlotinib and used levofloxacin to treat the infection. Hence, we used sintilimab monotherapy, and imaging showed good antitumor effects (Figure 2). During the treatment, the patient only had mild gastrointestinal symptoms such as nausea and poor appetite.

Personal and family history
The patient denied any other specific personal history. But she has family history of cancer, her grandmother died of lung cancer, whereas her father died of colorectal cancer.
Physical examination
Height: 151 cm; weight: 40.4 kg; body mass index: 17.71 kg/m². Physical examination was no positive signs.

Laboratory examinations
Other laboratory evaluation (Table 1) showed that urinary ketones were negative and blood pH was normal and the hypothalamic-pituitary-gonadal axis and hypothalamic-pituitary-adrenocortical axis were negative; but antithyroid autoantibodies were 17.80 IU/mL (normal< 4.0 IU/mL) and antithyroid peroxidase autoantibodies were 10.0 IU/mL (normal < 9.0 IU/mL). The islets antibodies tests were all negative, including anti-glutamic acid decarboxylase 65 (GADA) antibody, anti-islet cell antibody, and anti-insulin antibody tests were all negative. Moreover, zinc transporter 8 antibody levels were unavailable in our hospital. Human leukocyte antigen (HLA) class I and II, which was shown in Table 2, including HLA-A, B, C, DRB1, DQB1 and DPB1, were tested by polymerase chain reaction-sequence based typing (PCR-SBT).

Imaging examinations
According to the computed tomography scanning of the patient’s chest (Figure 3B), the tumor was shrinking, which indicated that anti-PD-1 therapy was effective.

FINAL DIAGNOSIS
The patient had no history of DM or autoimmune disease before treatment, and there was no medication, infection, thromboembolic event, or other factor that could cause hyperglycemia; according to the laboratory evaluation, thus, sintilimab-induced, new-onset autoimmune DM was diagnosed.

TREATMENT
Intravenous fluid infusion, continuous subcutaneous insulin infusion (insulin infusion pump therapy) and other supportive treatments were administered. After 10 d of insulin infusion pump therapy, the patient’s plasma glucose returned to normal levels. We performed a simple oral glucose tolerance test that revealed that the fasting and 0–2-h insulin levels were 0.29 and 2.50 IU/mL; fasting and 0–2-h C-peptide levels were 0.22 and 0.52 ng/mL, which indicated an insufficient function of pancreatic islet β
<table>
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<th>Laboratory data at presentation</th>
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<td><strong>BMI (kg/m^2)</strong></td>
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<td><strong>Finger prick glucose (mmol/L)</strong></td>
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</tr>
<tr>
<td><strong>IL-6 (0.00–5.00 pg/mL)</strong></td>
<td>0.00</td>
</tr>
<tr>
<td><strong>IL-10 (0.00–5.90 pg/mL)</strong></td>
<td>0.13</td>
</tr>
<tr>
<td><strong>TNF-α (0.00-6.00 pg/mL)</strong></td>
<td>0.81</td>
</tr>
<tr>
<td><strong>IFN-γ (0.00–6.00 pg/mL)</strong></td>
<td>1.36</td>
</tr>
<tr>
<td><strong>IL-17A (0.00–5.90 pg/mL)</strong></td>
<td>0.70</td>
</tr>
</tbody>
</table>

BMI: Body mass index; TSH: Thyroid-stimulating hormone; FT4: Free thyroxine; FT3: Free triiodothyronine; TT4: Total thyroxine; TT3: Total triiodothyronine; PTH: Parathyroid hormone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; ACTH: Adrenocorticotropic hormone; HGH: Human growth hormone; IL: Interleukin; TNF-α: Tumor necrosis factor alpha; IFN-γ: Interferon gamma; ATG: Anti-thyroglobulin antibodies; TPO: Thyroid peroxidases antibody; GAD: Anti-glutamic acid decarboxylase 65; ICA: Anti-islet cell antibody; IAA: Anti-insulin antibody; ZnT8: Zinc transporter8 antibody; ARR: Aldosterone/renin ratio.

Subsequently, she was switched to once-daily basal insulin detemir (long-acting insulin, 10 U) plus thrice-daily premeal insulin aspart (fast acting insulin, 11 U, respectively 3U, 4U, 3U three meals) subcutaneous injection for long-term treatment.
### Table 2 High-resolution genotyping of human leukocyte antigen class I and II of patient with diabetes induced by immune checkpoint inhibitor

<table>
<thead>
<tr>
<th>HLA type</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>DRB1</th>
<th>DQB1</th>
<th>DPB1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alleles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>02:01</td>
<td>35:03</td>
<td>04:01</td>
<td>04:01</td>
<td>03:01</td>
<td>02:01</td>
</tr>
<tr>
<td></td>
<td>24:02</td>
<td>51:05</td>
<td>14:02</td>
<td>14:03</td>
<td>03:02</td>
<td>02:01</td>
</tr>
</tbody>
</table>

HLA: Human leukocyte antigen.

**Figure 3** Course of treatment of patients with diabetes induced by immune checkpoint inhibitors. A: Changes of gastrin-releasing peptide precursor level during each period; B: Contrast-enhanced chest computed tomography during each period. Red arrows indicate the tumors.

### OUTCOME AND FOLLOW-UP

By the time the manuscript was completed, the patient was without evidence of SCLC recurrence with no further treatment since sintilimab (Figure 3). Other endocrine adverse effects such as thyroiditis and hypophysitis did not occur. We retrieved 36 relevant case reports from 2016 to 2020 in PubMed to determine the common features of ICI-DM (Table 3)[6-37]. Table 4 summarizes the key features.

### DISCUSSION

Sintilimab is a fully humanized IgG4 monoclonal antibody that binds to PD-1, then interferes with the interaction of PD-1 and its ligands (PD-L1 and PD-L2), thus
### Table 3: Reported cases of diabetes induced by immune checkpoint inhibitors

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Sex/Age (yr)</th>
<th>Primary diagnosis</th>
<th>Relevant history</th>
<th>Anti-PD-1/Anti-PD-L1 drug</th>
<th>Other chemotherapies</th>
<th>Presentation</th>
<th>Other side effects</th>
<th>HbA1c</th>
<th>C peptide</th>
<th>Antibodies</th>
<th>Time with anti-PD-1 (w)</th>
<th>HLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Araújo et al[6], 2017</td>
<td>F/73</td>
<td>NSCLC</td>
<td>N</td>
<td>Nivolumab</td>
<td>Carboplatin +pemetrexed</td>
<td>DKA</td>
<td>N</td>
<td>7.20%</td>
<td>0.06 ng/ml</td>
<td>GAD+</td>
<td>5</td>
<td>High risk: DR3-DQ2/DR4-DQ8</td>
</tr>
<tr>
<td>Li et al[7], 2020</td>
<td>M/73</td>
<td>NSCLC</td>
<td>N</td>
<td>Nivolumab</td>
<td>Sunitinib</td>
<td>DKA</td>
<td>N</td>
<td>10.90%</td>
<td>0.24 ng/mL</td>
<td>-</td>
<td>30</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Abdullah et al[8], 2019</td>
<td>M/68</td>
<td>Melanoma</td>
<td>N</td>
<td>Nivolumab</td>
<td>None</td>
<td>DKA</td>
<td>N</td>
<td>Unavailable</td>
<td>0.1 ng/mL</td>
<td>-</td>
<td>4</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Kapke et al[9], 2017</td>
<td>M/83</td>
<td>Oral squamous cell carcinoma</td>
<td>Hypothyroidism</td>
<td>Nivolumab</td>
<td>None</td>
<td>DKA</td>
<td>N</td>
<td>Unavailable</td>
<td>0.32 ng/mL</td>
<td>GAD+</td>
<td>12</td>
<td>High risk: DRB1<em>08, DRB1</em>11, DQB1<em>03, DQB1</em>04, DQA1<em>04, and DQA1</em>05.</td>
</tr>
<tr>
<td>Kapke et al[9], 2017</td>
<td>F/63</td>
<td>Urothelial carcinoma of the bladder</td>
<td>Hypothyroidism</td>
<td>Atezolizumab</td>
<td>Gemcitabine + cisplatin</td>
<td>DKA</td>
<td>N</td>
<td>Unavailable</td>
<td>0.02 ng/mL</td>
<td>GAD+</td>
<td>6</td>
<td>High risk: DRB1<em>03, DRB1</em>04, DQB1<em>03, DQB1</em>04, DQA1<em>03, and DQA1</em>05.</td>
</tr>
<tr>
<td>Lowe et al[10], 2016</td>
<td>M/54</td>
<td>Melanoma</td>
<td>N</td>
<td>Nivolumab +ipilimumab</td>
<td>None</td>
<td>DKA</td>
<td>Autoimmune, thyroiditis</td>
<td>Unavailable</td>
<td>&lt; 0.1 ng/mL</td>
<td>GAD+</td>
<td>19</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Rahman et al[11], 2020</td>
<td>M/64</td>
<td>Renal cell carcinoma</td>
<td>T2DM</td>
<td>Atezolizumab</td>
<td>Bevacizumab</td>
<td>DKA</td>
<td>N</td>
<td>Unavailable</td>
<td>Unavailable</td>
<td>GAD+</td>
<td>12</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Mengibar et al[12], 2019</td>
<td>M/55</td>
<td>Urothelial carcinoma of the bladder</td>
<td>Family history of T1D</td>
<td>Durvalumab</td>
<td>None</td>
<td>DKA</td>
<td>Hypothyroidism</td>
<td>8.40%</td>
<td>0.02 ng/mL</td>
<td>GAD+, IA2+</td>
<td>3</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Kichloo et al[13], 2020</td>
<td>F/77</td>
<td>Colonic adenocarcinoma</td>
<td>N</td>
<td>Pembrolizumab</td>
<td>FOLFOX (leucovorin, fluorouracil, oxaliplatin)</td>
<td>DKA</td>
<td>N</td>
<td>8.80%</td>
<td>Unavailable</td>
<td>-</td>
<td>44</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Delasos et al[14], 2020</td>
<td>M/77</td>
<td>Neuroendocrine tumor</td>
<td>N</td>
<td>Nivolumab</td>
<td>Carboplatin + etoposide</td>
<td>DKA</td>
<td>N</td>
<td>8.30%</td>
<td>Unavailable</td>
<td>-</td>
<td>28</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Hickmott et al[15], 2017</td>
<td>M/57</td>
<td>Urothelial cancer</td>
<td>N</td>
<td>Atezolizumab</td>
<td>Cisplatin + gemcitabine</td>
<td>DKA</td>
<td>N</td>
<td>7.50%</td>
<td>0.65 ng/mL</td>
<td>-</td>
<td>15</td>
<td>High risk: DRB1<em>11, DRB1</em>04, DRB3<em>02, DRB4</em>01, DQB1<em>03, DQB1</em>03</td>
</tr>
<tr>
<td>Sothornwit et al[16], 2017</td>
<td>F/52</td>
<td>NSCLC</td>
<td>N</td>
<td>Atezolizumab</td>
<td>None</td>
<td>DKA</td>
<td>Transaminitis</td>
<td>7.90%</td>
<td>0.1 ng/ml</td>
<td>GAD+</td>
<td>24</td>
<td>DRB1<em>03, DRB1</em>14, DQB1<em>02, DQB1</em>03 (DR3-6)</td>
</tr>
<tr>
<td>Study</td>
<td>Gender</td>
<td>Age</td>
<td>Diagnosis</td>
<td>Treatment</td>
<td>Additional Treatments</td>
<td>Symptoms</td>
<td>GLUCOSE</td>
<td>GAD</td>
<td>IA2</td>
<td>DRB1*</td>
<td>DQA1*</td>
<td>DQB1*</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------</td>
<td>-----</td>
<td>-----------</td>
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<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Changizadeh et al [17], 2019</td>
<td>M/44</td>
<td></td>
<td>Melanoma</td>
<td>Nivolumab + ipilimumab</td>
<td>None</td>
<td>DKA</td>
<td>N</td>
<td>6.50%</td>
<td>Unavailable</td>
<td>-</td>
<td>12</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Gunawan et al [18], 2018</td>
<td>M/52</td>
<td></td>
<td>Melanoma</td>
<td>Nivolumab + ipilimumab</td>
<td>None</td>
<td>hyperglycemia Ketonuria</td>
<td>Hypophysitis, thyroiditis, adrenal inefficiency</td>
<td>7.70%</td>
<td>0.05 nmol/L (0.016 ng/ml)</td>
<td>-</td>
<td>3</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Gunjur et al [19], 2018</td>
<td>F/77</td>
<td></td>
<td>Melanoma</td>
<td>Pembrolizumab</td>
<td>None</td>
<td>DKA</td>
<td>Thyroiditis</td>
<td>6.9% (normal range: &lt;6.5%)</td>
<td>0.07 ng/ml</td>
<td>GAD+IA2+</td>
<td>3</td>
<td>DRB1<em>04:16, DQB1</em>02:05 and DQA1*01:03</td>
</tr>
<tr>
<td>Atkins et al [20], 2018</td>
<td>M/50</td>
<td></td>
<td>Squamous cell carcinoma of the tonsil</td>
<td>Avelumab</td>
<td>Utomilumab</td>
<td>DKA</td>
<td>N</td>
<td>6.40%</td>
<td>63 pmol/L</td>
<td>GAD+</td>
<td>4</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Marchand et al [21], 2019</td>
<td>F/65</td>
<td></td>
<td>Melanoma</td>
<td>Nivolumab + ipilimumab</td>
<td>None</td>
<td>DKA</td>
<td>Hyperosinophilia</td>
<td>7.30%</td>
<td>&lt;0.1 ng/mL</td>
<td>-</td>
<td>12</td>
<td>DRB1<em>01:01 DQA1</em>01 DQB1<em>03:01 DRB1</em>11:01 DQA1<em>05 DQB1</em>05:01</td>
</tr>
<tr>
<td>Tzoulis et al [22], 2018</td>
<td>F/56</td>
<td></td>
<td>NSCLC</td>
<td>Nivolumab</td>
<td>Pemetrexed + cisplatin</td>
<td>DKA</td>
<td>N</td>
<td>8.20%</td>
<td>Undetectable</td>
<td>GAD+</td>
<td>7</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Pontharuchkareon et al [23], 2020</td>
<td>M/70</td>
<td></td>
<td>NSCLC</td>
<td>Pembrolizumab + ipilimumab</td>
<td>None</td>
<td>DKA</td>
<td>IAD</td>
<td>&lt; 0.1 ng/mL</td>
<td>-</td>
<td>14</td>
<td>Unavailable</td>
<td></td>
</tr>
<tr>
<td>Lee et al [24], 2020</td>
<td>M/67</td>
<td></td>
<td>NSCLC</td>
<td>Nivolumab</td>
<td>Carboplatin + paclitaxel</td>
<td>DKA</td>
<td>Thyroiditis</td>
<td>7.60%</td>
<td>&lt;0.1 ng/mL</td>
<td>GAD+</td>
<td>2</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Leonardi et al [25], 2019</td>
<td>M/66</td>
<td></td>
<td>NSCLC</td>
<td>Pembrolizumab</td>
<td>None</td>
<td>hyperglycemia Ketonuria</td>
<td>7.6% (4.2%–5.8%)</td>
<td>0.3 ng/mL</td>
<td>GAD+</td>
<td>12</td>
<td>Unavailable</td>
<td></td>
</tr>
<tr>
<td>Wong et al [26], 2020</td>
<td>F/55</td>
<td></td>
<td>Squamous cell lung carcinoma.</td>
<td>Atezolizumab</td>
<td>None</td>
<td>hyperglycemia Ketonuria</td>
<td>Unavailable</td>
<td>0.6nmol/L (0.19 ng/ml) ZnT8+</td>
<td>8</td>
<td>Unavailable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chokr et al [27], 2018</td>
<td>F/61</td>
<td></td>
<td>Melanoma</td>
<td>Nivolumab + ipilimumab</td>
<td>None</td>
<td>DKA</td>
<td>N</td>
<td>6.90%</td>
<td>&lt;0.1 ng/mL</td>
<td>-</td>
<td>9</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Chan et al [28], 2017</td>
<td>M/74</td>
<td></td>
<td>Melanoma</td>
<td>Nivolumab + ipilimumab</td>
<td>None</td>
<td>DKA</td>
<td>Transaminitis</td>
<td>Unavailable</td>
<td>Unavailable</td>
<td>-</td>
<td>14</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Zezza et al [29], 2019</td>
<td>F/60</td>
<td></td>
<td>Melanoma</td>
<td>Nivolumab + ipilimumab</td>
<td>None</td>
<td>DKA</td>
<td>N</td>
<td>7.60%</td>
<td>Unavailable</td>
<td>GAD+ICA+, IA2+</td>
<td>2</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Zezza et al [29], 2019</td>
<td>F/80</td>
<td></td>
<td>Melanoma</td>
<td>Nivolumab + ipilimumab</td>
<td>None</td>
<td>DKA</td>
<td>Thyroiditis</td>
<td>Unavailable</td>
<td>GAD+</td>
<td>3</td>
<td>Unavailable</td>
<td></td>
</tr>
<tr>
<td>Shibuya et al [30], 2019</td>
<td>F/79</td>
<td></td>
<td>Merkel cell carcinoma</td>
<td>Avelumab</td>
<td>None</td>
<td>Hyperglycemia Ketonuria</td>
<td>7.50%</td>
<td>&lt;0.1 ng/mL</td>
<td>-</td>
<td>20</td>
<td>High risk: DRB1<em>09:01:02 DRB1</em>14:54:01 DQA1<em>01:04 DQA1</em>03:02 DQB1<em>05:02:01 and DQB1</em>05:01</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** DKA = Diabetic ketoacidosis, IAD = Interstitial acidosis, ZnT8 = Zinc transporter 8.
activating and restoring the function of T cells, which contributes to an obvious antitumor effect. Accordingly, some normal tissues have been damaged in this process by the increase of cytokines. ICI-DM has rarely been reported as an irAE of anti-PD1/PD-L1 therapy, and primarily in case reports.

In our review of case reports, the main tumor types were melanoma (13/36, 36.1%) and non-SCLC (8/36, 22.2%). The different treatment regimens included monotherapy with anti-PD-1 (19/36, 52.7%) anti-PD-L1 (8/36, 22.2%) or a combination of anti-PD1/PD-L1 therapy, and primarily in case reports.

| Marchand et al[21], 2019 | M/65 Melanoma N Nivolumab None DKA Hashimoto 8.5% (74 mmol/mol) <0.1 ng/mL - 34 | High risk: DRB1*04:01 DQA1*02 DQB1*02:02 DRB1*07:01 DQA1*03 DQB1*03:01 |
| Okamoto et al[31], 2016 | F/55 Melanoma N Nivolumab Acarbazine, + nimustine, + cisplatin + tamoxifen Hyperglycemia Ketonuria N 7.00% 1.0 ng/mL - 48 | High risk: DRB1*04:05 DQB1*04:01 |
| Godwin et al[32], 2017 | F/34 NSCLC N Nivolumab Carboplatin + pemetrexed DKA N 7.1% (normal range 4.6-6.1%) <0.1 ng/mL GAD+, IA2+ ZnT8+ 3 A30:01, 30:02 (A30) D09:CTZ, 09:CTZ (DR9) |
| Smith-Cohn et al[33], 2017 | F/66 Cholangiocarcinoma N Pembrolizumab None Hyperglycemia N 8.7% (4.2%-5.8%) Unavailable GAD+ 12 Unavailable |
| Marchand et al[21], 2019 | M/83 Melanoma N Pembrolizumab None Hyperglycemia Hashimoto’s disease 9.40% 1.0 ng/mL - 12 DRB1*01:01 DQA1*01 DQB1*05:01/ DRB1*16:01 DQA1*01 DQB1*05:02 |
| Maamari et al[34], 2019-3 | F/47 Cardiac angiosarcoma N Pembrolizumab Ifosfamide, gemcitabine, docetaxel DKA N 6.40% 0.1 ng/mL GAD+ 3 Unavailable |
| Tassone et al[35], 2019-9 | M/42 Pulmonary adenocarcinoma N Nivolumab None DKA N Unavailable 0.2 ng/dL (2ng/ml) GAD+ 12 DRB1*03:15-DQB1*02:06 |
| Yilmaz et al[36], 2020-8 | M/49 Renal cell carcinoma N Nivolumab None DKA N 10.90% 2.4 ng/mL - 44 Unavailable |
| Wen et al[37], 2020 | M/56 Hepatocellular carcinoma N Sintilimab None DKA N 7.80% 1.12 ng/mL - 24 DRB1*12:01 DRB1*12:02; DQB1*05:03 DQB1*03:01; DQA1*01:04 DQA1*06:01 |

TIDM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; GAD: Anti-glutamic acid decarboxylase antibody; HLA: Human leukocyte antigen; irAE: Immune-related adverse effect; SCLC: Small cell lung cancer; NSCLC: Non-small cell lung cancer; DKA: Diabetic ketoacidosis; Ad: Adenocarcinoma; IAD: Isolated adrenocorticotropic hormone deficiency; N: None.
Table 4 Characteristics of patients with diabetes induced by immune checkpoint inhibitors

<table>
<thead>
<tr>
<th>Reported cases</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor types</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>13/36 (36.1)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>8/36 (22.2)</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>2/36 (5.6)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>3/36 (8.3)</td>
</tr>
<tr>
<td>Other cancers</td>
<td>10/36 (27.8)</td>
</tr>
<tr>
<td>ICBs</td>
<td></td>
</tr>
<tr>
<td>Anti PD-1</td>
<td>19/36 (52.7)</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>12</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>6</td>
</tr>
<tr>
<td>Sintilimab</td>
<td>1</td>
</tr>
<tr>
<td>Anti PD-L1</td>
<td>8/36 (22.2)</td>
</tr>
<tr>
<td>Avelumab</td>
<td>2</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>5</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>1</td>
</tr>
<tr>
<td>Anti PD-1+CTLA-4</td>
<td>9/36 (25.0)</td>
</tr>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>8</td>
</tr>
<tr>
<td>Pembrolizumab + ipilimumab</td>
<td>1</td>
</tr>
<tr>
<td>Demographic data</td>
<td></td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>16/20</td>
</tr>
<tr>
<td>Average age (yr)</td>
<td>58.8</td>
</tr>
<tr>
<td>Time of diagnosis after start of (w)</td>
<td>14.6</td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
</tr>
<tr>
<td>DKA</td>
<td>29/36 (80.6)</td>
</tr>
<tr>
<td>Hyperglycemia Ketonuria</td>
<td>8/36 (22.2)</td>
</tr>
<tr>
<td>HbA1c, % (avg)</td>
<td>7.8 26/36</td>
</tr>
<tr>
<td>Relevant history</td>
<td></td>
</tr>
<tr>
<td>T2DM</td>
<td>3/36 (8.3)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2/36 (5)</td>
</tr>
<tr>
<td>Family history of T1DM</td>
<td>2/36 (5)</td>
</tr>
<tr>
<td>None</td>
<td>29/36 (80.5)</td>
</tr>
<tr>
<td>Antibodies</td>
<td></td>
</tr>
<tr>
<td>GAD+</td>
<td>18/36 (50)</td>
</tr>
<tr>
<td>IA-2+</td>
<td>4/36 (10)</td>
</tr>
<tr>
<td>ZnT8+</td>
<td>2/36 (5)</td>
</tr>
<tr>
<td>Negative</td>
<td>12/36 (33.3)</td>
</tr>
</tbody>
</table>

NSCLC: Non-small cell lung cancer; PD-L1: Programmed death-ligand 1; DKA: Diabetic ketoacidosis; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; GAD: Anti-glutamic acid decarboxylase antibody.

CTLA-4 with anti-PD-1 (9/36, 25.0%). Diabetic ketoacidosis (DKA) was the first sign of diabetes in 29 of 36 (80.5%) case reports, which is similar to 85.7% in another study [38], and the average time from initiation of anti-PD-1/PD-L1 therapy to diagnosis of
ICI-DM was 14.6 wk (range 2–48 wk). Low C-peptide levels were present at diagnosis in 82% (23/28) of cases. In addition, 26 of 36 patients presented with a median glycated hemoglobin level of 7.6% (average: 7.8%; range: 6.4%–10.9%), which is the same as in other studies[39,40]. Most of the patients did not have relevant autoimmune history, which was only seen in 18.3% of our reviewed cases. These case reports have different definitions for ICI-DM. Since the syndrome has similarities with classic type 1 (T1)DM, most reports simply classified ICI-DM as T1DM, but ICI-DM has its own features. We found several significant features of ICI-DM: (1) Abrupt onset of hyperglycemia, and low to absent insulin C-peptide levels; (2) Rapid destruction of islets β cells, leading to endogenous insulin deficiency; and (3) High risk of DKA[39]. In addition to the above features, ICI-DM does not have a “honeymoon period” like juvenile T1DM, nor does it have GADA as in latent autoimmune DM in adults[41].

Similar to a previous study[39], our autoantibody analysis was positive in 50% of patients for GADA. Some studies have demonstrated that GADA-positive patients developed ICI-DM in the first 2 mo after initiation of therapy, and GADA-negative patients developed ICI-DM after 2 mo of treatment[42]. Patients with any positive diabetes autoantibodies at the time of presentation of ICI-DM have fewer cycles than those with negative autoantibodies. Our results showed that GADA-positive patients had ICI-DM onset at an average of 8 wk after immunotherapy compared with 22.8 wk in GADA-negative patients. It has been demonstrated that the interval from initiation of anti-PD-1/PD-L1 therapy and onset of ICI-DM is related to the presence/absence of GADA. Serological examination of GADA prior to anti-PD-1/PD-L1 therapy might be helpful for predicting the development of ICI-DM. In addition, several major histocompatibility complex and HLA molecules are associated with increased susceptibility to T1DM, especially HLA-DRB1, -DQB1 and -DQA1[43]. Different combinations of DRB1, DQB1 and DQA1 determine the extent of haplotype risk. The most susceptible HLA haplotypes are DRB1*0405–DQA1*0301–DQB1*0302, followed by DRB1*0401–DQA1*0301–DQB1*0302, DRB1*0301–DQA1*0501–DQB1*0201, and DRB1*0402–DQA1*0301–DQB1*0302. Subsequently, DQB1*0302 allele is the key susceptibility allele[44]. However, another study confirmed that DPB1*0301 and DPB1*0202 are also susceptible haplotypes for T1DM. Hence, the HLA typing of our patient (Table 2) showed a high risk of T1DM. Based on this evidence, there were seven patients with high-risk genes for T1DM among 13 patients tested. Accordingly, understanding the association between HLA and the development of ICI-DM by anti-PD-1/PD-L1 therapy is significant in predicting susceptible patients. When clinical features are discordant with the results of autoantibody testing, genetic risk score (GRS) could be an important addition to diagnosis of ICI-DM. This GRS summarizes risk-associated variation across the genome of T1DM[45]. One limitation of our case was the lack of information before sintilimab, such as autoimmune antibodies and genetic factors like HLA genotypes that may predispose to endocrine irAEs.

Multiple studies have indicated both the PD-1 and CTLA-4 pathways in the pathogenesis of T1DM and suggest a synergistic effect between these two negative regulatory receptors to enhance autoimmune disorders. Furthermore, the incidence of ICI-induced endocrine irAEs is significantly higher in patients treated with combination immunotherapy compared with single immunotherapy. The incidence of thyroid dysfunction is high in patients treated with single PD-1 antibodies. In contrast, the incidence of hypophysitis is highest in patients treated with ipilimumab[46]. Similarly, our review also found that combination of PD-1 inhibitor and anti-CTLA-4 therapy causes endocrine dysfunction. The most common combination was nivolumab and ipilimumab. An animal study found that single CTLA-4 blockers in nonobese diabetic (NOD) mice only induced diabetes in baby mice, while PD-1 blocked secondary diabetes in NOD mice at any age[47]. A recent case reported that ipilimumab induced T1DM. The mechanism by which single anti-CTLA-4 therapy induced ICI-DM was unclear and needs further study[48]. However, a randomized, double-blind, phase 3 study suggested that combination of immunotherapy significantly increases progression-free survival more than monotherapy does[49]. Therefore, it is important for clinicians to consider whether to continue to use combination therapy when endocrine irAEs appear.

T1DM is caused by destruction of pancreatic β cells by virus infection, genetic factors and autoimmune disorders[32]. Accordingly, the main mechanism of ICI-DM may be islet cell damage. There is an active interaction between β cells and immune cells during insulitis. This kind of interaction usually has a largely negative effect on β cells. An animal study has shown that PD-1 deficiency accelerates the occurrence and frequency of T1DM in NOD mice, and infiltration of pancreatic islets by T cells with strong T helper 1 polarization[50]. In addition, animal and human experiments have shown that PD-L1 in insulin-positive cells of T1DM, but absent in nondiabetic
individuals and type 2 DM, is mainly due to islet β cell expression[6]. The present data indicate that interferon (IFN)-α and IFN-γ are the main regulators of PD-L1 expression in human pancreatic β cells, especially IFN-γ. IFN-γ suppresses autoreactive T cells by upregulating PD-L1. In other words, PD-L1 protects islet β cells to delay progression of DM and even prevent its onset[50-52]. Yet, IFN-α and IFN-γ induce proinflammatory responses. For instance, HLA class I upregulation, cytokine production and endoplasmic reticulum stress are harmful to the human body, including the pancreas. Inhibition of signal transducer and activator of transcription 2 can prevent IFN-induced HLA class I expression, and at the same time allow PD-L1 upregulation[53], but this lacks clinical validation. Therefore, the level of PD-L1 expression may serve as an additional criterion for irAEs after ICI treatment. PD-L1 expression can also be used as a prognostic marker of immunotherapy[55]. In our patient, in spite of tumor necrosis factor-α, IL-1β and IFN-γ, all of the cytokines were normal during treatment with sintilimab, which suggest the particular pathogenic mechanism of ICI-DM. However, the precise mechanism mediating ICI-DM is still unclear. Further studies are required to elucidate the pathogenesis and background factors for this form of DM.

CONCLUSION

This is the second case of sintilimab-induced autoimmune DM. The first one was a recently published case report of autoimmune DM diagnosed in a patient with hepatocellular carcinoma[37]. What makes our case different from others is that there was no DKA in the process of DM. This may be because patients were regularly monitored for plasma glucose level. This illustrates the importance of regular monitoring of glucose during immunotherapy for inhibiting progression of DM. Furthermore, based on the information collected in our review, we recommend measuring PD-L1 expression, HLA typing, islet cell antibody testing, C peptide measurement, or even determining T1DM-associated GRS for clinicians before or during immunotherapy. We can compare symptom severity and therapeutic efficacy in DM patients with or without a history of DM after treatment with PD-1/PD-L1 inhibitors in the future, so as to evaluate whether patients with potential risk of DM are suitable for treatment with PD-1/PD-L1 inhibitors.

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Unicentric Castleman disease was misdiagnosed as pancreatic mass: A case report

Hong-Yan Zhai, Xin-Yuan Zhu, Gui-Ming Zhou, Li Zhu, Dan-Dan Guo, Hao Zhang

BACKGROUND
Castleman’s disease (CD) is a lymphatic proliferative disorder of unknown cause and is rarely seen clinically. It has been divided into unicentric and multicentric types. Unicentric CD (UCD) occurs as a solitary enlarged mass and mediastinal lymph nodes are the most common site. Surgical excision has proven to be curative for UCD. Multicentric CD (MCD) appears as a systemic disease with peripheral lymphadenopathy. MCD had a poor response to surgery and monoclonal antibodies with rituximab have become a research hotspot.

CASE SUMMARY
A 44-year-old woman presented with a pancreatic mass during routine physical examination. She had no obvious symptoms, such as fever, abdominal pain, abdominal distension, or jaundice. Ultrasound examination indicated a hypoechoic mass between the body of the pancreas, left lobe of the liver and stomach. It had a clear boundary, irregular shape, uneven echo, and no obvious blood flow signals. To clarify the diagnosis, contrast-enhanced ultrasound examination was performed, which showed a benign pancreatic lesion. Neuroendocrine or solid pseudopapillary tumor was a possible diagnosis. The patient underwent further contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging, which were suggestive of solid pseudopapillary tumor or neuroendocrine tumor. All the examinations failed to give a definitive diagnosis, and the patient underwent surgery. The final pathological and immunohistochemical results showed that the mass was CD.
This case highlights when lymphadenopathy is encountered clinically, CD should be considered and a biopsy should be performed.

Key Words: Castleman’s disease; Lymphadenopathy; Unicentric; Multicentric; Contrast-enhanced ultrasound; Case report

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Core Tip: Castleman’s disease (CD) is a lymphoproliferative disorder of unknown cause. We present a rare case of unicentric CD. A 44-year-old woman presented with a pancreatic mass during routine physical examination. The patient had no obvious symptoms. None of the three enhanced images gave a clear diagnosis. The patient underwent surgery. The final pathological and immunohistochemical results showed that the mass was CD. This case highlights when lymphadenopathy is encountered clinically, CD should be considered and a biopsy performed. It is especially important to rule out diseases with known causes first.

INTRODUCTION

Castleman’s disease (CD) is a lymphoproliferative disorder of unknown cause and is rarely seen clinically. The pathological features are obvious proliferation of lymph follicles, blood vessels and plasma cells. CD is divided into two main types: Unicentric CD (UCD) and multicentric CD (MCD). UCD occurs as a solitary enlarged mass and mediastinal lymph nodes are the most commonly affected. Surgical excision has proven to be curative for UCD. MCD appears as a systemic disease with peripheral lymphadenopathy. MCD has a poor response to surgery and monoclonal antibodies with rituximab have become a research hotspot. Here, we present a 40-year-old woman with characteristic clinical, radiological and histological findings of UCD, demonstrating an incidental retroperitoneal mass misdiagnosed as pancreatic tumor.

CASE PRESENTATION

Chief complaints
A 40-year-old woman presented to the ultrasound department of our hospital complaining of a pancreatic mass found by physical examination. She came to our hospital to clarify the diagnosis. She had no obvious conscious symptoms, such as fever, abdominal pain, abdominal distension, or jaundice.

History of present illness
The patient had no obvious conscious symptoms, such as fever, abdominal pain, abdominal distension, or jaundice.

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

Personal and family history
The patient had no personal or family medical history.

Physical examination
The patient’s temperature was 36.6 °C, heart rate 73 bpm, respiratory rate 16 breaths/min, blood pressure 120/70 mmHg and oxygen saturation in room air 98%.
Clinical abdominal examination did not reveal any positive signs. Our clinical considerations were benign or malignant tumor of the pancreas.

**Laboratory examinations**

Blood analysis showed normal prothrombin and partial thromboplastin times and D-dimer level. Urinalysis was normal for a-fetoprotein, ferritin, carcinoembryonic antigen, carbohydrate antigen-199, sugar chain antigen as well as human epididymal epithelial secretory protein.

**Imaging examinations**

Initial imaging with conventional ultrasound (US) examination, revealed a 3.2 cm × 2.5 cm hypoechoic mass between the body of the pancreas, left lobe of the liver and stomach, with clear boundaries, irregular shape, uneven echoes, and no obvious blood flow signals. In order to make a diagnosis, the patient underwent contrast-enhanced US (CEUS) examination. CEUS showed hyperenhancement of the lesion in the arterial phase, and slightly high enhancement in the venous phase. CEUS suggested differential diagnosis of benign pancreatic tumor, neuroendocrine tumor or solid pseudopapillary tumor, but the possibility of tumor in other organs could not entirely be excluded (Figure 1).

The lesion was further evaluated by computed tomography (CT) and magnetic resonance imaging (MRI). CT revealed a mixed density nodule located above the pancreatic body that was convex and shallowly lobulated, showing uneven progressive enhancement, and the degree of enhancement in each stage was lower than that of pancreatic parenchyma (Figure 2). MRI revealed an isointense lesion located above the pancreatic body that was clearly separated from the normal pancreas. The edge was enhanced in the arterial phase, and the degree of internal enhancement in each phase was lower than that of the pancreatic parenchyma. As most pancreatic adenocarcinomas have poor blood supply, they usually display low enhancement on arterial phase of enhanced images. However, the lesion in this case showed rich blood supply on CEUS, enhanced MRI, and enhanced CT, so pancreatic adenocarcinoma was ruled out. Therefore, we believed that the abnormal enhancement of the upper part of the pancreatic body was a solid pseudopapillary tumor or a neuroendocrine tumor.

**Further diagnostic work-up**

All the examinations failed to give a definitive diagnosis; therefore, the patient underwent surgery. During the surgery, we observed a 3 cm × 2 cm mass above the pancreatic body, with a clear boundary and tough texture, located anterior to the bifurcation of the splenic artery and the common hepatic artery, pushing the upper edge of the pancreas interior to it. Careful separation of the adhesion between the tumor and the surrounding tissues along the surface of the tumor ensured that the tumor was well demarcated from the pancreas.

**FINAL DIAGNOSIS**

Mass resection was performed and histological examination revealed lymphoid tissue proliferation, with lymphoid follicular hyperplasia, mantle hyperplasia, interfollicular plasma cell hyperplasia, and local vascular hyperplasia (Figure 3). Plasma cells showed strong immunostaining for CD138 and IgG. IgG4 was occasionally positive and the expression rate was < 40%. No restrictive expression of kappa and lambda was observed. B and T cells were positive for CD20 and CD30. CD21 and CD23 showed the follicular dendritic cell network. Germinal center cells were positive for Bcl-2, and weakly positive for CD10 and Bcl-6. Cxc113 and cyclin D11 were positive in a few scattered cells. Ki-67 was highly expressed in germinal centers (Figure 4). These results gave the most likely diagnosis as CD.

**TREATMENT**

The patient underwent surgery to remove the mass located above the pancreatic body.
Figure 1 Patient underwent contrast-enhanced ultrasound examination. Conventional and contrast-enhanced ultrasound of the hypoechoic mass (stellate) between the body of the pancreas (white arrow), left lobe of the liver (white star) and stomach (orange arrow), which has clear boundaries, irregular shape, uneven echoes, and no obvious blood flow signals. The hypoechoic mass showed homogeneous hyperenhancement in the arterial phase, and slightly high enhancement in the venous phase, and measured approximately 56 mm × 37 mm × 25 mm.

OUTCOME AND FOLLOW-UP

The patient had an uneventful postoperative clinical course. Two months after surgical removal of the mass, the patient was asymptomatic, and a new MRI scan showed complete removal of the tumor.

DISCUSSION

CD is a lymphoproliferative disorder of unknown cause and is rarely seen clinically. The pathological features are obvious proliferation of lymph follicles, blood vessels and plasma cells. Clinically, it is characterized by significant enlargement of deep or superficial lymph nodes. Since its first recognition in 1956, understanding of CD has improved after segregation of UCD and MCD, showing distinctive prognosis and treatment approaches.

The incidence and prevalence of CD has become difficult to evaluate due to its rare occurrence in the general population, and it affects both sexes equally. UCD is usually found to have a peak incidence in the second to fourth decades of life. In most cases, UCD occurs as an isolated mediastinal lymph node enlargement. Patients present with a single lymph node with painless enlargement and slow growth, ranging from several centimeters to approximately 20 cm in diameter. Mediastinal lymph nodes are the most commonly affected, followed by cervical, axillary and abdominal lymph nodes. Occasionally, they are found in external tissues such as larynx, vulva, pericardium, subcutaneous muscle, lung, and orbit, as well as intracranially. Most patients have no systemic symptoms and a few complain of cough, dyspnea or other constitutional symptoms. Patients can survive for a long time after tumor resection, which is a benign course of disease.

MCD is rarer than UCD and tends to present later in the sixth and seventh decades. MCD has a constellation of systemic symptoms with peripheral lymphadenopathy involving multiple compartments throughout the neck, chest, abdomen and pelvis. It also has an association with human immunodeficiency virus and human herpesvirus-8 infections. In a few patients, multiple neuropathy, organ enlargement (liver and spleen), endocrine disease, serum immunoglobulin and skin disease were found simultaneously. MCD often presents with an invasive venereal course that is accompanied with infection.
Figure 2  The lesion was further evaluated by computed tomography and magnetic resonance imaging. A: Magnetic resonance imaging (MRI) showed a lesion of isointensity (white arrow) located above the pancreas body (stellate) which was clearly separated from the normal pancreas; B: Contrast-enhanced MRI revealed that the edge was enhanced in the arterial phase, and the degree of internal enhancement in each phase was lower than that of the pancreatic parenchyma; C: Computed tomography (CT) showed a nodule of mixed density (white arrow) located above the pancreatic body, which was convex and shallowly lobulated, measuring approximately 37 mm x 25 mm in maximum dimensions; D: Contrast-enhanced CT showed uneven progressive enhancement, and the degree of enhancement in each stage was lower than that of pancreatic parenchyma.

Figure 3  Hematoxylin and eosin staining revealed lymphoid tissue proliferation, with lymphoid follicular hyperplasia, mantle hyperplasia, interfollicular plasma cell hyperplasia, and local vascular hyperplasia.

Frizzera et al[6] proposed the diagnostic criteria of CD (Table 1). It should be pointed out that it may be difficult to make a definite and accurate clinical pathological diagnosis based on histopathology or clinical manifestations alone, and the two must be combined, especially for MCD.
<table>
<thead>
<tr>
<th>Unicentric</th>
<th>Multicentric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swollen lymph nodes in a single site</td>
<td>Significant swollen lymph node and involvement of multiple peripheral lymph nodes</td>
</tr>
<tr>
<td>Characteristic hyperplastic histopathological changes and exclude possible primary disease</td>
<td>With characteristic hyperplastic histopathological changes</td>
</tr>
<tr>
<td>No systemic symptoms</td>
<td>Multiple system involvement performance</td>
</tr>
<tr>
<td>Long-term survival after tumor removal</td>
<td>Rule out known possible causes</td>
</tr>
</tbody>
</table>

Table 1 Castleman’s disease diagnostic criteria proposed by Frizzera et al[6] in 1985

![Image of immunostaining results]

Figure 4 Plasma cells showed strong immunostaining for CD138 and IgG. IgG4 was occasionally positive and the expression rate was < 40%. No restrictive expression of kappa and lambda was observed. B and T cells were positive for CD20 and CD30. CD21 and CD23 showed the FDC network. Germinal center cells were positive for Bcl-2, and weakly positive for CD10 and Bcl-6. Cxcl13 and cyclin D11 were positive in a few scattered cells. Ki-67 was highly expressed in germinal centers.

The differential diagnosis of CD includes lymphoma and any other causes of lymphadenopathy. Initial investigations encompass a CT scan that reveals the location, extent and number of lymph nodes involved, which are then visualized with homogeneously intense contrast enhancement[7]. MRI and positron emission tomography/CT[8] can be used to clarify the involvement of any soft tissues. Due to the diversity of the clinical and pathological manifestations of CD, sometimes it is difficult to distinguish from scrofula, malignant lymphoma, mediastinal neurogenic tumor (ectopic paraganglioma), ectopic gland tumor, connective tissue disease, blood vessels and immune cell lymphadenopathy[9,10]. When patients present with lymph node enlargement, we should think of CD, and excisional biopsy is usually required to establish the final diagnosis. Combining medical history, physical examination, laboratory examination and pathological examination, it is important to initially rule out diseases of known cause.

In the present case, the patient was initially misdiagnosed with a pancreatic tumor by enhanced CT, enhanced MRI and CEUS. Based on CEUS, we highly suspected that the mass might be derived from the pancreas, and/or it might be a tumor from other parts of the body. We initially differentiated the diagnosis between benign and malignant lesions. The pancreatic adenocarcinoma usually present hypoenhancement on arterial phase of CEUS. Patients with focal pancreatitis have symptoms of upper abdominal pain and digestive systems, and the enhancement of focal pancreatitis was similar to normal pancreatic parenchymas, and most of them were overall isoenhancement of synchronization. Patients with functional pancreatic neuroendocrine tumors have corresponding symptoms, even non-functional pancreatic neuroendocrine tumors have abundant blood vessels. Pancreatic adenocarcinoma is charac-
terized by high enhancement in the arterial phase of CEUS, which occurs earlier than in normal pancreatic parenchyma, with high enhancement or equal enhancement in the venous phase[11]. Solid pseudopapilloma has different proportions of cystic and solid components. Those with the dominant solidity may show significantly high enhancement in the arterial phase of CEUS, but subsided enhancement in the venous phase. Based on the above performance, the contrast enhancement mode of the mass in the present case was most consistent with a pancreatic neuroendocrine tumor and a solid pseudopapilloma. However, the enhancement pattern of this case was not exactly consistent with pancreatic tumors. The patient had no symptoms, and the boundary of the tumor was clear, which led us to confirm whether it was not a tumor of the pancreas. Therefore, MRI was recommended for further diagnosis. Because MRI has high accuracy in diagnosing pancreatic tumors[12], patients with an early diagnosis of non-functioning well-differentiated neuroendocrine carcinomas of the head of the pancreas using MRI have a good outcome.

Surgical excision has proven to be curative for UCD. Just like the patient in our manuscript, in some reports[13-15], no recurrence was found either clinically or radiologically that underwent surgical excision. Moreover, surgical excision was seen to decrease the mortality rates (17.6% to 3.8%) in UCD in a systematic review of 404 published cases[2,16]. In contrast, MCD had a poor response to surgery and worse prognosis when compared to UCD. MCD does not have a proven treatment regimen. Multicentric type is ineffective after surgery, the prognosis is poor, and the median survival time is about 14-30 mo; Severe infections, multiple organ failure, and transformation to malignant tumors are the main causes of death in such patients. However, monoclonal antibodies, anti-IL-6 receptor monoclonal antibodies or chemotherapy with rituximab has have become a research hotspot[17-19].

CONCLUSION

CD is a lymphoproliferative disorder and is rarely seen clinically. The pathological features are obvious proliferation of lymph follicles, blood vessels and plasma cells. CD divided into unicentric and multicentric types. UCD occurs as a solitary enlarged mass and shows a benign disease course. Surgical excision has proven to be curative. MCD presents as a systemic disease with peripheral lymphadenopathy and has a poor response to surgery. When patients with lymph node enlargement are encountered clinically, we should consider CD, and excisional biopsy is usually required. It is particularly important to first rule out diseases that are known causes of lymphadenopathy.

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Iguratimod in treatment of primary Sjögren’s syndrome concomitant with autoimmune hemolytic anemia: A case report

Juan Zhang, Xin Wang, Jing-Jing Tian, Rong Zhu, Rui-Xue Duo, Yi-Chen Huang, Hai-Li Shen

Abstract

BACKGROUND
Primary Sjögren’s syndrome (pSS) concomitant with autoimmune hemolytic anemia (AIHA) but without eye and mouth dryness is exceedingly rare. Iguratimod (IGU) has been widely used in the treatment of pSS. However, there are few reports about the application of IGU in pSS concomitant with AIHA.

CASE SUMMARY
Here, we present the case of a patient with pSS concomitant with AIHA but without eye and mouth dryness. The patient was initially diagnosed with hyperplastic anemia and AIHA while pSS was missed, and was finally diagnosed with pSS concomitant with AIHA. The patient was treated with IGU along with prednisone and hydroxychloroquine, and her hemoglobin, reticulocytes and IgG returned to normal levels.

CONCLUSION
IGU was effective for and well tolerated by our patient with pSS concomitant with AIHA, and may be a promising therapy for the treatment of this disease.

Key Words: Autoimmune hemolytic anemia; Iguratimod; Primary Sjögren’s syndrome; Case report

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**Specialty type:** Immunology

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

**Peer-review model:** Single blind

**Peer-review report’s scientific quality classification**
- Grade A (Excellent): 0
- Grade B (Very good): 0
- Grade C (Good): 0
- Grade D (Fair): 0
- Grade E (Poor): 0

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**INTRODUCTION**

Primary Sjögren’s syndrome (pSS) is one of the most common autoimmune diseases, and is characterized by salivary and lacrimal gland dysfunction and lymphocytic infiltration[1,2]. Autoimmune hemolytic anemia (AIHA), a rare autoimmune disease, is characterized by hemolysis mediated by autoantibodies directed against red blood cells (RBCs)[3]. The most common manifestation of hematologic involvement in pSS is leukopenia, while pSS concomitant with AIHA is rare[4]. Currently, there is no standardized treatment regimen for AIHA, although the First International Consensus Group recommended second-line treatment for AIHA in 2017, including azathioprine, mycophenolate or ciclosporin[5]. Iguratimod (IGU), a novel modified anti-rheumatic drug, has shown both good efficacy and safety in the treatment of pSS[6,7]. However, whether IGU can be used in the treatment of pSS concomitant with AIHA remains to be further elucidated. Here, we present the case of a patient with pSS concomitant with AIHA who was successfully treated with IGU.

**CASE PRESENTATION**

**Chief complaints**

In 2015, a 31-year-old Chinese female presented with dizziness and fatigue without obvious inducement, and received Chinese medicine treatment (the specific medication was unknown) at a local Chinese medicine clinic. However, her symptoms did not remit, and she was admitted to the emergency department of Lanzhou Military Region General Hospital on November 23, 2015.

**History of present illness**

There was no history of present illness.

**History of past illness**

There was no history of past illness.

**Personal and family history**

There was no personal and family history.

**Laboratory examinations**

Laboratory tests results revealed abnormal decreases in hemoglobin (Hb, 46 g/L; reference range, 120-160 g/L) and RBCs (0.91 × 10^12 cells/L; reference range, 3.5-6.0 × 10^12 cells/L), and abnormal increases in the erythrocyte sedimentation rate (ESR; 78 mm/h; reference range, 0-20 mm/h) and hs-CRP (1.64 mg/L; reference range, 0-0.5 mg/L). Biochemical examination results revealed 41.4 g/L IgG (reference range, 8-16 g/L), 4.19 g/L IgA (reference range, 0.7-3.3 g/L), 0.63 g/L IgM (reference range, 0.5-2 g/L), 0.37 g/L complement C3 (reference range, 0.9-1.8 g/L), and 0.1 g/L complement C4 (reference range, 0.1-0.4 g/L). Urine Bence-Jones protein electrophoresis was negative. Bone marrow aspiration results indicated hyperplastic anemia. She was treated with ferrous sulfate oral solution, folic acid tablets and vitamin B12 (the specific dose was unknown).
As the symptoms did not improve, she was admitted to the hematology department of Lanzhou Military Region General Hospital on November 27, 2015. In addition to abnormal Hb, ESR, hs-CRP, IgA, IgG and complement C3, laboratory test results also revealed abnormal increases in rheumatoid factor (RF: 399 IU/mL; reference range: 0-80 IU/mL), total bilirubin (32.0 µmol/L; reference range: 1.5-20 µmol/L) and indirect bilirubin (22.5 µmol/L; reference range: 1-20 µmol/L). The patient was positive for antinuclear (ANA; titer > 1:320; speckled pattern), anti-Sjögren's syndrome A (SSA) and anti-SSB antibodies, and negative for serum immunofixation electrophoresis. The direct Coombs test results were strongly positive (anti-IgG and anti-C3d). Bone marrow aspiration results still indicated hyperplastic anemia. She was diagnosed with AIHA and connective tissue disease, and was treated with oral prednisolone (1 mg/kg/d), leflunomide (20 mg/d) and a washed red frozen blood cell transfusion. Thereafter, her condition improved, and she was discharged 10 d later. However, due to the abnormal decrease in Hb when the dose of prednisone was reduced to less than 20 mg/d, she was admitted to the hematology department again on September 17, 2018. The symptoms improved after treatment with prednisone (40 mg/d), hydroxychloroquine (HCQ; 0.2 g twice a day) and a washed frozen red blood cell transfusion.

Considering the repeated recurrence of the above symptoms and the abnormal increase of RF in the rare case, the patient was referred to the rheumatology department of Lanzhou University Second Hospital on September 27, 2018. In addition to being positive for ANA, anti-SSA and anti-SSB antibodies, her abnormal examination results also included 105 g/L Hb, 4.9% reticulocytes (RET; reference range: 0-1.5%), 46.71 g/L IgG, 4.15 g/L IgA, 82 Ru/mL RF-IgA (reference range: 0-20 Ru/mL) and > 200 Ru/mL RF-IgM (reference range: 0-20 Ru/mL). The Schirmer test result was positive, and minor salivary gland biopsy revealed focal lymphocytic infiltration of the exocrine glands.

**FINAL DIAGNOSIS**

The patient was diagnosed with pSS concomitant with AIHA.

**TREATMENT**

Immunosuppressants such as cyclosporin A or mycophenolate were rejected because the patient could not afford these drugs. She was initially treated with IGU (25 mg twice a day) in addition to the combination therapy of prednisone (40 mg/d) and HCQ (0.2 g twice a day).

**OUTCOME AND FOLLOW-UP**

The patient was followed up every 1-2 mo, and the dose of prednisolone was gradually tapered (10% every 2 wk until reaching 5 mg/d for maintenance). During the 24 mo of follow-up, her Hb, RET and IgG returned to normal levels (Table 1).

**DISCUSSION**

Here, we present a rare case of pSS concomitant with AIHA but without eye and mouth dryness that was successfully treated with IGU. To our knowledge, this is the first case report describing the efficacy of IGU in the treatment of pSS concomitant with AIHA, and the findings from this case report indicate that IGU might broaden the treatment options available for patients with pSS concomitant with other rare diseases.

AIHA is a rare but clinically significant complication of pSS, only 2.8% of patients with pSS were explicitly diagnosed with AIHA in a large cross-sectional study[4]. In certain patients, the typical symptoms (sicca symptoms) of pSS do not appear, and the symptoms of AIHA develop before the diagnosis of pSS, which might result in a delay in diagnosis[8]. In this rare case in which the patient did not experience eye and mouth dryness, the initial diagnosis was hyperplastic anemia and AIHA while pSS was missed; however, the patient was finally diagnosed with pSS concomitant with AIHA.
based on abnormally elevated RF. In addition, a previous report revealed that ANA, anti-SSA, anti-SSB antibody positivity and lower complement levels were common in pSS concomitant with AIHA[9], which was consistent with our case. Taken together, these findings indicate that more comprehensive clinical examination and evaluation should be carried out to improve the diagnostic accuracy of pSS concomitant with AIHA.

Currently, there is no standardized treatment regimen for the treatment of pSS concomitant with AIHA. IGU is a novel anti-rheumatic drug approved only in China and Japan[6,7]. Evidence has shown that IGU can be considered as an effective and safe drug for the clinical therapy of pSS[7]. However, whether IGU can be used for the treatment of pSS concomitant with AIHA remains unknown. In our case, due to the cost of treatment and preventable adverse reactions, the patient received IGU as a second-line treatment under background treatment with a glucocorticoid combined with HCQ. The results showed that the patient responded well to IGU, and her Hb, RET and IgG returned to normal levels during the 24 mo of follow-up. The following mechanisms might explain the clinical efficacy of IGU in the treatment of pSS concomitant with AIHA. AIHA is a rare autoimmune disease in which autoantibodies directed toward RBC antigens lead to RBC accelerated destruction[3]. Several immunologic mechanisms are involved in the pathogenesis of AIHA, including autoantibodies, antibody-dependent cell-mediated cytotoxicity, phagocytes, B and T lymphocytes, Tregs, cytokines, and the complement system[10]. IGU is an anti-inflammatory and immunomodulatory compound[11]. IGU can significantly inhibit the production of inflammatory cytokines (such as interleukin-6, interleukin-8, and tumor necrosis factor-a) in animal models of arthritis or autoimmune diseases[12]. In addition, IGU plays a significant immunomodulatory role in the synovial tissue of patients with rheumatoid arthritis by regulating T and B lymphocyte subsets and inhibiting the production of cytokines and immunoglobulins[6,13]. Therefore, the improvement in symptoms of patient with pSS concomitant with AIHA might result from the immunomodulation of B lymphocytes. However, the mechanism underlying the clinical efficacy of IGU in the treatment of pSS concomitant with AIHA needs to be determined in further investigations. The present study revealed that IGU was effective for and well tolerated by our patient with pSS concomitant with AIHA.

Clinicians should be reminded that when hemolytic anemia occurs in young women, they should be alert to the possibility of autoimmune diseases. More comprehensive clinical examination and evaluation, including autoantibodies, immunoglobulins, and complement levels, should be carried out to improve the diagnostic accuracy. The treatment of AIHA should take into account the primary disease, and the dose of glucocorticoids should be gradually tapered. For patients with poor glucocorticoid responses, immunosuppressants should be added as soon as possible.

There are some limitations in this case report that should be kept in mind. First, the classification of AIHA was not performed in our patient due to hospital condition limitations. Second, the proportion of B lymphocytes was not dynamically monitored during the treatment. Whether B lymphocytes are involved in the possible therapeutic mechanism of IGU in pSS concomitant with AIHA is not clear. Finally, this case report involved experience with a single patient. Prospective studies with a large sample size are needed to provide more information about the safety and efficacy of IGU in patients with pSS concomitant with AIHA.

**CONCLUSION**

The findings from our case report showed that AIHA may occur in pSS, and the diagnosis of pSS should be considered even in patients with a diagnosis of AIHA. For
our patient with pSS concomitant with AIHA, IGU was effective and well tolerated. The findings from this case report also indicate that IGU might broaden the treatment options available for patients with pSS concomitant with other rare diseases.

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Primary central nervous system lymphoma presenting as a single choroidal lesion mimicking metastasis: A case report

Hee Ryeong Jang, Kyu-Hyoung Lim, Kyungyul Lee

Abstract

BACKGROUND
Primary choroidal lymphoma is usually an indolent B-cell lymphoma and rarely progresses to extraocular sites. Herein, we report a case of primary choroidal lymphoma diagnosed as diffuse large B-cell lymphoma (DLBL), which progressed to the brain parenchyma after 4 mo.

CASE SUMMARY
A 78-year-old man presented with diminution of vision in his right eye. A choroidal lesion suspected of metastatic lesion was observed in the right eye by ophthalmologic examination. To discover the primary tumor, imaging investigations were performed but no malignant lesion was detected. After 4 mo, the patient returned to the clinic presenting with neurological symptoms. Brain magnetic resonance imaging revealed an abnormal contrast-enhancing mass in the left cerebellum. A stereotactic biopsy was performed, and DLBL was confirmed. The patient received the high dose methotrexate-based chemotherapy and he achieved complete remission.

CONCLUSION
Primary choroidal lymphoma is usually known to have a benign clinical course without systemic involvement. We present a rare case of primary choroidal lymphoma diagnosed as DLBL that progressed to the brain parenchyma within months.

Key Words: Primary choroidal lymphoma; Diffuse large B-cell lymphoma; Primary central nervous system lymphoma; Case report

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kyuhyoung.lim@gmail.com
Core Tip: Primary choroidal lymphoma is a rare subset of primary intraocular lymphoma and shows a benign clinical course with no systemic involvement. Our case report involves a primary choroidal lymphoma demonstrating rare extraocular progression within months.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i4.1291

INTRODUCTION
Primary intraocular lymphoma (PIOL) is a rare subset of primary central nervous system lymphoma (PCNSL) and includes vitreoretinal, choroidal, and iridal lymphomas [1]. Among PIOLs, primary choroidal lymphoma is a very rare disease, and only a small number of cases have been reported in the literature. Previously reported primary choroidal lymphomas were usually low-grade B-cell lymphomas, which rarely progressed to the central nervous system [2,3]. Herein, we report a very rare case of primary choroidal lymphoma diagnosed as diffuse large B-cell lymphoma (DLBL), which initially presented as a unilateral choroidal lesion mimicking metastasis.

CASE PRESENTATION

Chief complaints
A 78-year-old male came to the hospital presenting with a diminution of vision in his right eye.

History of present illness
His blurred vision had been aggravated for several weeks.

History of past illness
The patient had no relevant medical history, such as that of diabetes mellitus or hypertension. In the past, the patient had undergone short-term treatment for occupational pneumoconiosis resulting from his work as a coal miner for >10 years.

Personal and family history
No special history of personal and family.

Physical examination
An ophthalmological examination revealed exudative subretinal detachment with a choroidal lesion suspicious of metastasis in the right eye (Figure 1A).

Laboratory examinations
Lactate dehydrogenase was moderately elevated at 387 U/L (normal range: 119-229 U/L).

Imaging examinations
To identify the primary tumor, the patient was referred to the Department of Hematology-oncology at our institute. Brain magnetic resonance imaging (MRI) (Figure 2A) and computed tomography (CT) of the neck, chest, and abdomen-pelvis showed no malignant lesions.
Figure 1 Course of ophthalmoscopy examinations. A: Image showing multifocal, creamy yellow, subretinal infiltrates during the first clinical visit; B: Image showing the spread of the creamy yellow, subretinal infiltrates toward the mid-periphery of the fundus. The image was taken 4 mo after the first clinical visit; C: Subretinal infiltrates appear to be markedly decreased after six cycles of systemic chemotherapy.

Figure 2 Findings of brain magnetic resonance imaging. A: Image showing no evidence of space-occupying intracranial or diffusion-restricted lesions. The image was taken at the first clinical visit; B: Image showing an irregular contrast-enhancing lesion, measuring approximately 3.8 cm × 3.8 cm in size, with diffusion restriction in the left cerebellum. The image was taken 4 mon after the first clinical visit; C: Image showing no evidence of abnormal contrast-enhancing lesion in the cerebellum after six cycles of systemic chemotherapy.

FINAL DIAGNOSIS

Four months later, the patient revisited the clinic because of dysarthria, headache, and right-sided weakness. No apparent aggravation of visual acuity was observed. The same findings of ophthalmoscopy as at the first visit were confirmed (Figure 1B). Brain MRI showed a single, irregular, contrast-enhancing mass in the left cerebellum (Figure 2B). The patient underwent a stereotactic biopsy of the mass and was diagnosed with DLBL (Figure 3). Further imaging, including CT and positron emission tomography/CT, revealed no systemic involvement. There was no evidence of lymphoma involvement in the cerebrospinal fluid and bone marrow.

TREATMENT

The patient received high-dose methotrexate (HD-MTX)-based chemotherapy, which comprised methotrexate (3.5 g/m²), vincristine (1.4 mg/m², capped at 2 mg), and prednisolone (100 mg/d), with the addition of procarbazine (100 mg/m²) in the first, third, and fifth cycles. Intrathecal injection was not given in this patient because there was no evidence of lymphoma involvement in the CSF test before and after the first cycle of HD-MTX based chemotherapy.
Figure 3 Representative microscopic images of diffuse large B-cell lymphoma in the brain. A: Infiltration of large, atypical cells with prominent nucleoli around the granular layer of the cerebellum (hematoxylin and eosin stain, magnification: 200 ×); B: Infiltration of large, atypical cells with prominent nucleoli around the granular layer of the cerebellum (hematoxylin and eosin stain, magnification: 400 ×); C: Tumor cells show strong positivity for the B-cell surface marker CD20 on immunohistochemistry (Immunohistochemical stain, magnification: 200 ×).

OUTCOME AND FOLLOW-UP

After completing six cycles of HD-MTX-based chemotherapy, the patient’s neurological symptoms, such as right-sided weakness, dysarthria, and blurred vision, markedly improved. The abnormal, contrast-enhancing mass in the left cerebellum disappeared on brain MRI (Figure 2C), and the creamy yellow, subretinal infiltrates were markedly decreased (Figure 1C); these findings were compatible with complete remission. Maintenance therapy was recommended, but the patient and caregiver refused the treatment due to concerns about the side effects of additional chemotherapy and radiotherapy. The patient and his main caregiver were seriously concerned about the risk of cognitive decline that can be caused by additional treatments. Complete remission was maintained for approximately 17 mo without the maintenance chemotherapy.

DISCUSSION

Intraocular lymphoma is extremely rare and accounts for approximately 1.86% of intraocular malignancies[4]. Intraocular lymphoma is a heterogeneous group of malignancies located in different tissues, including the vitreous, retina, choroid, ciliary body, and iris, within the eye. It also refers to forms of primary or secondary to central nervous system lymphoma or disseminated systemic disease[3,5].

Primary intraocular lymphoma is considered a subset of PCNSL, and it progresses to the central nervous system in 15%-25% of PCNSL cases[3]. Primary vitreoretinal lymphoma is the most common intraocular lymphoma, followed by uveal lymphoma.

Choroidal lymphoma is a subset of uveal lymphoma. It can be subdivided into primary and secondary lymphoma based on the presence of systemic lymphoma at the time of ocular presentation. Primary choroidal lymphomas are defined as the absence of prior systemic lymphomas or concurrent extraocular lymphomas [6]. Several studies have reported clinical differences between primary and secondary choroidal lymphomas[2,7].

Primary choroidal lymphomas are mainly low grade B-cell lymphomas such as extranodal marginal zone B-cell lymphoma, are usually unilateral, and typically do not progress to the central nervous system parenchyma. Secondary choroidal lymphoma is characterized by the presence of previously known cancer or concurrent systemic lymphomas at the initial ocular presentation.

In contrast to primary choroidal lymphomas, secondary choroidal lymphomas are more likely to demonstrate bilateral involvement and preexistent lymphomas. More than half of secondary choroidal lymphomas have been confirmed as high-grade B-cell lymphomas, such as DLBL[2,8].

Unlike the previously reported cases of primary choroidal lymphoma, this case was characterized by the pathological findings of DLBL and disease progression to the brain parenchyma within a few months. In most of the previous cases of primary choroidal lymphoma, management involved local treatment or observation, whereas in our case, HD-MTX-based chemotherapy was administered, and the treatment response was complete remission.
CONCLUSION

Primary choroidal lymphoma is generally known to have a benign clinical course without systemic involvement. We reported a rare case of primary choroidal lymphoma diagnosed as DLBL, characterized by an aggressive clinical course that progressed to the brain parenchyma within a few months.

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Surgical treatment of acute cholecystitis in patients with confirmed COVID-19: Ten case reports and review of literature

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Author contributions: Bozada-Gutiérrez K designed and performed the research, contributed to the analysis and wrote the paper; Trejo-Avila M designed the research, contributed to the analysis, wrote the paper, provided clinical advice and supervised the report; Chávez-Hernández F designed and performed the research, contributed to the analysis; Parraguirre-Martínez S performed the research, provided histopathological images and interpretation, contributed to the analysis; Valenzuela-Salazar C, Herrera-Esquivel J and Moreno-Portillo M designed the research, contributed to the analysis, provided clinical advice and supervised the report.

Informed consent statement: Informed consent was waived by competent authorities due to the use of anonymous data and due to its retrospective nature.

Abstract

BACKGROUND
Research concerning postoperative outcomes of confirmed coronavirus disease 2019 (COVID-19) patients revealed unfavorable postoperative results with increased morbidity, pulmonary complications and mortality. Case reports have suggested that COVID-19 is associated with more aggressive presentation of acute cholecystitis. The aim of the present study is to describe the perioperative assessment and postoperative outcomes of ten patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with concomitant acute cholecystitis who underwent cholecystectomy.

CASE SUMMARY
We report a total of 10 SARS-CoV-2 positive patients with concomitant acute cholecystitis that underwent cholecystectomy. Six patients were males, the mean age was 47.1 years. Nine patients had moderate acute cholecystitis, and one patient had severe acute cholecystitis. All patients were treated with urgent/early laparoscopic cholecystectomy. Regarding the Parkland grading scale, two patients received a Parkland grade of 3, two patients received a Parkland grade of 4, and six patients received a Parkland grade of 5. Eight patients required a bail-out procedure. Four patients developed biliary leakage and required endoscopic retrograde cholangiopancreatography with biliary sphincterotomy. After surgery, five patients developed acute respiratory distress syndrome (ARDS) and required intensive care unit (ICU) admission. One patient died after cholecystectomy due to ARDS complications. The mean total length of stay (LOS) was 18.2 d. The histopathology demonstrated transmural necrosis (n = 5), vessel obliteration with ischemia (n = 3), perforation (n = 3), and acute peritonitis (n = 10).
CONCLUSION
COVID-19 patients with acute cholecystitis had difficult cholecystectomies, high rates of ICU admission, and a prolonged LOS.

Key Words: COVID-19; SARS-CoV-2; Cholecystectomy in COVID-19; Acute cholecystitis in COVID-19; Case report

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Core Tip: Several studies have described multiple gastrointestinal complications in patients with coronavirus disease 2019, including advanced stages of cholecystitis. We found in the present study that patients with confirmed severe acute respiratory syndrome coronavirus 2 infections who presented with acute cholecystitis, tended to have a higher grade on the Parkland grading scale (including gallbladder perforation, empyema and total wall necrosis), had difficult laparoscopic cholecystectomies with an increased need for a bail-out procedure, had high rates of intensive care unit admission, and had a prolonged length of hospital stay.

INTRODUCTION

Research concerning postoperative outcomes of confirmed COVID-19 patients revealed unfavorable postoperative results with increased morbidity, pulmonary complications and mortality[2-5].

Several studies have described gastrointestinal symptoms in patients with COVID-19, with nearly 25% of patients referring abdominal pain[6]. Association with other gastrointestinal complications for example, liver injury and late cholestasis, have been reported[7]. Concerning the gallbladder, some studies have described the presence of acute ischemic gangrenous cholecystitis, with or without perforation, and with or without associated cholecystitis[8-30]. Studies have suggested that COVID-19 is associated with more aggressive presentation of acute cholecystitis[15,19,24,27,28].

The guidelines for the treatment of acute cholecystitis before the pandemic recommended early laparoscopic cholecystectomy (Lap-C) for patients with mild acute cholecystitis as the treatment of choice[31-33]. For patients with moderate acute cholecystitis the treatment of choice is urgent/early Lap-C when advanced laparoscopic techniques are available. The indications for urgent Lap-C in confirmed COVID-19 patients should not differ from those without COVID-19[19].

Since the beginning of the pandemic in 2020, several surgical societies have published their recommendations to treat acute cholecystitis[2,34]. The firsts recommendations were to avoid surgeries and to adopt a non-operative management when possible[28,35]. The finding of virus particles in the peritoneal fluid and the idea that pneumoperitoneum could allow the transmission of virus led many surgical societies to publish recommendations for gastrointestinal laparoscopic surgery[34,36-38]. More recent recommendations sustain that laparoscopy is not more likely to spread the COVID-19 infection than open surgery, and minimally invasive surgery provides better outcomes that laparotomy[2].

Since acute cholecystitis represents a very frequent cause of hospital admission worldwide[39], it is important to know the perioperative outcomes of patients with confirmed COVID-19 and cholecystitis, also it is important to know what to expect during surgeries.
The aim of the present study was to describe the perioperative assessment and postoperative outcomes of patients with confirmed SARS-CoV-2 infection with concomitant acute cholecystitis who underwent urgent cholecystectomy.

CASE PRESENTATION

Chief complaints
We included symptomatic and asymptomatic SARS-CoV-2 positive patients (asymptomatic carriers) who required urgent/early cholecystectomy. During the pandemic all the patients that were admitted to our hospital were screened for SARS-CoV-2 infection.

Regarding the chief complaints, patients presented with the characteristic right upper quadrant pain related to acute cholecystitis.

History of present illness
All patients had concomitant acute cholecystitis with SARS-CoV-2 infection. We included patients with the SARS-CoV-2 infection confirmed either by reverse-transcriptase polymerase chain reaction (RT-PCR) assay of a nasopharyngeal swab or a rapid antigenic test. Several variables were recorded including demographic parameters and preoperative quick Sequential Organ Failure Assessment (qSOFA) score. Data is shown in Table 1.

History of past illness
Of the ten patients, four had history of past illness. The most frequent comorbidity was hypertension (n = 4). The complete list of comorbidities is presented in Table 1.

Personal and family history
The personal and family history was noncontributory.

Physical examination
On physical examinations patients had right upper quadrant pain (n = 10), right upper quadrant mass (n = 6), and positive Murphy’s sign (n = 10).

Demographic data included age (years), gender, body mass index in kg/m², comorbidities, smoking status, American Society of Anesthesiology classification. The preoperative qSOFA score was calculated and we divided the patients in high risk (> 2 point) or not high risk patients (0-1 points).

Laboratory examinations
Preoperative laboratory examinations are shown in Table 1. Of relevance, the mean preoperative C-reactive protein level was 20.1 mg/dL, the mean total bilirubin was 1.29 mg/dL, and the mean ferritin level was 565 ng/mL.

Imaging examinations
All patients underwent chest computed tomography (CT) scans prior to surgery. Also, all patients underwent gallbladder ultrasound. We diagnosed acute cholecystitis according to Tokyo Guidelines (TG18) ultrasound criteria (thickened gallbladder wall, enlarged gallbladder, pericholecystic fluid collection).[32,41]

FINAL DIAGNOSIS

Regarding the timing of COVID-19 diagnosis, nine patients were diagnosed preoperatively and one was diagnosed postoperatively. Of the 10 patients, four were asymptomatic SARS-CoV-2 carriers. The rest of patients (n = 6) presented with symptomatic disease and preoperative CT scans with COVID-19 pneumonia (bilateral ground-glass opacities with consolidation).

We diagnosed and graded the severity of acute cholecystitis according to the 2018 TG18[32,41]. All patients were diagnosed with definite acute cholecystitis according to the TG18. Regarding the severity assessment, nine patients had grade II (moderate) acute cholecystitis and one patient had grade III (severe) acute cholecystitis. Additionally, one patient was diagnosed with grade II acute cholangitis, and the other patient had concomitant mild acute pancreatitis. Both patients were operated after
Table 1 Demographic information of confirmed coronavirus disease 2019 patients with acute cholecystitis (n = 10) (mean ± SD)

<table>
<thead>
<tr>
<th>Classification</th>
<th>n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
</tr>
<tr>
<td>Age (yr), mean (range)</td>
<td>47.1 (20-74)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (range)</td>
<td>28.4 (20-43)</td>
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<td>Current Smokers, n (%)</td>
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</tr>
<tr>
<td>ASA classification, n (%)</td>
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</tr>
<tr>
<td>I</td>
<td>2</td>
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<tr>
<td>II</td>
<td>4</td>
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<td>III</td>
<td>4</td>
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<td>Comorbidities, n (%)</td>
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<td>CRD</td>
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<tr>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>Preoperative qSOFA score, n (%)</td>
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<tr>
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<td>4</td>
</tr>
<tr>
<td>High risk (&gt; 2)</td>
<td>6</td>
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<tr>
<td>COVID-19 symptoms</td>
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<td>6</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
</tr>
<tr>
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<td></td>
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<tr>
<td>Hemoglobin (g/dL)</td>
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<td>Platelets (n × 10⁹/μL)</td>
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<tr>
<td>Leucocytes (n/μL)</td>
<td>11.95 (5.6)</td>
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<tr>
<td>CRP (mg/dL)</td>
<td>20.1 (12.5)</td>
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<tr>
<td>Total Bilirubin (mg/dL)</td>
<td>1.29 (1.7)</td>
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<tr>
<td>Gamma-glutamyl transferase (IU/L)</td>
<td>163.1 (198.1)</td>
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<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>86.1 (102.8)</td>
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<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td>59.9 (46.7)</td>
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<tr>
<td>Alkaline fosfatase (IU/L)</td>
<td>199 (189.7)</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>215.1 (63.3)</td>
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<tr>
<td>Albumin (g/dL)</td>
<td>4.17 (0.4)</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>565 (304.5)</td>
</tr>
<tr>
<td>Creatinine (md/dL)</td>
<td>1.02 (0.5)</td>
</tr>
</tbody>
</table>

BMI: Body mass index; CRD: Chronic renal disease; qSOFA: Quick Sequential Organ Failure Assessment; CRP: C-reactive protein.

resolution of cholangitis and pancreatitis, respectively.
TREATMENT

All surgeries were performed at a COVID-19 dedicated operating theater and all the medical staff were equipped with personal protective equipment. Laparoscopic cholecystectomies were performed with a 3 or 4 trocar technique depending the case, using a 12-mm umbilical trocar (optical), a 12-mm trocar in the sub-xiphoid area, and a 5-mm in the right flank. We performed diagnostic laparoscopy and we graded the intraoperative findings according with the Parkland scale. After that, bile and purulent collections were drained and intraabdominal adhesions were taken down. The decision to perform a bail-out procedure was done when the critical view of safety was difficult to achieve. In our hospital, we employ the reconstituting subtotal cholecystectomy or the open conversion as bailout procedures. The reconstituting subtotal cholecystectomy consisted in making an incision in the gallbladder, aspirating the contents including the stones, removing the peritonealized portion of the gallbladder, except the lowest portion (infundibulum and Hartmann’s pouch), and partially excising the posterior wall adherent to the liver. After that, the lowest part of the gallbladder is closed with sutures obliterating the cystic duct, leaving a closed gallbladder remnant[15,41].

During laparoscopy we filtered the pneumoperitoneum through filters able to remove most viral particles as suggested by several authors[2,42,43]. Two patients required preoperative endoscopic retrograde cholangiopancreatography (ERCP). One patient had cholestasis and a type I Mirizzi syndrome was found at ERCP. The other patient had grade II acute cholangitis and required early endoscopic treatment (ERCP biliary drainage).

All patients were treated with urgent/early Lap-C. Eight surgeries were completed via laparoscopy and two patients required conversion to open cholecystectomy due to operative difficulty.

Regarding the Parkland grading scale, all patients were found to have severe inflammation (grades 3-5): Two patients had pericholecystic fluid, adhesions to the gallbladder body, hyperemia and distended gallbladder (Parkland 3); One patient had adhesions obscuring the majority of the gallbladder and one patient had Mirizzi syndrome (Parkland 4); And six patients had Parkland 5 (six patients with complete necrosis of the gallbladder body infundibulum and cystic duct, three of them with gallbladder perforation) see Figure 1. Six cases were treated with subtotal reconstituting cholecystectomy, because a critical view of safety could not be achieved.

The mean estimated blood loss (EBL) was 258 mL, the mean operative time was 133.5 min, and eight patients required intraabdominal closed drainage.

OUTCOME AND FOLLOW-UP

Operative outcomes included modality of cholecystectomy (laparoscopic, open or converted), EBL in mL, operative time in minutes, and requirement of intraabdominal drainage. We graded the intraoperative findings according with the Parkland grading scale for cholecystitis[12]. Preoperative or postoperative need for ERCP and findings were registered.

Postoperative complications were classified and presented according with the Clavien-Dindo classification. The need for intensive care unit (ICU), vasopressors and invasive mechanical ventilation were recorded. The hospital length of stay (LOS) in days was registered.

Five patients developed biliary leak after subtotal cholecystectomy. Of these patients, two had low-output leak, while three patients had high-output biliary leak. Patients with low-output leaks were treated with closed suction drainage alone, while patients with high-output leaks needed ERCP with biliary sphincterotomy and biliary stent placement. The complete list of postoperative complications classified according to Clavien-Dindo is shown in Table 2.

After surgery five patients required ICU admission, and one patient was admitted preoperatively and remained in the ICU after surgery. The five patients were on invasive mechanical ventilation and vasopressor therapy. These patients developed acute respiratory distress syndrome (ARDS) related to SARS-CoV-2. One patient died after cholecystectomy and due to ARDS complications.

Considering the complete cohort of patients, the mean total LOS was 18.2 d.

The histopathological diagnosis was performed using hematoxylin-eosin (H&E) stained slides (Table 3). As demonstrated in Figure 2, H&E slides displayed the inflammatory infiltration ($n = 10$), with transmural necrosis ($n = 5$), hemorrhagic infarction ($n$
Table 2 Description of postoperative complications according with the Clavien-Dindo classification (n = 10)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Hydroelectrolytic imbalance</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Antiemetics</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Antipyretic (for fever ≥ 38.3)</td>
<td>4</td>
</tr>
<tr>
<td>Grade II</td>
<td>Blood transfusions</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Total parenteral nutrition</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Postoperative Ileus</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Delirium</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Biliar leak</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Wound infection</td>
<td>3</td>
</tr>
<tr>
<td>Grade IIIa</td>
<td>Evisceration</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>ERCP</td>
<td>3</td>
</tr>
<tr>
<td>Grade IVa</td>
<td>Respiratory</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Hepatic</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Dialysis</td>
<td>2</td>
</tr>
<tr>
<td>Grade IVb</td>
<td>Multiorganic failure</td>
<td>5</td>
</tr>
<tr>
<td>Grade V</td>
<td>Death of a patient</td>
<td>1</td>
</tr>
</tbody>
</table>

ERCP: Endoscopic retrograde cholangiopancreatography.

We found in the present study that patients with confirmed SARS-CoV-2 infections with concomitant acute cholecystitis tended to have high grades on the Parkland grading scale (including gallbladder perforation, empyema and total wall necrosis), difficult Lap-C with an increased need for a bail-out procedure (open conversion or subtotal cholecystectomy), high ICU admission rates, high rates of postoperative biliary leaks that required ERCP (with biliary stent placement), and prolonged length of hospital stay.

Several studies have described the presentation of acute cholecystitis concomitant with a SARS-CoV-2 infection. A literature review of the research concerning COVID-19 and acute cholecystitis is summarized in Table 4. We have noticed that the majority of studies that have been published during the pandemic are case reports and letters to the editor (see Table 4). The first case report of histopathological findings of an acute ischemic gangrenous cholecystitis as a late complication in a COVID-19 patient was
Table 3 Perioperative outcomes of coronavirus disease 2019 patients with acute cholecystitis

<table>
<thead>
<tr>
<th>Perioperative outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCP result</td>
<td></td>
</tr>
<tr>
<td>Preop Mirizzi syndrome 1</td>
<td>1</td>
</tr>
<tr>
<td>Preop Cholangitis + CBD stones</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative Biliary leak</td>
<td>3</td>
</tr>
<tr>
<td>ERCP Biliary stent</td>
<td>3</td>
</tr>
<tr>
<td>Modality of cholecystectomy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>8</td>
</tr>
<tr>
<td>Lap converted to open</td>
<td>2</td>
</tr>
<tr>
<td>Type of cholecystectomy</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
</tr>
<tr>
<td>Sub-total</td>
<td>6</td>
</tr>
<tr>
<td>Parkland grading scale, n (%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Estimated blood loss (mL), mean (range)</td>
<td>258 (30-500)</td>
</tr>
<tr>
<td>Operative time (min), mean (range)</td>
<td>133.5 (70-190)</td>
</tr>
<tr>
<td>Intraabdominal drainage, n (%)</td>
<td>8</td>
</tr>
<tr>
<td>ICU admission, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes, Preoperative</td>
<td>1</td>
</tr>
<tr>
<td>Yes, Postoperative</td>
<td>4</td>
</tr>
<tr>
<td>ICU treatment, n (%)</td>
<td></td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>5</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>5</td>
</tr>
<tr>
<td>Hospital LOS (days), mean (range)</td>
<td>18.2 (3-50)</td>
</tr>
<tr>
<td>Histopathology results, n (%)</td>
<td></td>
</tr>
<tr>
<td>Ischemic/segmental necrosis</td>
<td>3</td>
</tr>
<tr>
<td>Transmural necrosis</td>
<td>5</td>
</tr>
<tr>
<td>Perforated</td>
<td>3</td>
</tr>
<tr>
<td>Mucosal ulcerations</td>
<td>1</td>
</tr>
<tr>
<td>Acute peritonitis</td>
<td>10</td>
</tr>
<tr>
<td>GB empyema</td>
<td>4</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>2</td>
</tr>
</tbody>
</table>

ERCP: Endoscopic retrograde cholangiopancreatography; CBD: Common bile duct; Lap: Laparoscopic; ICU: Intensive care unit; LOS: Length of stay; GB: Gallbladder.

published by Bruni et al.[21]. Since then, the description of gangrenous cholecystitis in patients with COVID-19 has been found in at least six other studies[15,18,19,24,27,28]. In our series, 3 patients had wall ischemia and segmental necrosis, and 5 patients had complete transmural necrosis. Of note, some of these case reports outlined the presence of gangrenous cholecystitis but without cholelithiasis (acalculous)[18,19,27]. In our series, only one patient presented with acalculous cholecystitis, and the rest of the patients had cholelithiasis. This could represent a different physiopathological pathway that should be further investigated. Nevertheless, patients with both
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study design</th>
<th>Country</th>
<th>Sample size, n (%)</th>
<th>Age/sex (F:M)</th>
<th>COVID-19 diagnosis</th>
<th>Tokyo class</th>
<th>Treatment</th>
<th>Morbidity/PO complications</th>
<th>ICU, n (%)</th>
<th>LOS (d)</th>
<th>Mortality</th>
<th>Findings/histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Çakır and Kabuli [8], 2021</td>
<td>Retrospective study</td>
<td>Turkey</td>
<td>18</td>
<td>M: 14 (78%); F: 4 (22%); Age: 73.3 (67-81)</td>
<td>RT-PCR</td>
<td>GI: 3 (16.7%); GII: 9 (50%); GIII: 6 (33.3%)</td>
<td>THGD</td>
<td>No complications</td>
<td>3 (16.6%)</td>
<td>16 (3-32)</td>
<td>3 (16.6%)</td>
<td>NR</td>
</tr>
<tr>
<td>Barabino et al [9], 2021</td>
<td>Retrospective study</td>
<td>Italy</td>
<td>37: 36 non-COVID; 1 COVID</td>
<td>Age: 64 (38-94); Male: 21 (56.7%); Female: 16 (43.3%)</td>
<td>RT-PCR</td>
<td>GI: 13 (35.1%); GII: 15 (40.5%); GIII: 8 (21.6%); COVID: GII</td>
<td>Antibiotic only 11 (29.7%); THGD 8 (21.6%); L 18 (48.7%); COVID: THGD 1</td>
<td>Emergency LC 1; Bleeding 1; Cholangitis 2</td>
<td>2</td>
<td>9 (2-12)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Martinez Caballero et al [10], 2021</td>
<td>Multicentre-combined (retrospective-prospective) cohort study</td>
<td>Spain</td>
<td>42</td>
<td>Age: COVID: 83 (65-87); COVID: 28 M/14 F</td>
<td>Clinics 10.9%; Imaging test 11.3%; RT-PCR 12.5%</td>
<td>GI: 112 (43.6%); GII: 121 (47.1%); GIII: 24 (9.3%)</td>
<td>Antibiotic therapy 47.9%; Surgical treatment 31.5%; THGD 20.6%</td>
<td>Gallbladder perforation 8.4%</td>
<td>23%</td>
<td>Non-COVID: 5 d (3-8); COVID: 11.9%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Çiyiltepe et al [11], 2021</td>
<td>Retrospective study</td>
<td>Turkey</td>
<td>65 non-COVID; 7 COVID</td>
<td>Age: 57.3; F: 40 (55.6)/M: 32 (44.4)</td>
<td>GI: 35 (48.6%); GII: 37 (51.3%)</td>
<td>11 THGD</td>
<td>-</td>
<td>-</td>
<td>9.2 (6-20)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Somuncu et al [12], 2021</td>
<td>Retrospective study</td>
<td>Turkey</td>
<td>4 COVID; 32 non-COVID</td>
<td>Age: 53 (26-78); M: 17/F: 19</td>
<td>Thorax CT -</td>
<td>Antibiotic therapy 14; THGD 14 (39%); LC 8</td>
<td>-</td>
<td>-</td>
<td>7 (2-20)</td>
<td>1: Cardiac arrest</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Puig et al [13], 2021</td>
<td>Case report</td>
<td>Spain</td>
<td>2</td>
<td>M: 65/57</td>
<td>RT-PCR</td>
<td>GIII: 2</td>
<td>Percutaneous cholecystostomy 2</td>
<td>Pulmonary tromboembolysis 2</td>
<td>2</td>
<td>34</td>
<td>0</td>
<td>-</td>
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<tr>
<td>Abaleka et al [14], 2021</td>
<td>Case report</td>
<td>United States</td>
<td>1</td>
<td>Age: 76; F</td>
<td>RT-PCR</td>
<td>Grade II</td>
<td>Antibiotics</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
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<tr>
<td>Lovece et al [15], 2020</td>
<td>Case report</td>
<td>Italy</td>
<td>1</td>
<td>Age: 42/M</td>
<td>RT-PCR</td>
<td>Grade III</td>
<td>LC</td>
<td>Gallbladder perforation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Famularo and Spada [16], 2021</td>
<td>Letter/case report</td>
<td>Italy</td>
<td>1</td>
<td>90/M</td>
<td>RT-PCR +</td>
<td>NR</td>
<td>THGD</td>
<td>No</td>
<td>No</td>
<td>26</td>
<td>No</td>
<td>NR</td>
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<tr>
<td>Vaishnav and Patel [17], 2021</td>
<td>Observational/prospective</td>
<td>India</td>
<td>16</td>
<td>50/F: 7 (29%); M: 17 (70%)</td>
<td>RT-PCR + CT</td>
<td>GIII</td>
<td>LC</td>
<td>No</td>
<td>NR</td>
<td>4.9</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Alhassan et al [18], 2020</td>
<td>Case report</td>
<td>Qatar</td>
<td>1</td>
<td>40/F</td>
<td>Confirmed 14 d prior</td>
<td>AAC</td>
<td>Antibiotics</td>
<td>No</td>
<td>Yes (1, 100%)</td>
<td>NR</td>
<td>No</td>
<td>-</td>
</tr>
</tbody>
</table>

etiology required cholecystectomy.

An editorial by Cirillo et al.[22], reported the finding of acalculous hemorrhagic cholecystitis in a patient with a SARS-CoV-2 infection who needed emergent cholecystectomy. In our histopathological analysis we found that 2 patients had hemorrhagic changes in the gallbladder wall after surgery. Our report differs from the report of Cirillo et al.[22], in the fact that they preoperatively diagnosed the hemorrhage by CT scan with active contrast extravasation around and inside a

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Country</th>
<th>Subjects</th>
<th>Confirmation</th>
<th>Gender</th>
<th>Age</th>
<th>Emergency procedure</th>
<th>N-ph</th>
<th>N-f</th>
<th>N-m</th>
<th>Complexity</th>
<th>Etiology</th>
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<tbody>
<tr>
<td>Asti et al [19], 2020</td>
<td>Letter/case report</td>
<td>Italy</td>
<td>3</td>
<td>Confirmed</td>
<td>40-66</td>
<td>F: 1 (33%); M: 2 (66%)</td>
<td>AAC</td>
<td>LC</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Acalculous, gangrene</td>
</tr>
<tr>
<td>Balaphas et al[20], 2020</td>
<td>Letter/case report</td>
<td>Switzerland</td>
<td>2</td>
<td>Confirmed</td>
<td>83-84</td>
<td>F: 1 (50%); M: 1 (50%)</td>
<td>RT-PCR</td>
<td>AAC</td>
<td>LC/Antibiotics</td>
<td>NR</td>
<td>Yes (1, 50%) No</td>
<td>qRT-PCR revealed the presence of SARS-CoV-2 in the gallbladder wall</td>
</tr>
<tr>
<td>Bruni et al [21], 2020</td>
<td>Case report</td>
<td>Italy</td>
<td>1</td>
<td>RT-PCR +</td>
<td>59</td>
<td>M</td>
<td>AC/GIII</td>
<td>OC</td>
<td>NR</td>
<td>Yes (1, 100%) No</td>
<td>Gangrenous, Hemorrhagic, vasculitis</td>
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</tr>
<tr>
<td>Cirillo et al [22], 2020</td>
<td>Letter/case report</td>
<td>Italy</td>
<td>1</td>
<td>Confirmed</td>
<td>79</td>
<td>M</td>
<td>AAC</td>
<td>Cholecystectomy</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>Perforated acalculous cholecystitis</td>
</tr>
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<td>Giulio et al [23], 2020</td>
<td>Letter/case report</td>
<td>Italy</td>
<td>1</td>
<td>RT-PCR +</td>
<td>45</td>
<td>F</td>
<td>AC/GII</td>
<td>LC</td>
<td>No</td>
<td>NR</td>
<td>30</td>
<td>NR</td>
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<tr>
<td>Gupta et al [24], 2020</td>
<td>Retrospective original article</td>
<td>India</td>
<td>5</td>
<td>Confirmed</td>
<td>53.2</td>
<td>NR</td>
<td>AC</td>
<td>OC</td>
<td>Bile leak</td>
<td>NR</td>
<td>4-9</td>
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<td>Kabir et al [25], 2020</td>
<td>Letter/case report</td>
<td>Singapore</td>
<td>1</td>
<td>Middle-aged/M</td>
<td>RT-PCR +</td>
<td>Gangrenous cholecystitis</td>
<td>Subtotal reconstituting OC</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Lisotti et al [26], 2020</td>
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<td>Italy</td>
<td>1</td>
<td>CT suspicious</td>
<td>80</td>
<td>F</td>
<td>AC/GII</td>
<td>EUS-GBD</td>
<td>No</td>
<td>No</td>
<td>1</td>
<td>NR</td>
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<tr>
<td>Mattone et al[27], 2020</td>
<td>Case report</td>
<td>Italy</td>
<td>1</td>
<td>RT-PCR +</td>
<td>66</td>
<td>M</td>
<td>AAC</td>
<td>Initially THGDLC</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>Gangrenous gallbladder</td>
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<td>F Narvaez et al[28], 2020</td>
<td>Brief report/review</td>
<td>United States</td>
<td>1</td>
<td>NR/F</td>
<td>Confirmed</td>
<td>AC</td>
<td>LC</td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>Near-gangrenous gallbladder</td>
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<tr>
<td>Safari et al [29], 2020</td>
<td>Case report</td>
<td>Iran</td>
<td>1</td>
<td>RT-PCR + CT</td>
<td>75</td>
<td>F</td>
<td>AC/GII</td>
<td>LC</td>
<td>NR</td>
<td>Yes (1, 100%) Yes</td>
<td>9</td>
<td>NR</td>
</tr>
<tr>
<td>Ying et al [30], 2020</td>
<td>Case report</td>
<td>China</td>
<td>1</td>
<td>RT-PCR +</td>
<td>68</td>
<td>F</td>
<td>AC/GII</td>
<td>THGD</td>
<td>No</td>
<td>No</td>
<td>25</td>
<td>No</td>
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</tbody>
</table>
perforated gallbladder. The presence of hemorrhage from an inflamed gallbladder is rare and larger studies are needed to confirm an association with SARS-CoV-2 infection.

Considering the potential association of SARS-CoV-2 with gallbladder disease, several hypothesis have been formulated. One hypothesis is that the systemic inflammation, the immune system changes induced by SARS-CoV-2, and the immunotherapy employed to treat it, may contribute to the late onset of cholecystitis by pro-inflammatory pathways[15]. Also, the findings of small-vessel thrombosis and gallbladder wall ischemia suggested a correlation with the coagulopathy and prothrombotic state induced by this coronavirus[21,44]. Furthermore, it has been suggested that due to the expression of angiotensin-converting enzyme 2 receptor in gallbladder epithelial cells, SARS-CoV-2 could target that cells[45]. Taking into account these inflammatory changes, we found on the histopathological examination of our patients, acute peritonitis, acute inflammatory infiltrates, as well as ischemic and necrosis associated with small vessel thrombi, and hemorrhagic changes in the gallbladder wall of our patients.

Regarding the treatment of acute cholecystitis, some authors reported the treatment with antibiotics[46], others reported percutaneous cholecystostomy[16,26], and others published their outcomes after laparoscopic or open cholecystectomy[46,47] (Table 4). The relevance of our study is that we described the outcomes of 10 patients with positive COVID-19 tests who required urgent cholecystectomy. Urgent/early cholecystectomies were performed due to gallbladder perforation (n = 3) and gangrenous cholecystitis (n = 8), where medical treatment with antibiotics only or cholecystostomy were considered insufficient treatments[19,32,41].

Figure 1 Intraoperative findings of confirmed coronavirus disease 2019 patients with acute cholecystitis. A: Gangrenous and perforated; B: Fundus and body wall necrosis; C: Wall necrosis; D: Gangrene extended to the infundibulum and cystic duct.
Concerning the intraoperative findings, we found that patients were operated on at a very advanced stage of acute cholecystitis with severe inflammation (a Parkland score > 3); thus, the critical view of safety was very difficult to achieve. The majority of our patients required a bail-out procedure for a safe cholecystectomy. As mentioned in the results section, 2 underwent conversion to laparotomy and 6 required sub-total reconstituting cholecystectomy. Of note, 3 of the 6 patients who needed sub-total cholecystectomy required ERCP due to biliary leak. Leaks developed in patients with complete gangrenous cholecystitis that extended to the infundibulum and to the cystic duct. Therefore, it is important to consider that in patients with suspected gallbladder necrosis, ischemia could extend to the cystic duct, thereby increasing the risk of postoperative biliary leakage or fistula. In our series, patients who develop postoperative bile leakage where treated with ERCP. Endoscopic management of biliary leaks (sphincterotomy with or without biliary stent) is associated with more than 90% of biliary leak healing or closure. ERCP is currently considered the first-line treatment option for biliary leaks, specially cystic stump leaks. Surgeons should be aware that when treating patients with difficult cholecystectomies, the goals are to resolve the septic process and to prevent secondary damage. As reported in previous COVID-19 cases, as well as in our series, operated patients during this pandemic tended to have severe inflammation of the gallbladder thus increasing the risks of postoperative complications including bile duct injury. As suggested by international guidelines, choosing a bail-out procedure (subtotal cholecystectomy or open conversion) based on intraoperative findings is recommended to avoid a secondary damage. Both bail-out procedures have been reported to reduce bile duct injury and overall postoperative complications, although it has been recognized that laparoscopic subtotal cholecystectomy is associated with increased rates of postoperative bile leakage in comparison with open conversion.
There are some limitations to our study that need to be mentioned. The most important limitation is that this was a single-center study with a small sample, which predisposes the study to all the biases inherent to the design (selection, information and confusion biases). Further prospective and multi-center studies should be performed and published, in order to better understand the effects of COVID-19 on acute cholecystitis. However, despite these limitations we consider that the results of this study could help us to describe some of the implications of SARS-CoV-2 infections in patients who require urgent/early Lap-C.

CONCLUSION

In conclusion, we found in the present study that patients with confirmed SARS-CoV-2 infections who presented with acute cholecystitis, tended to have a higher grade on the Parkland grading scale (including gallbladder perforation, empyema and total wall necrosis), had difficult laparoscopic cholecystectomies with an increased need for a bail-out procedure, had high rates of ICU admission, and had a prolonged length of hospital stay. As suggested by our case series and previously published literature, we advise to surgeons performing cholecystectomy in confirmed SARS-CoV-2 patients to be prepared for a difficult surgery and to consider a bail-out procedure to prevent secondary damage.

ACKNOWLEDGEMENTS

We would like to thank all medical and nurse staff dedicated to COVID-19 surgical care at our Hospital. Special thanks to Dr. Karina Flores, for sharing her surgical images.

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Hydrogen inhalation promotes recovery of a patient in persistent vegetative state from intracerebral hemorrhage: A case report and literature review

Yan Huang, Feng-Ming Xiao, Wen-Jie Tang, Jing Qiao, Hai-Feng Wei, Yuan-Yun Xie, You-Zhen Wei

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Abstract

BACKGROUND
Persistent vegetative state (PVS) is a devastating and long-lasting clinical condition with high morbidity and mortality; currently, there are no available effective interventions.

CASE SUMMARY
We report the case of an 11-year-old boy with PVS caused by severe intracerebral bleeding in the left hemisphere following anticoagulation treatment. The patient’s PVS severity showed no notable improvement after 2-mo neuroprotective treatment and rehabilitation, including nerve growth factor and baclofen, hyperbaric oxygen, and comprehensive bedside rehabilitation therapies. Daily inhalation treatment (4-6 h) of high-concentration hydrogen (H₂) gas (66.6% H₂ + 33.3% O₂) was provided. Surprisingly, the patient’s orientation, consciousness, ability to speak, facial expressions, and locomotor function were significantly improved following approved studies. Written informed consent was obtained from the patient’s family to participate in the study. The authors declare that they have no conflicts of interest to disclose.
Huang Y et al. Hydrogen ameliorates persistent vegetative state

and revised the manuscript according to the CARE Checklist (2016).

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H2 gas inhalation, along with improvements in essential general health status, after H2 gas inhalation treatment, which was consistent with stabilized neuropathology in the left hemisphere and increased Hounsfield unit values of computed tomography in the right hemisphere. The patient finally recovered to a near normal conscious state with a Coma Recovery Scale-Revised Score of 22 from his previous score of 3.

CONCLUSION
Phase 1 clinical trials are needed to explore the safety and efficacy of H2 gas inhalation in patients with PVS.

Key Words: Hydrogen gas; Intracerebral hemorrhage; Consciousness recovery; Persistent vegetative state; Case report

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Core Tip: We report a case in which hydrogen (H2) gas inhalation promoted the recovery of an 11-year-old boy with persistent vegetative state (PVS) caused by severe intracerebral bleeding in the left hemisphere following anticoagulation treatment. The patient’s PVS severity showed no notable improvement after a 2-mo routine neuroprotection treatment and rehabilitation. Surprisingly, the patient’s orientation, consciousness, ability to speak, facial expressions, and locomotor function were significantly restored, after high-concentration H2 gas inhalation treatment. This case indicates that inhalation of H2 may be an effective intervention candidate for patients with loss of consciousness.

INTRODUCTION
Urgent development of novel therapies for intracerebral hemorrhage (ICH) is required due to the high mortality of ICH and the lack of effective therapies[1]. Molecular hydrogen (H2) is known to protect neurons against reactive oxygen species (ROS) induced by cerebral ischemia/reperfusion (I/R) injury[2,3]. Previous experimental studies have shown that H2 gas can also alleviate inflammation and apoptosis[4], in addition to reducing neuronal damage in several rat models of diseases by suppressing the expression of S100 calcium-binding protein B, phosphorylation of c-Jun N-terminal kinase, and reactive astrogliosis[5-7]. H2 gas inhalation selectively reduces hydroxyl radical and peroxynitrite levels in vitro and exerts an antioxidant effect, reflected by decreased brain concentrations of 4-hydroxynonenal (a specific marker for lipid peroxidation), and 8-hydroxyguanosine (a nucleic acid oxidation marker) in a rat middle cerebral artery occlusion model[2]. Clinical studies have also indicated the effectiveness of H2 gas in the treatment of hepatic, renal, cardiac, and pulmonary diseases, including chronic obstructive pulmonary disease and coronavirus disease 2019[8-10]. H2 gas inhalation or H2-rich saline treatment has beneficial effects on early brain injury after subarachnoid hemorrhage[11,12], delayed brain injury in subarachnoid hemorrhage, and unilateral common carotid artery occlusion with the endovascular perfusion method[13]. Here, we report the case of an 11-year-old boy treated by high-concentration H2 gas inhalation that helped with the recovery from persistent vegetative state (PVS) caused by ICH, which is the first clinical report of high-dose H2 gas therapy in a child in a PVS after ICH.
Huang Y et al. Hydrogen ameliorates persistent vegetative state

CASE PRESENTATION

Chief complaints
An 11-year-old boy treated with anticoagulation after aortic valve replacement surgery presented to the pediatric intensive care unit in our hospital following fever and abdominal pain for 2 d, and coma for 2 h on May 27, 2020.

History of present illness
An emergency brain surgical intervention was carried out immediately to relieve the intracranial pressure and, subsequently, reduce brain injury. Assisted by neuronavigation, both left ventricle and hematoma drains were established under general anesthesia. In addition, critical life support consisting of tracheostomy, intracranial pressure probe implantation, and mechanical ventilation was also established.

Approximately 6 wk (41 d) after surgery, the patient was still in a completely bedridden vegetative state (VS) with a Coma Recovery Scale-Revised (CRS-R) score [14] of 3 (auditory function: 0, visual function: 0, motor function: 1, verbal function: 0, communication: 0, and arousal: 2). Although his life support relied on nasal tube-feeding, the patient had normal heartbeat and breathing rates.

As the patient’s VS status did not show signs of improvement for more than 4 wk after brain surgery, he was transferred to the rehabilitation department of the same hospital and was diagnosed with PVS, and neuroprotective treatments and rehabilitation training were initiated. The neuroprotective treatments included nasal administration of nerve growth factor, baclofen, and hyperbaric oxygen. The functional rehabilitation therapies included comprehensive bedside rehabilitation therapies, such as anticonvulsive treatment, range-of-motion maintenance, and swallowing and feeding training. Unfortunately, despite these therapeutic interventions for 4 more weeks, his PVS symptoms and severity showed no improvement. Therefore, it was necessary to explore a new and safe therapeutic intervention with potential effects on the patient who had been in a VS for over 2 mo.

History of past illness
At the age of 3 years, the patient underwent repair of an atrial septal defect and ventricular septal defect due to complex congenital heart disease. In October 2018, the patient underwent aortic valve replacement surgery. He received warfarin anticoagulant therapy for nearly 2 years after aortic valve replacement.

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

Physical examination
The patient could occasionally open his eyes and yawn, but he had no response to pain stimulation, and could not distinguish between his family members and strangers. Moreover, he was unable to listen and follow instructions or speak. Furthermore, his body posture was abnormal, with bent elbows and ulnar deviation, wrist flexion, fists with high tonic metacarpophalangeal joints, and stiff, straightened lower limbs with inverted feet. His muscle tone was significantly high in the lower limbs with a modified Ashworth spasm scale score of 2. Additionally, the patient had no voluntary movement control and could not hold his head steady, sit down, stand alone, or walk. The patient, however, had normal reflexes, including biceps reflex +, triceps reflex +, cough reflex +, knee reflex +++, Achilles tendon reflex +++, and Babinski sign and ankle clonus +.

Laboratory examinations
Blood analysis revealed mild leukocytosis of 8.35 × 10⁹/L, with predominant neutrophils (67%), and normal hematocrit and platelet count. Prothrombin and partial thromboplastin times were normal, and D-dimer was slightly increased at 1.08 mg/L. Blood biochemistry analyses and urine analysis were normal. Electrocardiogram showed a sinus rhythm, frequent atrial premature beats, abnormal left atrium, large left ventricle, and complete left bundle branch block.

Imaging examinations
A computed tomography (CT) scan of the patient showed irregularly shaped and low-density CT images of the left frontal, parietal, and basal ganglia regions, which covered most of the left hemisphere (Figures 1A, 1C, and 1E). Similar low-density CT
Effects of hydrogen therapy. A, C, and E: Severe and large-scale hemorrhage before treatment was observed in the left hemisphere, including significantly reduced computed tomography (CT) image density that covered the left prefrontal and parietal regions and the majority of the occipital gyrus; the left lateral ventricle was significantly enlarged compared to the right ventricle, and the midline brain structures also deviated from the normal position due to the hematoma and brain edema; B, D, and F: After treatment, the left hemisphere was significantly damaged by hemorrhage with a markedly enlarged left lateral ventricle and severe cerebral atrophy. However, significantly alleviated cerebral softening was observed in the right hemisphere, revealed by an increased CT number (Hounsfield units) in multiple brain regions (yellow circles), compared to those of similar brain regions (yellow circles) before treatment. The neuropathology stabilized in the left hemisphere and was alleviated in the right hemisphere after hydrogen gas inhalation treatment.

Images were also observed in the posterior horn of the bilateral ventricles and the third and fourth ventricles near the sickle and sulci regions of the left brain. The left lateral ventricle was compressed and narrowed by the hematoma and cerebral edema compared to that of the right ventricle, and midline brain structures were also slightly shifted to the right.

**FINAL DIAGNOSIS**

PVS, coagulation dysfunction, ICH, brain hernia, and postsurgical syndrome after aortic valve replacement.

**TREATMENT**

H₂ has been used in the treatment of patients in critical situations such as traumatic brain injury and cerebral ischemia, and no side effects have been reported to date[15]. After a thorough discussion and explanation of the patient’s status with his family and with their permission, high-concentration H₂ (66.6% H₂ and 33.3% O₂) inhalation treatment was administered. The treatment was given twice daily, for 2-3 h each time, for 5 mo. The initial H₂ gas inhalation treatment started 2 mo after the patient developed PVS.
OUTCOME AND FOLLOW-UP

To our surprise, the patient gradually began to show signs of improvement, such as spontaneous eye opening and occasional flexion/extension of his left lower limb shortly after treatment. A CT scan after treatment showed that the hematoma in the left hemisphere was replaced by an irregular cavity filled and surrounded by degenerated brain parenchyma indicated by shadows of low density on CT images after H₂ gas inhalation treatment, but the area with shadows of low density on CT images was reduced compared to that before treatment. The left lateral ventricle was markedly enlarged due to drainage of the left lateral ventricle and hematoma, as well as significant neuronal degeneration in the patient’s left brain (Figures 1B, 1D, and 1F). These shadows of low density on CT images in the left hemisphere may have been caused by cerebral edema and ICH, and reduction of the shadows of low density on CT images indicated that the brain hemorrhage and edema were stabilized by H₂ gas inhalation treatment compared to that before treatment. Furthermore, the median CT number, i.e., the X-ray attenuation coefficient, was 26 Hounsfield units (HU), 27 HU, 26 HU, 30 HU, and 34 HU in the precentral gyrus (Figure 1B), corpus callosum-forceps minor, internal capsule, corpus callosum-forceps-major (Figure 1C), and putamen in the patient’s right hemisphere (Figure 1F), respectively, after H₂ gas inhalation treatment. These values were increased as compared to 23 HU, 24 HU, 25 HU, 24 HU, and 33 HU in the precentral gyrus (Figure 1A), corpus callosum-forceps minor, internal capsule, corpus callosum-forceps-major (Figure 1C), and putamen in the patient’s right hemisphere (Figure 1E), respectively, before treatment. The increased CT numbers in the right hemisphere after treatment were possibly due to decreased cerebral edema and were critical to the recovery of brain function in the patient. Due to the significantly improved condition of the patient, the nasogastric tube was withdrawn, and he was switched from tube feeding to an oral liquid diet 1 mo after treatment.

In the 2 mo after the first administration of treatment, the patient’s orientation and consciousness, visual pursuit, and localization to noxious stimulation also gradually recovered (Figure 2). The patient could follow simple instructions, open his mouth when his lips were touched with a spoon, chew soft food, and voluntarily bend and straighten his left lower limb. Moreover, the patient was making steady improvement with longer treatments of H₂ gas inhalation. Ninety days after the initiation of treatment, his motor function was significantly improved, and he was able to make reproducible movements following instructions and autonomously lift his left limbs. His ability to produce facial expressions was vastly improved compared to that before H₂ gas inhalation. He could briefly communicate with others and speak words and phrases. Five months after initiation of treatment with H₂ gas inhalation, the patient had recovered to a near normal state of consciousness with a CRS-R score of 22 (auditory function: 4, visual function: 5, motor function: 5, verbal function: 3, communication: 2, and arousal: 3) along with improved speech ability.

Furthermore, the patient had functional recovery (Table 1) and fine motor function improvements (Table 2) 6-7 mo after the initiation of treatment. The patient could understand simple instructions, identify items, and read numbers. He could make requests with a hand gesture, steadily hold his head straight, independently turn his body over to the right side, lift his hands up and reach his head, touch his eyes and nose with his hands, and make voluntary movements with his lower left limb.

In brief, these clinical observations suggested a possible beneficial role of high concentration H₂ gas inhalation in consciousness recovery, muscle tone, and locomotor function in this patient with ICH-induced PVS.

DISCUSSION

The brain of the PVS patient presented in this case report suffered mechanical damage due to abnormally high cerebral pressure, inflammation, oxidative stress, and other unknown injuries[16-19]. The patient failed to respond to neuroprotective treatment along with other methods of rehabilitation but steadily recovered after administration of high-concentration H₂ gas inhalation treatment. CT scans revealed that the patient’s left hemisphere was severely damaged with an enlarged left lateral ventricle and significantly atrophied cerebral parenchyma. However, the CT numbers in the right hemisphere were notably increased after treatment. Other treatment effects included consciousness recovery, significantly alleviated motor and cognitive functional deficits, improved speech and facial expressions, and improvements in general health.
Table 1 Improvements in gross motor function in the patient following hydrogen inhalation treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 mo</th>
<th>2 mo</th>
<th>3 mo</th>
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<th>8 mo</th>
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<tbody>
<tr>
<td>Lying &amp; rolling</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9.8</td>
<td>29.41</td>
<td>25.49</td>
</tr>
<tr>
<td>Sitting</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8.33</td>
</tr>
<tr>
<td>Crawling &amp; kneeling</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Standing</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Walking, running &amp; jumping</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Total score</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.96</td>
<td>5.68</td>
<td>6.76</td>
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</table>

Table 2 Improved fine motor function scores following treatment with hydrogen gas inhalation

<table>
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<th>2020-12-08</th>
<th>2021-03-08</th>
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<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Visual tracking</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Upper limb joint activity</td>
<td>7</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Grasping ability</td>
<td>9</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Operation ability</td>
<td>12</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Hand-eye coordination</td>
<td>17</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Total score</td>
<td>51.64</td>
<td>29.36</td>
<td>59.38</td>
</tr>
</tbody>
</table>

Figure 2 Schematic overview of the clinical progress in the improvement in Coma Recovery Scale-Revised scores and the recovery from persistent vegetative state in this patient. The patient failed to respond to brain surgery and brain protection and rehabilitation for nearly 2 mo. One month after hydrogen gas inhalation treatment, the Coma Recovery Scale-Revised (CRS-R) score of the patient increased from 3 to 6. After 2 more months of treatment, the patient’s consciousness was significantly restored and showed greater subsequent improvements with significantly improved motor function, the ability to speak and express requests, and general health. By the end of the 5-mo treatment period with hydrogen gas inhalation, the patient had nearly recovered and stabilized to a normal consciousness state with a CRS-R score of 22. CRS-R: Coma Recovery Scale-Revised.

The possible underlying mechanisms of H₂ gas inhalation in this PVS patient may be closely related to its antioxidative and anti-inflammatory effects.

ICH is devastating and life-threatening, and is associated with severe disability and a high mortality rate, accounting for 10% to 15% of deaths caused by stroke[20]. The initial mechanisms of injury after ICH include mechanical destruction by accidental and abnormally increased intracerebral pressure, hematoma expansion, and/or
herniation caused by the hematoma itself[21]. Subsequent inflammation, oxidative stress, and impairment in blood flow around the hematoma contribute to edema formation, delayed cell death, and neurological deficits[17]. For example, excessive generation of ROS causes peroxidation of lipid-rich structures of the blood-brain barrier (BBB), resulting in life-threatening BBB disruption and vasogenic cerebral edema[22]. Increased oxidative stress-induced injury occurs in almost all types of brain cells (including neurons, astrocytes, and microglia) and is also closely related to ICH-induced inflammation[19,23]. Therefore, attenuation of early brain injury by targeting oxidative stress and inflammation is a feasible intervention strategy in ICH. Previous studies have also revealed that antioxidative and anti-inflammatory agents can reduce brain atrophy and recover striatal function and memory after ICH[16,24,25].

Since Ohsawa et al.[2] reported that H2 gas has antioxidant and anti-apoptotic properties that protect the brain against I/R injury and stroke by selectively neutralizing hydroxyl radicals, H2 gas has reached the biomedical research forefront as a therapeutic medical gas. Accumulated clinical and experimental biomedical evidence in a variety of models of different diseases has suggested that molecular H2 administered either through gas inhalation or aqueous solution consumption, can act as a scavenger to selectively alleviate ROS and exert potent cellular protective effects. Rat models of middle cerebral artery occlusion, rats with subarachnoid hemorrhage, and a mouse model of ICH have been used to explore the neuroprotective effects of H2 gas [18,19]. These studies demonstrated that H2 treatment could decrease oxidative stress, reduce cerebral infarction and hemorrhagic transformation, improve neurological functions, attenuate BBB disruption, and improve neurobehavioral function by ameliorating oxidative injury to lipids, proteins, and DNA. Therefore, oxidative stress relief may have been one of the underlying mechanisms of H2 gas inhalation in this PVS patient regarding his recovery and other functional improvements.

Another mechanism underlying brain injury is its secondary inflammatory responses induced by ICH. Inflammation occurs immediately after ICH and includes astrocyte/microglia/macrophage activation and cytokine release [e.g., interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α)]. These factors are involved in the breakdown of the extracellular matrix, cellular integrity, and the BBB, in edema development, and in cell death processes[26-30]. Moreover, brain inflammatory responses develop into a chronic stage and result in further brain function damage, such as cognitive deficits[31]. Previous studies have shown that the anti-inflammatory properties of treatments may be effective in protecting the brain from secondary injuries caused by ICH; for example, melatonin can alleviate inflammatory responses and reduce DNA damage and mitochondrial injury after ICH[32].

H2 can protect tissues and cells from a variety of diseases. For instance, H2 gas inhalation can protect lung function by ameliorating airway inflammation in a murine allergic airway inflammation model[33]. Molecular H2 can also protect the heart from cardiotoxicity and hepatotoxicity induced by doxorubicin by inhibiting inflammation and apoptosis[34]. H2 also reduces inflammatory responses after exercise by decreasing inflammatory cytokines (TNF-α, IL-1β, and IL-6)[35]. Moreover, the anti-inflammatory effects of H2 have been proven by its regulation of microglia in the nervous system after ischemic stroke[36]. Studies have also suggested that H2 inhibits the degree of inflammation via inactivation of the NF-kB pathway and the NLRP3 inflammasome[24,37]. Therefore, anti-inflammation by H2 gas inhalation might have also played a role in promoting this patient’s recovery from PVS.

It is worth noting that not all PVS patients were responsive to molecular H2 treatment in our clinical research. We tried high-concentration H2 inhalation in patients with acute necrotizing encephalopathy, but there was no significant therapeutic effect regarding the recovery of consciousness in some patients after several weeks of high-concentration H2 inhalation. Considering that the pathophysiological mechanisms of neural injury and recovery of consciousness in brain diseases are complicated, the effectiveness of H2 gas treatment might be dependent on the severity of brain damage and the multiple underlying mechanisms of molecular H2. Therefore, it may or may not be effective for all inflammation and oxidation-based diseases[38].

In summary, a patient with PVS caused by ICH did not respond to routine neuronal rehabilitation treatment but recovered consciousness and locomotor function and restored his speech and emotional expression abilities following the administration of high-concentration H2 inhalation treatment for 5 mo. Although the exact underlying mechanisms remain unclear, molecular H2 may protect the brain from ICH due to its antioxidative stress and anti-neuroinflammatory properties.
CONCLUSION

Phase 1 clinical trials are needed to determine the safety and efficacy of H₂ gas inhalation in PVS.

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Ultrasound-guided needle release plus corticosteroid injection of superficial radial nerve: A case report

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Abstract

BACKGROUND
The radial nerve (RN) splits into two main branches at the elbow: The superficial branch of RN (SBRN) and the deep branch of RN. The SBRN can be easily damaged in acute trauma due to its superficial feature.

CASE SUMMARY
A 55-year-old male patient injured his right wrist 10 mo ago. Debridement, suturing and bandaging were performed in the emergency room. Six months after the scar had healed, he felt numbness and tingling in the dorsal surface of the thumb of the right hand. So the surgery of resection and SBRN anastomosis were performed. The pathological findings showed it as traumatic neuroma. Four months after surgery, the patient felt numbness and tingling in the right dorsal surface of the thumb again. The tenderness was marked in the operated area. Ultrasound indicated that the SBRN was adhered to the surrounding tissue. The patient refused further surgical treatment and underwent ultrasound-guided needle release plus corticosteroid injection of the SBRN. Four weeks later, the tenderness in the surgical area was reduced by 70%, the numbness in the dorsal surface of the thumb of the right hand was reduced by 40% and the nerve swelling evaluated by ultrasound was reduced. Four months passed, he did not feel any numbness or tingling sensation of his right wrist. This is the first report of ultrasound-guided needle release plus corticosteroid injection of the SBRN.

CONCLUSION
Ultrasound can evaluate the condition of the RN, and the relationship with surrounding tissues. Ultrasound-guided needle release plus corticosteroid injection is an effective and safe treatment for SBRN adhesion.

Key Words: Ultrasound-guided; Needle release; Superficial radial nerve; Traumatic neuroma; Corticosteroid injection; Case report
Core Tip: A patient felt numbness and tingling in the right dorsal surface of the thumb four months after traumatic neuroma resection and the superficial branch anastomosis. Ultrasound revealed that the superficial branch was adhered to the surrounding tissue. Four weeks after ultrasound-guided needle release plus corticosteroid injection of the superficial branch, the tenderness and numbness both reduced thus indicating ultrasound-guided needle release plus corticosteroid injection is an effective and safe treatment for superficial branch adhesion.

INTRODUCTION
The radial nerve (RN) is the largest branch of the brachial plexus posterior cord. It splits into two main branches at the elbow: The superficial branch of RN (SBRN) and the deep branch of RN\[^{1,2}\]. The RN supplies the skin of the dorsal forearm, the dorsal-radial region of the hand and the muscle of the extensor compartment\[^{1,2}\].

Ultrasound (US) is currently used as an imaging modality to observe nerves, especially superficial nerves\[^{3}\]. The RN has a twisted course in the upper limb and is superficial enough to be accurately found using an ultrasonic high frequency probe\[^{1,2}\]. Herein, we report a patient who had numbness and tingling in the dorsal surface of the thumb after traumatic neuroma resection plus SBRN anastomosis. Treatment consisted of US-guided needle release plus corticosteroid injection of the SBRN. Tenderness and numbness were reduced 4 wk after treatment.

CASE PRESENTATION

Chief complaints
A 55-year-old male patient presented to the department of ultrasound with numbness and tingling in the dorsal surface of the right thumb.

History of present illness
The patient injured his right wrist 10 mo previously. Debridement, suturing and bandaging were performed in the emergency room. Six months after the scar had healed, he felt numbness and tingling in the dorsal surface of the right thumb and was diagnosed with traumatic neuroma. Traumatic neuroma resection and SBRN anastomosis were performed. Four months after this treatment, he felt numbness and tingling in the right dorsal surface of the thumb, with obvious tenderness in the operated area.

History of past illness
No data were available.

Personal and family history
No data were available.

Physical examination
Tinel’s sign was found to be positive on percussion of the right wrist.

Laboratory examinations
No data were available.
**Imaging examinations**

US revealed that the SBRN was adhered to the surrounding tissue.

**FINAL DIAGNOSIS**

US indicated that the SBRN had adhered to the surrounding tissue after traumatic neuroma resection and SBRN anastomosis (Figure 1).

**TREATMENT**

All treatment procedures were performed with the probe covered with surgical gloves. We used an acoustic coupling agent on the probe inside the surgical gloves (Figure 2). The patient’s skin was disinfected 3 times with complex iodine. A sterile surgical towel was then placed. A 4 mL aliquot of a mixed solution which contained 2 mL 0.9% sodium chloride and 2 mL 2% lidocaine (in a ratio of 1:1) was injected. Then local anesthesia layer by layer was performed via the SBRN surface.

The adhesion between the SBRN and the subcutaneous soft tissue was separated under US guidance. Due to the needle angle, we performed needle release to the middle incision (transverse incision level) as it was difficult to go further. Needle release was then performed from the incision distal area to the proximal area, above the level of the transverse incision. Separation of posterior and bilateral adhesions of the SBRN was carried out on both the short and long axis (transverse incision level). During needle release, the process was considered satisfactory when there was no resistance between the syringe and the tissues around the RN. Finally, a mixture of 1 mL corticosteroid (betamethasone) and 2 mL 2% lidocaine was injected into the area of severe adhesion on the short axis (Figure 3).

**OUTCOME AND FOLLOW-UP**

Four weeks later after ultrasound-guided needle release plus corticosteroid injection of superficial radial nerve, the tenderness in the surgical area was reduced by 70%, the numbness in the dorsal surface of the right thumb was reduced by 40% and the nerve swelling evaluated by US was reduced. Four months passed, he did not feel any numbness or tingling sensation of his right wrist.

**DISCUSSION**

Because of cost-effectiveness and non-invasive characteristics, US has gained popularity in diagnosing peripheral nerve diseases[4]. US can not only detect the nerve but can also reveal the location and the relationship to other structures[5]. In most studies, nerves in US images are always described as hypoechoic fascicles with surrounding hyperechoic tissue, appearing as a typical honeycomb structure[6]. The nerve is usually observed on US axial view from the proximal to distal area and is tracked along an extended length. Color Doppler is used to observe vessels which can serve as anatomical landmarks near the nerve. In US images, a muscle innervated by a nerve which is smaller and hyperechoic compared to the contralateral side indicates atrophy and thus may indicate an abnormal nerve.

The RNs are normal when they had a stippled honeycomb appearance with hypoechoic areas corresponding to the nerve fascicles and surrounding hyperechoic rims corresponding to endoneurium, perineurium, and epineurium on the short axis of US images[7]. The RN can be damaged during acute trauma by direct laceration or contusion, by traction in high-impact trauma with bone separation or by osseous fragments[2]. Humeral shaft fractures are the most common injuries to the RN[8,9]. The RN can also be compressed or stretched in patients who have undergone surgery. The SBRN can easily be affected by penetrating trauma especially the point which pierces the fascia due to its superficial characteristics. The symptoms include pain, dyesthesia and drop wrist. Conservative treatments include rest, nonsteroidal anti-inflammatory drugs (NSAIDs) and physical therapy. If symptoms persist 12 wk after conservative treatment, then surgery is strongly recommended[10].
In this case, we found that after traumatic neuroma resection and nerve anastomosis, the patient felt numbness in the dorsal surface of the right thumb and obvious tenderness in the surgical area. US revealed that the SBRN was adhered to the surrounding tissues. NSAIDs administered for 3 mo were ineffective. The patient refused further surgical treatment. Thus, we used US-guided needle release plus corticosteroid injection to relieve the adhesion between the SBRN and the subcutaneous soft tissue for the first time. Under US guidance, we observed the needle in real-time thus improving accuracy and safety. A short-axis view of the nerve and an in-plane view of the needle were performed in order to view the outline of the SBRN and the approach of the needle. We also rotated between short-axis and long-axis views of the SBRN. The process of acupuncture release was continued until there was no resistance between the syringe and the tissues around the RN. A mixture of 1 mL corticosteroid (betamethasone) and 2 mL 2% lidocaine was then injected around the SBRN in the area of severe adhesion. The injection of corticosteroids can reduce pain and swelling.

There are several lessons to be learned from this study. First, due to skin scar formation and subcutaneous soft tissue adhesion, local infiltration anesthesia is difficult to inject subcutaneously; therefore, preoperative local infiltration anesthesia combined with skin surface anesthesia can be used, thus making the patient feel less pain and more comfortable. Secondly, the puncture was carried out in the plane so that the needle tip could be observed during the whole process in order to avoid injury to the nerve. Thirdly, the SBRN is very superficial, thus probe compression can lead to deformation making it difficult to identify the nerve. Therefore, at puncture initiation, it should be noted that the insertion site should be superficial and should not allow
pressure from the probe. Last, ultrasound-guided needle release has significant effect in many kinds of neural adhesion. We also tried other adhesive treatments for nerves, such as ultrasound-guided needle release of sciatic nerves and deep branches of the sciatic nerve. They all worked well.

**CONCLUSION**

Ultrasound is an effective method for evaluating the condition of the RN, as it can assess the RN and main terminal branches, observe any abnormalities and the relationship with surrounding tissues. Ultrasound-guided needle release plus corticosteroid injection is an effective and safe treatment for SBRN adhesion.

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Inverted Y ureteral duplication with an ectopic ureter and multiple urinary calculi: A case report

Wen-Xin Ye, Li-Gang Ren, Li Chen

In the clinical treatment of diseases related to ureteral duplication, it is very important to make a clear diagnosis before surgery because different types of ureteral duplication correspond to different treatment options. Inverted Y ureteral duplication with ectopic ureters and multiple urinary calculi is clinically rare. This case can help clinicians increase their understanding of this disease and gain some experience in its diagnosis and treatment.

CASE SUMMARY
A 36-year-old male who was previously healthy presented to the hospital with lumbar pain. Percussion of the right kidney area showed the patient had pain. Computed tomography scans revealed multiple urinary calculi in the right urinary system. Computed tomography urography revealed a duplicated ureteral malformation with an ectopic ureter. A transurethral ureteroscopic holmium laser lithotripsy was performed successfully. Intraoperative retrograde ureterography was performed, and the ectopic ureter was visible. We informed the family of the intraoperative findings and suggested laparoscopic ectopic ureterectomy for the ectopic ureteral stones. Unfortunately, the family temporarily refused laparoscopic surgery. The patient did not feel any discomfort after one year of follow-up.

CONCLUSION
Inverted Y ureteral duplication with an ectopic ureter and multiple urinary calculi is rare. Clinicians must be highly vigilant, make a correct diagnosis before surgery, determine the type of ureteral duplication and the distribution of urinary calculi, and then draw up a reasonable treatment plan to avoid unnecessary complications.

Key Words: Ureteral duplication; Inverted Y; Ectopic ureter; Urinary calculi; Case report
INTRODUCTION

Ureteral duplication is defined as two ureters in the ipsilateral urinary system. A ureter with an abnormal positioning is called an ectopic ureter, and it often has an orifice outside the bladder triangle in duplicated ureteral malformations. Inverted Y duplicated ureteral malformation with ectopic ureteral calculi is uncommon in the literature, and only a few cases have been reported[1]. There are no relevant reports on cases with multiple urinary calculi in the renal pelvis and ureters.

CASE PRESENTATION

Chief complaints
A 36-year-old man was admitted to the hospital with complaints of right lumbar pain for one month.

History of present illness
The patient saw a doctor due to right lumbar pain for one month. He had no gross hematuria, chills, fever, or urinary incontinence. No history of trauma was reported.

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

Personal and family history
The patient denied any family history and had no notable history.

Physical examination
The patient was conscious. His vital signs were as follows: body temperature, 36.5 °C; pulse, 82/min; respiration rate, 18/min; blood pressure, 130/72 mmHg; right kidney area percussion pain was positive; and abdominal findings were unremarkable.

Laboratory examinations
Laboratory data were unremarkable except for urine red blood cells (++) on urinalysis.

Imaging examinations
Computed tomography scans revealed one stone in the right upper ureter, multiple stones in the right lower ureter, and other stones in the right kidney (Figure 1). Computed tomography urography and three-dimensional reconstructions revealed that the middle of the right ureter was divided into two branches, one ureter descended to the bladder with a normal bladder opening and the other ureter descended to the vicinity of the right seminal vesicle with an ectopic opening, suggesting duplicated ureteral malformation with an ectopic ureter (Figure 2).
FINAL DIAGNOSIS

From the imaging findings and intraoperative retrograde ureterography, the final diagnosis was as follows: A right inverted Y duplicated ureteral malformation; right fusion broncho-ureteral stones; multiple stones in the ectopic ureter; and a right kidney stone (Figure 3).

TREATMENT

Excluding the operative contraindications, a right transurethral ureteroscopic holmium laser lithotripsy was performed on November 10, 2020. No ectopic ureteral opening was found in the urethra or bladder by endoscopy, and ureteroscopy was used to enter the right ureter through a normal bladder opening along the guidewire. There was a stone in the upper ureter, approximately 1.5 cm × 1.0 cm in size, and a stone was present in the lower calyx of the right kidney, approximately 1.0 cm × 1.0 cm in size. A holmium laser was used to pulverize the stones. The ureteral sheath was placed into the right ureter, and the contrast agent was injected. The ectopic ureter was observed by fluoroscopy using a C model arm X-ray machine. A duplicated ureteral bifurcation could be observed with a flexible ureteroscope (Figure 4), and the intraoperative diagnosis was an inverted Y ureteral duplication and ectopic ureteral multiple...

Figure 1 Abdominal computed tomography scans. A: One stone in the right upper ureter; B: Multiple stones in the right lower ureter; C: Other stones in the right kidney.
stones. We informed the patient’s family members regarding the intraoperative findings and recommended that he undergo laparoscopic ectopic ureterectomy. Unfortunately, the family temporarily refused laparoscopic surgery.
Figure 4  Duplicated ureteral bifurcation could be seen by endoscopy.

OUTCOME AND FOLLOW-UP
The KUB was rechecked on the second day after surgery (Figure 5), and then the patient was discharged. The double J tube was removed 3 wk after the operation. The patient did not feel any discomfort after one year of follow-up.

DISCUSSION
Inverted Y ureteral duplication is a rare congenital malformation of the ureter. There are a few reports in the literature. Similar to other types of duplicated ureteral malformations, the incidence of inverted Y ureteral duplication in women is higher than that in men[2]. In inverted Y ureteral duplication, two distal ureters can fuse into one and then enter the renal pelvis. Usually, one ureter opens into the bladder, and the other ureter has an ectopic opening or the end of the ureter has atresia. The mechanism of its formation is not clear, but it is currently thought that its formation is related to the fusion of two independent ureteral bud tips into one tube before connecting to the metanephros[3].

The clinical symptoms of patients with an inverted Y duplicated ureteral malformation are diverse, and they mainly depend on the location of the ectopic ureteral opening. The opening of ectopic ureters into the vulva or reproductive organs can cause incontinence[4,5]; the opening of ectopic ureters into the bladder and form ureteral cysts can cause bladder outlet obstruction[6]; the opening of ectopic ureters into the seminal vesicles can cause discomfort in the lower abdomen or infertility[7]; and ureteral stones in the ectopic ureter may cause abdominal pain or gross hematuria [1].

An inverted Y duplicated ureteral malformation cannot be diagnosed by clinical symptoms and is mainly diagnosed by ureterography. Retrograde ureterography routinely develops by X-rays and can also develop by contrast-enhanced ultrasound [8].

There is no standard for the treatment of inverted Y duplicated ureteral malformations or their comorbidities. Asymptomatic patients with inverted Y duplicated ureteral malformations can be followed up for observation. For comorbidities caused by ectopic ureters, corresponding treatment can be performed. When ectopic ureteral cysts cause bladder outflow obstruction, removal of the endoscopic cyst is feasible[9]. For ectopic ureters that cause incontinence or intraureteral stones, laparoscopic ectopic ureterectomy is feasible[10], and replantation of the ureter can also be considered.[1].

In this case, the inverted Y ureteral duplication combined with multiple urinary calculi not only contributed to the stones in the renal pelvis and the fused broncho-ureter, but also contributed to the development of multiple stones in the ectopic ureter. It is not clear whether the ectopic ureteral stones developed from the kidney or another primary site. Fused broncho-ureteral stones can cause hydronephrosis, which
Figure 5  KUB after the operation showed that stones in the right upper ureter and renal pelvis had disappeared, a double J tube was placed, and multiple stones in the ectopic ureter were visible.

can manifest as lumbar pain, while ectopic ureteral stones may not cause clinical symptoms and are often ignored. The methods for treating urinary calculi in different parts of the urinary tract are different. In this case, a transurethral ureteroscopic holmium laser lithotripsy was used to treat fused broncho-ureteral calculi and intrarena pelvic calculi, and the results were satisfactory. Our only regret is that the patient refused to treat the ectopic ureteral stones, and surgical specimens could not be obtained. During the one-year follow-up, the patient had no obvious symptoms, such as lumbar pain. However, because of long-term entrapment and stimulation by urinary calculi, urinary calculi can cause urinary tract infections and can increase the risk of cancer, and it is recommended that patients with an ectopic ureter have it removed as soon as possible during follow-up. The most minimally invasive and effective method currently reported in the literature is laparoscopic ectopic ureterectomy.

CONCLUSION

For patients with an inverted Y ureteral duplication and multiple urinary calculi, it is important to clarify the type of ureteral malformation and the location of the stones, and these identifications can have a positive effect on the treatment. For stones in the renal pelvis and ureters with normal openings, endoscopic lithotripsy can be used to achieve good results. For stones in an ectopic ureter, it is difficult to find or locate the ectopic ureteral opening, and most patients are advised to have the ectopic ureter removed. At present, laparoscopic ectopic ureterectomy is a common procedure, and the consequent outcome is usually good.

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Multiple miscarriages in a female patient with two-chambered heart and situs inversus totalis: A case report

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Abstract

BACKGROUND
Single atrium with single ventricle, or a two-chambered heart, is an extremely rare congenital malformation. Few cases with two-chambered heart surviving to adulthood have been reported.

CASE SUMMARY
We reported an adult female patient with a two-chambered heart and situs inversus totalis accompanied by multiple pregnancies and abortions. Magnetic resonance imaging detected a two-chambered heart. B-ultrasound-guided uterine aspiration was performed to absorb 8 g and 10 g of organized villus and decidual tissues, respectively, with a small amount of bleeding. Postoperatively, cyanosis and fatigue-induced shortness of breath were gradually relieved. The patient has currently outlived all similar cases reported so far.

CONCLUSION
Hemodynamic changes in pregnant women with two-chambered heart impaired cardiac function, responsible for hypoperfusion and miscarriage.

Key Words: Two-chambered heart; Situs inversus totalis; Abortion; B-ultrasound; Electrocardiography; Case report

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Core tip: The two-chambered heart is characterized by common atrioventricular valves connecting the single atrium and single ventricle. Most patients with two-chambered
Introduction

Single ventricle occurs in 0.5–1/100000 live births, accounting for 1%–2% of all cases with neonatal congenital heart diseases[1]. Single ventricle with single atrium, or the two-chambered heart, is clinically rarer and associated with worse prognosis, with the patients often dying several months after birth and rarely surviving to adulthood[2]. Fewer than 10 cases with two-chambered heart surviving to adulthood have been reported worldwide[3-7], including a Japanese patient who has survived the longest (42 years). The two-chambered heart is characterized by a single atrium and a single ventricle connected by a common atrioventricular valve. Since most patients carrying this heart defect die before or around the age of 20 years[3-6], pregnancy in these patients is very rare, and how this disease affects the pregnancy outcome is rarely described. Here, we report a case of two-chambered dextrocardia and multiple miscarriages.

Case Presentation

Imaging Examinations

Cardiac color doppler ultrasound (Figure 1) revealed single ventricle dextrocardia (57 mm × 50 mm), anatomical left ventricular morphology, and small stumps only in the main ventricular septum; single atrium (67 mm × 41 mm); aorta located on the left posterior side, and pulmonary artery on the right front side, both originating from the main ventricle cavity; pulmonary valve thickening and adhesion, with limited opening; main pulmonary artery diameter of 14 mm; ill-defined left and right pulmonary arteries; aorta diameter of 36 mm; and right-sided aortic arch with right-sided descending aorta. Abdominal B-ultrasound (Figure 2) showed situs inversus totais. The liver and spleen were on the left and right sides, respectively. Electrocardiography revealed dextrocardia, sinus tachycardia and left ventricular hypertrophy. Abdominal B-ultrasound (Figure 3) showed an antverted uterus, with a volume of about 72 mm × 65 mm × 50 mm. A liquid dark area with a volume of 21 mm × 27 mm × 9.8 mm was visible in the uterine cavity, with no obvious yolk sac and embryo echo observed. The left ovary (2.8 cm × 1.7 cm × 1.5 cm) was located on the right side, with the apex towards the right (Figure 4). Cardiac magnetic resonance imaging (Figure 5) revealed single ventricle with anatomical left ventricular morphology, single atrium and a common atrioventricular valve. Other tests: chromosome karyotyping in blood cells and villous tissues showed no suppressive, pathogenic and clear chromosomal microdeletion/microduplication syndromes or aneuploidy abnormalities, based on the GRCH37/hg19 N reference genome, representing the X or Y chromosome (Figure 6).

Laboratory Examinations

Blood gas analysis showed a PaO₂ of 44 mmHg (normal level: 80–100 mmHg) and a
PaCO$_2$ of 31.7 mmHg (normal level: 35–45 mmHg). Routine blood test revealed red blood cell count of $7.37 \times 10^{12}$ (normal level: $3.8 \times 10^{12} – 5.1 \times 10^{12}$), hemoglobin 209.0 g/L (normal level: 115–150 g/L), progesterone 9.3 nmol/L and human chorionic gonadotropin (hCG) at 4288.0 mIU/mL. The indicators of blood biochemistry, liver and renal functions, myocardial enzyme and coagulation function were all unremarkable.

**Physical examination**

The examination showed blood pressure (BP) of 134/52 mmHg, heart rate 137 beats/min, respiratory rate 18 breaths/min, and 68% SPO$_2$ (mask oxygen inhalation). After a 30-min rest, BP was 103/62 mmHg, heart rate 86 beats/min and SPO$_2$ 75%. The patient was conscious, and her average IQ was evaluated by Wechsler Adult Intelligence Scale. Her height was 161 cm, weight 41 kg, body mass index 15.8, with high zygomatic arch, irregular teeth, and obvious cyanosis of the lips. No significant filling of the jugular vein was seen, and clubbing digits as a symptom of cyanotic heart disease and arachnodactyly related to Marfan’s syndrome were observed. The strongest point of the apex beat was located in the 5th intercostal space of the right
Figure 3 Abdominal B-ultrasound findings. The angle between the cervix and the uterine body is located behind the uterus. The uterus has left and right mirror inversion. BL: Bladder; UT: Uterus; GS: Gestation sac.

Figure 4 X-ray showing the heart is on the right side of the chest, with the apex to the right.

midclavicular line, and a grade 3/6 systolic blowing murmur was heard along the right sternal border. The abdomen was soft, with the lower part slightly dilated and no tenderness, rebound tenderness, or muscle tension. No enlargement was palpated in subcostal areas of the liver and spleen. Gynecological examination revealed an unobstructed vagina containing moderate amounts of dark red blood. The uterine orifice was closed, with no tissue incarceration or significant active bleeding.

Personal and family history
Menstrual, marital and childbearing history: the patient had regular menstrual periods, starting at age 14 years (menstruation, 5/25 d). She got married at age 24 years to a healthy husband. Consanguineous marriage was refused. Eight pregnancies were reported; all of which resulted in spontaneous abortions. She had no history of specific infections (e.g., rubella) during pregnancy, and no intake of teratogenic drugs or radiation exposure were reported. No known family history of congenital heart defects was reported.

History of past illness
The patient had a history of congenital heart disease (the specific type was unknown).
History of present illness
She had a history of cyanosis since birth, which was aggravated by crying and recurrent syncope since age 2 years. Normally, she was active and asymptomatic. Chest distress, shortness of breath and exacerbated cyanosis only occur during a heavy workload. Her last menstruation occurred on December 27, 2016. A detect rise in urinary hCG was found on January 10, 2017. Intrauterine pregnancy was revealed, but no embryo or fetal vascular pulsation was detected by B-ultrasound. She was advised re-examination within a week. However, for various reasons, she did not undergo any further check. Five days prior to revisit, she noticed vaginal bleeding and developed chest tightness, shortness of breath, dyspnea, and exacerbated cyanosis of the lips occurred 1 d prior to the visit.

Chief complaints
A 40-year-old woman presented with cyanosis for 40 years, cessation of menstruation for > 3 mo, vaginal bleeding started 5 d ago, and chest tightness, shortness of breath and exacerbated cyanosis the day before.

FINAL DIAGNOSIS
The following diagnoses were: (1) Missed abortion; (2) Complex congenital heart disease with dextrocardia, single atrium, single ventricle, and grade III cardiac function; (3) Situs inversus totalis; and (4) Secondary erythrocytosis.
TREATMENT

After admission, she rested in bed and was given high-flow mask oxygen inhalation to improve cardiac function. B-ultrasound-guided uterine aspiration was performed to absorb 8 g organized villus and 10 g decidual tissues, with little bleeding.

OUTCOME AND FOLLOW-UP

One day after the operation, the patient was discharged. Postoperatively, cyanosis and fatigue-induced shortness of breath were gradually relieved. Three days after the procedure, off-bed activities were reported, and vaginal bleeding stopped after 5 d. She returned to normal life after 1 wk. At 12, 24 and 36 mo after discharge, the patient revisited the hospital for evaluation. She could engage in daily housework and worked as an online salesperson. The patient has had no further pregnancy. After a cold, cyanosis was aggravated, and relieved after recovery. She reported no routine medication.

DISCUSSION

Only a few patients with two-chambered heart surviving to adulthood have been reported, including two in Poland aged 23 and 19 years[3], one in Iran aged 22 years [4], one in Sri Lanka aged 25 years[5], one in China aged 20 years[6], one in Japan aged 42 years[7] and one in the United States aged 25 years[8]. Here, we reported a rare case with two-chambered heart, situs inversus totalis and multiple miscarriages (Figure 7). The current patient was 44 years old at last follow-up. She had undergone no surgical interventions and could tolerate multiple miscarriages and survived to date, which is rare in clinical practice. Familial single ventricle has been reported[9], and sisters with the same parents have been successively diagnosed with this disease, suggesting that such isolated, similar and rare congenital cardiac malformations might be associated with genetic factors.

The current patient had adverse pregnancy outcome and early abortion eight times, and genetic factors could not be entirely ruled out. Therefore, chromosomes in peripheral blood and intrauterine villus tissues were assessed, and no related chromosomal abnormalities were detected. The possibility of chromosomal anomalies was excluded. The 30%–50% increase in cardiac output is associated with pregnancy. The hemodynamic changes during pregnancy may have deleterious effects on cardiac function, and poor cardiac function may in turn lead to insufficient uterine perfusion and subsequent abortion. Markov et al[10] reported a woman with a two-chamber heart alone who survived to the age of 40 years and experienced multiple failed pregnancies (premature birth or miscarriage) for unknown reasons. In this case, B ultrasound showed that the angle between the uterine neck and the uterine body was located behind the uterus, indicating that the uterus was completely inverted. Although the sizes of the ovary and uterine were normal, the inverted uterine and hypoxia condition might be other causes of multiple miscarriages.

Consistent with Blackford’s study[11], the findings of familial single ventricular patients[9] and a long-term follow-up study of a 61-year-old patient with single ventricle[12] support that pulmonary stenosis might be the main reason for longer survival of single ventricular patients. In the current case, pulmonary subvalvular stenosis was present, and pulmonary vascular resistance was normal, with no significant pulmonary hypertension. This suggests that there may be less mixing of arteriovenous blood. In addition, the oxygen dissociation curve was shifted to the right, oxygen utilization was increased, and compensatory erythrocytosis and tolerance to hypoxia were found. Therefore, the patient could survive to adulthood. The formation of a two-chambered heart is likely associated with Marfan’s syndrome [13]. The present patient had arachnodactyly, a high palatal arch, dentition dislocation and irregularity, with no bone, eye or aorta abnormalities, and was suspected of Marfan’s syndrome and situs inversus totalis, which is clinically rare.

The current two-chambered heart patient has outlived all similar cases reported so far, and remains active, with no major health issues beyond the congenital heart malformation and multiple abortions.
CONCLUSION

The two-chambered heart is a complex congenital heart defect and few people survive to adulthood. Pregnancy may adversely affect cardiac function in patients with a two-chambered heart, and poor cardiac function may lead to hypoperfusion of the uterus and subsequent abortion. Patients with a two-chambered heart should seek appropriate counseling with regard to potential health risks.

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Chidamide combined with traditional chemotherapy for primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma: A case report

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Abstract

BACKGROUND

Traditional chemotherapy has benefited many patients with non-Hodgkin's lymphoma, but results in a very poor response in patients with rare lymphomas or refractory lymphomas. Previous studies have shown that chidamide has potential anti-lymphoma activity and reverses lymphoma cell chemoresistance to increase the chemosensitivity of lymphoma cells to traditional chemotherapy.

CASE SUMMARY

A 14-year-old boy was admitted to our hospital with a 5-d history of generalized erythema, papules, and blisters. Initially, the disease was refractory to potent anti-allergic and anti-infective treatment, and his condition progressively worsened. Skin biopsy revealed primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. Considering that the disease is extremely rare in clinical practice, existing case reports have shown poor efficacy with traditional chemotherapy alone. We recommend chidamide combined with traditional chemotherapy for treatment. The regimen was as follows: Chidamide 30 mg/biweekly, cyclophosphamide 1100 mg/day, pirarubicin 70 mg/day, vincristine 2 mg/day, dexamethasone 20 mg/day-5, etoposide 100 mg/day-5, in a 21 d cycle. The treatment effect was considerable, and complete remission was achieved after 4 cycles of treatment, after which the patient completed a total of 6 cycles of treatment. Subsequently, the patient regularly took chidamide 20 mg/biweekly as maintenance therapy for 1 year. To date, the patient has been disease-free for 3 years.

CONCLUSION

This case suggests that the combination of chidamide and traditional chemotherapy is effective in primary cutaneous aggressive epidermotropic CD8+
He ZD et al. Chidamide-based regimen for PTL-unspecified

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Core Tip: The long-term efficacy of traditional chemotherapy in the treatment of primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma is poor, and the main mechanism is the emergence of chemoresistance in lymphoma cells. Chidamide induces apoptosis and growth arrest of lymphoid and hematologic tumor cells and enhances the sensitivity of lymphoma cells to traditional chemotherapy. This case suggests that chidamide may enhance the efficacy of traditional chemotherapy, and that chidamide combined with traditional chemotherapy may be a promising treatment option for primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.

INTRODUCTION

Primary cutaneous aggressive epidermotropic CD8+ cytotoxic cell T-cell lymphoma is a rare subtype of cutaneous T-cell lymphoma, accounting for less than 1% of all cutaneous T-cell lymphomas. Only dozens of cases have been reported worldwide, and there is no optimal treatment. According to existing reports, the majority of patients with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma currently receive doxorubicin-based traditional chemotherapy. There are case reports of treatment with CHOP, CHOPE, and Hy-CVAD regimens, but the efficacy is poor. All result in short-term benefits, with an overall survival of 12-32 mo [1]. The main reason for the poor long-term efficacy of primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma to traditional chemotherapy is that lymphoma cells are prone to chemoresistance [2]. Chidamide has potential anti-hematological tumor activity and enhances the chemosensitivity of lymphoma cells. It has been recognized for the treatment of relapsed or refractory peripheral T-cell lymphoma. Based on the above theory, we boldly tried the combination of chidamide with traditional chemotherapy (CHOPE) in a patient with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma with promising results.

CASE PRESENTATION

Chief complaints
A 14-year-old boy was admitted to the Department of Dermatology with a 5-d history of generalized erythema, papules, and blisters and was transferred to the Department of Medical Oncology.

History of present illness
The patient had generalized erythema, papules, and blisters with itching since August 18, 2017. Three days after the onset of symptoms, some blisters formed blood blisters with tan crusts on the surface, accompanied by pain, and fever, fear of cold, and chills, with a maximum body temperature of 41 °C.

Physical examination
The patient’s body temperature was 37.8 °C, heart rate was 110 bpm, respiratory rate...
was 20 breaths/min, and blood pressure was 99/67 mmHg. Scattered blood blisters were observed throughout the body, with the most severe blood blisters on the trunk, consistent with the distribution of skin transverse striae (Figure 1). Erosive surfaces of varying sizes were seen in the oral cavity, trunk, extremities, and perineum. Physical examination of the heart, lungs, and abdomen was unremarkable.

**Laboratory examinations**

After admission, a blood test was performed and the patient’s white blood cell count was 5.86 × 10^9/L, hemoglobin concentration was 146.70 g/L, and platelets were 129.80 × 10^9/L. His biochemical results were as follows: Total protein, 61.2 g/L; albumin, 29.5 g/L; creatinine, 54 μmol/L; lactate dehydrogenase, 351 U/L; β-2 microglobulin, 3.6 mg/L; interleukin-6, 13.34 pg/mL. The results of bone marrow biopsy showed slight microscopic bone marrow hyperplasia, cell volume accounted for 40%, tertiary hematopoietic cells were present, granulocyte/erythrocyte ratio was slightly increased, and cell morphology was normal (Figure 2A). The skin of the left thigh was biopsied, and the pathology results indicated primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (Figure 2B). The results of immunohistochemistry revealed the following: CD3 (+), CD2 (-/+), CD4 (-/+), CD5 (-/+), CD7 (+), CD8 (+ +), CD56 (-), TiA-1 (+), GB (+), AIK (-), CD30 (-), CD20 (-), and CD10 (-); EBERs (-); TCR-α gene rearrangement (-).

**Imaging examinations**

Positron emission tomography/computed tomography (PET/CT) showed mildly increased systemic cutaneous glucose metabolism, which was considered to be cutaneous lymphoma. Mild systemic skin swelling and a diffuse mild increase in glucose metabolism, especially in the local skin of both armpits, right upper quadrant, and posterior coccyx were observed (Figure 3). Multiple small lymph nodes of different sizes with increased glucose metabolism were observed in both armpits and groins.

**FINAL DIAGNOSIS**

Based on pathological biopsy, laboratory examinations, imaging examination and clinical manifestations, the patient was finally diagnosed with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.

**TREATMENT**

The patient was diagnosed more than 20 d after the onset of symptoms, and chidamide combined with CHOPE regimen was administered as the patient’s first cycle of treatment as follows: Chidamide 30 mg/biw, cyclophosphamide 1100 mg/d1, doxorubicin 70 mg/d1, vincristine 2 mg/d1, dexamethasone 20 mg/d1-5, etoposide 100 mg/d1-5, in a 21 d cycle. The patient completed a total of 6 cycles of treatment and subsequently entered maintenance therapy.

**OUTCOME AND FOLLOW-UP**

After 4 cycles of treatment, the patient returned to the hospital for follow-up, and his skin rash on the face, neck, trunk, and extremities had disappeared (Figure 4A). The blood tests showed that the white blood cell count was 6.14 × 10^9/L, hemoglobin concentration was 123 g/L, and platelets were 225 × 10^9/L. His biochemical results were as follows: Total protein, 68.2 g/L; albumin, 36 g/L; creatinine, 60 μmol/L; lactate dehydrogenase, 225 U/L; β-2 microglobulin 1.96 mg/L; interleukin-6, 5.3 pg/mL. PET/CT showed that after chemotherapy for cutaneous lymphoma, the original lesions were inactivated and no new lesions were observed (Deauville score: 1 point). No clear structural or glucose metabolism abnormalities were noted (Figure 3B). Complete remission was observed. The patient had grade III bone marrow suppression during the 5th cycle of chemotherapy, and continued to complete chemotherapy as planned after repeated blood tests were normal after leukocyte-elevating therapy. After completing 6 cycles of treatment, he regularly took chidamide 20 mg/biw as maintenance therapy for 1 year. No significant hematological toxicity or
gastrointestinal adverse events occurred during maintenance therapy with chidamide. The last follow-up was performed 2 wk ago and the patient's condition was stable without recurrence (Figure 4B).

DISCUSSION

Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma was first reported as a rare histopathological subtype of cutaneous T-cell lymphoma in 1999 by Berti et al[3]. It was first classified as a non-specific provisional entity by the World Health Organization/European Organization for Research and Treatment of Cancer in 2005[4]. This type of lymphoma is characterized by the presence of localized or diffuse papules, nodules, or tumors, which present as central ulceration or necrosis, or plaques with surface hyperkeratosis[5]. Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma is highly aggressive and can rapidly spread to various organs, such as the lungs, testes, central nervous system, or oral mucosa, with a poor response to traditional chemotherapy[6]. Some patients can benefit from doxorubicin-based multiagent chemotherapy for a short time, but most patients relapse a short time after treatment and even develop resistance to traditional chemotherapy and then it transforms into relapsed or refractory lymphoma. Treatment is still a great clinical challenge.

Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma is clinically heterogeneous, and its course progresses rapidly. Treatment options for advanced disease are limited, and significantly effective treatment options deserve active exploration. Numerous studies have shown that histone deacetylase inhibitors (HDAC inhibitors) are used to treat malignant tumors, such as cutaneous T-cell lymphoma and peripheral T-cell lymphoma. Moreover, HDAC inhibitors are now
Figure 2 Bone marrow and skin biopsies. A: Bone marrow biopsy. Slight microscopic bone marrow hyperplasia, cell volume accounted for 40%, tertiary hematopoietic cells were present, granulocyte/erythrocyte ratio was slightly increased, and cell morphology was normal; B: Skin biopsy of left thigh. There was hyperkeratosis of the skin epidermis, hemorrhage in the papilla of the dermis, and local or diffuse small lymphocyte infiltration in both the epidermis and subcutaneously.

Figure 3 The patient underwent positron emission tomography/computed tomography before treatment and reexamination after 4 cycles of treatment. A: Positron emission tomography/computed tomography (PET/CT) before treatment. The figure showed mild systemic skin swelling and diffuse mild increase in glucose metabolism, especially in the local skin of both armpits, right upper quadrant, and posterior coccyx. Multiple small lymph nodes of different sizes with increased glucose metabolism were observed in both armpits and groins; B: PET/CT after treatment. The figure showed no clear structural or glucose metabolism abnormalities.

increasingly being used in combination with other types of anticancer drugs for the treatment of various malignancies. Chidamide is an innovative drug independently developed in China, which can exert anti-tumor activity by reversing tumor cell resistance, increasing tumor cell chemosensitivity, potently regulating immunity and potential direct anti-tumor effects[7,8]. In December 2014, chidamide was approved by
China Food and Drug Administration for the treatment of relapsed or refractory peripheral T-cell lymphoma. Previous studies have shown that chidamide can induce apoptosis and growth arrest of lymphoid or hematologic tumor cells, and can also reverse tumor cytotoxic resistance to increase tumor cell chemosensitivity. Wei Guan et al\cite{9} retrospectively analyzed 17 cases of refractory or relapsed T-lymphocytic lymphoma/leukemia (T-LBL/ALL) and found that chidamide has pleiotropic regulatory immune function and can enhance the sensitivity of tumor cells to chemotherapeutic drugs. Jiang et al\cite{10} found that chidamide inhibited the proliferation and induced apoptosis of tumor cells and exerted potential anti-leukemia activity. Chidamide can also increase the chemosensitivity of tumor cells by disrupting the Smo/gli-1 pathway and the downstream signaling target p-AKT. Yan et al\cite{8} found that the combination of chidamide and syndilimab enhanced the efficacy of syndilimab in NK/T cell lymphoma. Based on the above theory, we speculate that a treatment regimen combining chidamide may be a promising therapeutic strategy for refractory T-cell lymphoma. Common adverse events of chidamide include thrombocytopenia, leukopenia, neutropenia, QTc prolongation, fatigue, fever, and gastrointestinal symptoms. Studies have shown that the incidence of adverse events is low and easily controlled, with only a few patients discontinuing treatment due to serious adverse events\cite{7,11}.

The present patient with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma achieved complete remission following treatment with chidamide combined with CHOPE regimen. On the one hand, this may have been due to the potential antitumor activity of chidamide, and on the other hand, it may have been because chidamide reverses tumor cell chemoresistance to increases tumor cell

Figure 4 Follow-up photographs of the patient. A: Photographs of the patient after completion of 4 treatment cycles. Generalized scattered blood blisters disappeared, and residual scattered skin pigmentation was observed; B: Photographs of the last follow-up. No abnormal lesions were observed.
chemosensitivity. In this case, the patient experienced short-term hematological toxicity during chemotherapy with chidamide combined with CHOPE regimen, but recovered quickly after leukocyte-elevating therapy. The patient successfully completed 6 cycles of therapy. In addition, no significant adverse events occurred in this patient during maintenance therapy. This regimen was well tolerated and provides a promising therapeutic strategy for the treatment of primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.

CONCLUSION

In conclusion, we found that a combination of chidamide and a traditional chemotherapy regimen is a safe and effective treatment for primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, but its long-term efficacy requires further evaluation. For patients with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma refractory to traditional therapy (e.g., CHOP), we recommend early combination therapy with chidamide. This study also had limitations: Due to the rarity of primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, analysis of the results obtained in this report requires caution. Whether the good efficacy in this patient was the result of synergy between traditional chemotherapy and chidamide or a separate effect of chidamide cannot be determined. In the future, we will continue to collect data to assess the efficacy and safety of chidamide in combination with CHOPE in patients with primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.

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Fatal rhabdomyolysis and disseminated intravascular coagulation after total knee arthroplasty under spinal anesthesia: A case report

Dae Hun Yun, Eun Ha Suk, Wan Ju, Eun Hyoung Seo, Hyun Kang

BACKGROUND
Rhabdomyolysis develops as a result of skeletal muscle cell collapse from leakage of the intracellular contents into circulation. In severe cases, it can be associated with acute kidney injury and disseminated intravascular coagulation, leading to life threatening outcomes. Rhabdomyolysis can occur in the perioperative period from various etiologies but is rarely induced by tourniquet use during orthopedic surgery.

CASE SUMMARY
A 77-year-old male underwent right total knee arthroplasty using a tourniquet under spinal anesthesia. About 24 h after surgery, he was found in a drowsy mental state and manifested features of severe rhabdomyolysis, including fever, hypotension, oliguria, high creatine kinase, myoglobinuria, and disseminated intravascular coagulation. Despite supportive care, cardiac arrest developed abruptly, and the patient was not able to be resuscitated.

CONCLUSION
Severe rhabdomyolysis and disseminated intravascular coagulation can develop from surgical tourniquet, requiring prompt, aggressive treatments to save the patient.

Key Words: Rhabdomyolysis; Total knee arthroplasty; Tourniquet; Disseminated intravascular coagulation; Case report

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widely performed in elderly patients, physicians should be aware of the possibility of tourniquet-induced rhabdomyolysis after surgery. Careful use of a tourniquet and maintaining an adequate hemodynamic state in the perioperative period is important to prevent rhabdomyolysis. Nonspecific symptoms, such as altered mental state, can obscure a prompt diagnosis and delay early treatment. Regular monitoring and careful evaluations are necessary to detect rhabdomyolysis early, and aggressive therapies, including early vigorous hydration, are required.

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INTRODUCTION
Rhabdomyolysis is a clinical syndrome caused by the destruction of skeletal muscle fibers, which leads to the leakage of intracellular contents into circulation. Various toxic materials, such as creatine kinase (CK), lactate dehydrogenase, myoglobin, aspartate transaminase (AST), and electrolytes, are released to the bloodstream, causing systemic symptoms, including hyperkalemia, hypovolemia, acute kidney injury (AKI), metabolic acidosis, compartment syndrome, cardiac dysrhythmia, and disseminated intravascular coagulation (DIC) in severe cases[1]. Rhabdomyolysis can be classified according to the mechanism of injury, such as hypoxic, physical, chemical, or biological, or classified as acquired or inherited. Trauma is the most common cause, with less common causes being toxins, drugs, alcohol, infection, sepsis, excessive workouts, myopathies, endocrinopathies, thermal injury, and electrolyte abnormalities [2].

As a form of trauma, surgery can induce rhabdomyolysis due to ischemic muscle injury from long-term immobilization or excessive tissue compression during the surgery. Recently, there have been increasing numbers of descriptions of rhabdomyolysis which developed in the perioperative period. The use of a pneumatic tourniquet, which is widespread in extremity orthopedic surgery to create a bloodless operation field, is rarely associated with morbidity and mortality but can induce rhabdomyolysis. In this report, we present an unusual case of tourniquet-induced rhabdomyolysis after total knee arthroplasty (TKA) under spinal anesthesia, which was ultimately fatal.

CASE PRESENTATION

Chief complaints
A 77-year-old male (weight: 51 kg, height: 170 cm) exhibited a drowsy mental state about 24 h after TKA.

History of past illness
The patient had been diagnosed with unstable angina 8 years prior, which was treated with a coronary stent insertion. He had been subsequently treated with Sigmart (nicorandil 5 mg; JW Pharmaceutical, Seoul, South Korea), aspirin (enteric coated tab, 100 mg), Almarl (arotinolol 5 mg; HK inno.N, Seoul, South Korea), and Herben (diltiazem 30 mg; HK inno.N).

Perioperative management for TKA
Prior to surgery, chest X-ray was normal. Echocardiogram showed a left ventricular ejection fraction of 61%, grade 2 diastolic dysfunction, mild aortic regurgitation, trivial mitral regurgitation and tricuspid regurgitation. All hematological parameters were unremarkable, with normal blood urea nitrogen/creatinine (BUN/Cr) of 11.0/0.8 mg/dL and low hemoglobin of 11.9 g/dL.
Aspirin was stopped 7 d before surgery, and no medication was administered on the morning of surgery. After arriving at the operating room, initial vital signs were blood pressure (BP) of 144/79 mmHg, heart rate (HR) of 68 beats/min, and SpO₂ of 97%. Bupivacaine (0.5%, 10 mg) was injected into the subarachnoid space at T10 for the spinal block. Intravenous dexmedetomidine was infused (0.5 μg/kg/min for first 10 min, then at 0.4-0.6 μg/kg/min) for sedation. A pneumatic thigh tourniquet was applied intraoperatively at an inflation pressure of 300 mmHg for 100 min. Total anesthesia time was 2 h and 10 min. During surgery, 600 mL of crystalloid was administered and 150 mL of urine were collected. Estimated blood loss was 90 mL. Intraoperative vital signs showed BP of 100-130/50-70 mmHg, HR of 45-55 beats/min, and SpO₂ of 97%-99% (Figure 1).

On arrival in the recovery room, initial vital signs were BP of 97/55 mmHg, HR of 41 beats/min and SpO₂ of 100%. During the first hour of recovery, vital signs were maintained as follows: BP of 95-100/55-60 mmHg, HR of 40-45 beats/min, and SpO₂ of 98%-100%. About 90 mL of urine and 70 mL of blood were drained, and 400 mL of crystalloid was administered.

**Postoperative management for TKA**

After surgery, post-operative pain was managed with an intravenous patient-controlled analgesia (AutoFuser; ACE Medical, Beverly Hills, CA, United States), including 1 mg fentanyl (Hana Pharm, Seoul, South Korea), of which the baseline infusion rate, bolus demand dose, and lock-out time were 2 mL/h, 2 mL, 15 min. Antibiotics (Refosporin, 1 g and cefazedone sodium 1 g; both from Hanall Biopharma, Seoul, Korea) were also injected bid. The morning following surgery, the patient complained of severe pain on the right thigh and overnight shivering. Tridol Injection (tramadol hydrochloride 50 mg/mL; Yuhan Pharm, Seoul, South Korea) was injected for pain control.

**Physical examination**

When the mental change was identified, the patient’s mental state was assessed with a Glasgow coma scale score of 8/15 (M5/V2/E1). At that time, vital signs were BP of 110/70 mmHg, HR of 122 beats/min, body temperature of 37.9 °C, and SpO₂ of 86%-90%. Electrocardiogram was normal.

On physical examination, the patient’s right thigh, which had been cuffed with tourniquet during the operation, was stiff and had turned a dark brown, without swelling, whereas the surgical site and distal extremity were unaffected. Urine collected in a Foley bag was dark colored, and the urine output every 8 h after operation was 100 mL, 220 mL, and 250 mL, respectively, for a total of 570 mL/d, which indicated oliguria.

**Laboratory examinations**

Immediately after surgery in the recovery room, laboratory results were within the normal range, with the exception for some derangement in the coagulation panel. About 19 h after surgery, CK was markedly increased to 2763 IU/L (normal: 56-244 IU/L), creatine kinase-myocardial band (CK-MB) was elevated to 13.26 ng/mL (normal: < 4.87 ng/mL), and AST and BUN/Cr were also elevated. However, troponin-I was normal at 0.100 ng/mL (normal: < 0.16 ng/mL). Prolonged coagulation battery, thrombocytopenia, and high levels of fibrinogen degradation product and D-dimer were detected in the early postoperative phase, and serial tests demonstrated progressive deterioration of DIC. Additional laboratory tests performed during the intensive care unit (ICU) stay showed continued deterioration of the parameters. Serial changes in the parameters are summarized in Table 1.

**Imaging examination**

Immediately after the mental change was identified, brain magnetic resonance imaging (MRI) was performed for differential diagnosis. Mild small vessel disease was identified, but no notable hemorrhage or infarction was evident.

**Further diagnostic work-up**

As the patient persisted in the drowsy mental state, additional tests found that serum myoglobin was 1027 ng/mL (normal: 28-72 ng/mL), and random urine analysis revealed that urine myoglobin was 25.3 ng/mL and red blood cell count was 100/high powered field (HPF) (normal: 0-4/HPF).
Table 1 Serial changes in the laboratory parameters in perioperative period

<table>
<thead>
<tr>
<th>Time</th>
<th>CK, 56-244 IU/L</th>
<th>AST, 5-37 IU/L</th>
<th>LDH, 160-520 IU/L</th>
<th>BUN, 8-22 mg/dL</th>
<th>Cr, 0.8-1.2 mg/dL</th>
<th>K, 3.5-5.0 mEq/L</th>
<th>Platelet count, 150-400 ×10^3/mL</th>
<th>PT/aPTT, 10.4-13.5/36.0-39.0 s</th>
<th>PT INR, 0.85-1.15 INR</th>
<th>Fibrinogen, 170-410 mg/dL</th>
<th>D-dimer, 0-0.55 mg/mL</th>
<th>FDP, 0-5 mg/mL</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop.</td>
<td>27</td>
<td>11</td>
<td>0.8</td>
<td>4.1</td>
<td>111</td>
<td>11.3/30.8</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After surgery</td>
<td>111</td>
<td>26</td>
<td>10.4</td>
<td>0.7</td>
<td>3.5</td>
<td>91</td>
<td>122/28.8</td>
<td>1.09</td>
<td>198</td>
<td>4.14</td>
<td>10.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 h after surgery (next day morning)</td>
<td>2763</td>
<td>93</td>
<td>15.2</td>
<td>1</td>
<td>3.5</td>
<td>52</td>
<td>13.8/32.8</td>
<td>1.24</td>
<td>150</td>
<td>80</td>
<td>148</td>
<td>7.383</td>
<td></td>
</tr>
<tr>
<td>31 h after surgery (during ICU)</td>
<td>121</td>
<td>464</td>
<td>20.4</td>
<td>1.2</td>
<td>3.7</td>
<td>44</td>
<td>17.3/37.9</td>
<td>1.58</td>
<td>361</td>
<td>48.3</td>
<td>117</td>
<td>7.406</td>
<td></td>
</tr>
<tr>
<td>33 h after surgery (during CPR)</td>
<td>3455</td>
<td>128</td>
<td>502</td>
<td>19.5</td>
<td>1.4</td>
<td>5.3</td>
<td>16</td>
<td>31.7/120.3</td>
<td>3.02</td>
<td>171</td>
<td>80</td>
<td>140</td>
<td>7.511</td>
</tr>
</tbody>
</table>

aPTT: Activated partial thromboplastin time; AST: Aspartate transaminase; BUN: Blood urea nitrogen; CK: Creatine kinase; CPR: Cardiopulmonary resuscitation; Cr: Creatinine; FDP: Fibrinogen degradation product; ICU: Intensive care unit; INR: International normalized ratio; LDH: Lactate dehydrogenase; PT: Prothrombin time.

**FINAL DIAGNOSIS**

Tourniquet-induced rhabdomyolysis was diagnosed based on the serum CK level (5 times the upper limit of normal range), myoglobinuria, and physical examination. Laboratory findings revealed that AKI (AKIN criteria stage 1, urine output < 0.5 mL/kg/h for 6-12 h and serum Cr increase 0.3 mg/dL within 48 h) and DIC accompanied the rhabdomyolysis.

**TREATMENT**

About 1 h after the change in the patient’s mental status, BP dropped to 88/62 mmHg, and norepinephrine (0.5-1 μg/kg/min) was infused to maintain systolic BP above 100 mmHg. After brain MRI examination, the patient was admitted to the ICU. An arterial line was placed in the left radial artery for continuous monitoring of blood pressure, and a central line was secured in the right internal jugular vein for adequate fluid supply and cardiovascular monitoring. A nephrologist was consulted, and fluid treatment of 5 L/d was prescribed. Dialysis was scheduled due to progressive renal impairment. Fluid loading was initiated with normal saline at 400 mL/h for 2 h, and then decreased to 250 mL/h. For renoprotection, Lasix (furosemide, 20 mg injection; Handok, Seoul, South Korea) and sodium bicarbonate (40 mL injection of 8.4%; Jeil Pharmaceutical, Daegu, South Korea) were administered for diuresis and urine
alkalization, respectively. The urine output was 110 mL for the first 3 h and 600 mL for next 4 h. Denogan (propacetamol hydrochloride 1 g injection; Yungjin Pharmaceutical, Seoul, South Korea) was administered to control fever. About 2 h after fluid administration, the patient’s mental status was restored to alert. His vital signs were as follows: BP of 90-110/60-70 mmHg, HR of 104 beats/min, body temperature of 36.2 °C, and SpO₂ of 98% on room air. However, after 2 h, the patient’s body temperature elevated again to 38.0 °C. Serial vital signs were summarized in Table 2.

OUTCOME AND FOLLOW-UP

Approximately 5 h after the patient’s mental state was restored, his BP and HR dropped suddenly, followed by cardiac arrest. Cardiopulmonary resuscitation was performed for about 1 h; however, the patient was not resuscitated. At the will of the guardian, we stopped further resuscitation, and he expired.

DISCUSSION

Rhabdomyolysis has been described during the perioperative period after various types of surgeries, including urologic, spinal, coronary bypass graft, bariatric, and head and neck. Risk factors for developing rhabdomyolysis during surgery and subsequent post-operative period are: prolonged surgical duration, improper positioning, male sex, obesity, age < 10 or > 60 years, diabetes, hypertension, kidney disease, endocrine disease, chronic drug users, and sepsis [3-6].

Excessive or prolonged compression by a pneumatic tourniquet during a lower extremity surgery can bring about tissue ischemia, both beneath the cuff and in the distal tissue, which can therefore lead to rhabdomyolysis. However, this is a rare outcome, as only a few cases of rhabdomyolysis after tourniquet application in lower extremity surgery have been reported [7-12]. Tourniquet-induced rhabdomyolysis occurs regardless of the anesthetic type and is generally related to longer tourniquet application times and unusually high tourniquet pressures. Therefore, it is important to control the tourniquet application time and pressure to prevent rhabdomyolysis.

Although optimal tourniquet pressure and inflation time for prevention of muscle injury have not been clearly defined, several methods are used to determine the optimal inflation pressure for lower extremity. The first is determined by adding 100-150 mmHg above the arm systolic blood pressure [13], and a second is by adding 50-75 mmHg to the pressure required to obliterate the peripheral pulse on Doppler probe [14]. Additionally, Horlocker et al [15] recommended the tourniquet inflation time < 120 min to prevent nerve injury during TKA not pertaining to muscle injury. In TKA,
Table 2 Serial vital signs in the perioperative period

<table>
<thead>
<tr>
<th>Time</th>
<th>SBP in mmHg</th>
<th>DBP in mmHg</th>
<th>HR in beats/min</th>
<th>BT in °C</th>
<th>SpO₂ %</th>
<th>Progress note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before surgery</td>
<td>120</td>
<td>70</td>
<td>50</td>
<td>36.6</td>
<td>100</td>
<td>After arrival on operation room</td>
</tr>
<tr>
<td>After surgery</td>
<td>95</td>
<td>58</td>
<td>48</td>
<td>35.8</td>
<td>100</td>
<td>During recovery room</td>
</tr>
<tr>
<td>6 h after surgery</td>
<td>120</td>
<td>70</td>
<td>61</td>
<td>36.4</td>
<td>100</td>
<td>Drowsy mental state</td>
</tr>
<tr>
<td>12 h after surgery</td>
<td>100</td>
<td>60</td>
<td>75</td>
<td>36.1</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>24 h after surgery</td>
<td>110</td>
<td>70</td>
<td>110</td>
<td>37.9</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>28 h after surgery</td>
<td>100</td>
<td>70</td>
<td>103</td>
<td>36.6</td>
<td>98</td>
<td>During ICU, mental state was recovered</td>
</tr>
<tr>
<td>31 h after surgery</td>
<td>100</td>
<td>60</td>
<td>113</td>
<td>38</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>33 h after surgery</td>
<td>50</td>
<td>20</td>
<td>37</td>
<td>52</td>
<td></td>
<td>During CPR</td>
</tr>
</tbody>
</table>

BT: Body temperature; CPR: Cardiopulmonary resuscitation; DBP: Diastolic blood pressure; HR: Heart rate; ICU: Intensive care unit; SBP: Systolic blood pressure; SpO₂: O₂ saturation by pulse oximetry.

tourniquet is usually used at 300 mmHg of pressure until completion of cementing and total inflation time is limited to 120 min. If the operation is expected to be longer, the tourniquet should be deflated for a minimum of 20 min every 60-90 min[16].

Besides the optimal use of tourniquet, the safe inflation pressure and time seem to be dependent on several variables. For example, underlying conditions of a patient are also important in predicting the development of rhabdomyolysis after tourniquet application. Additionally, factors, including age, blood pressure, co-morbidities and the condition of the extremity, should also be considered when assessing the risks of developing rhabdomyolysis after using a tourniquet during surgery. To our knowledge, only two descriptions of rhabdomyolysis after TKA have been reported[8,9]. Karcher et al[8] reported rhabdomyolysis, AKI, and liver dysfunction in an obese patient after TKA using a short period (50 min) of tourniquet application at 350 mmHg and Palmer et al[9] described a case of rhabdomyolysis and AKI after TKA in an elderly patient with chronic obstructive airway disease, hypertension, coronary artery disease, and heart failure, in which the tourniquet application time was 92 min at 350 mmHg. Both cases had relatively high tourniquet pressure and underlying risk factors, including advanced age, obesity, and cardiovascular disease.

Rhabdomyolysis can be precipitated by hypotension or hypovolemia due to the distortion of perfusion to the affected muscles. Glassman et al[17] suggested that permissive hypertension would prevent the development of rhabdomyolysis by improving perfusion to compressed muscles. In TKA, tourniquet use significantly decreases intraoperative blood loss but cannot decrease total blood loss[18], therefore sufficient fluid should be supplied postoperatively after tourniquet deflation when persistent bleeding is ongoing. In our patient, the tourniquet pressure and duration did not exceed the recommended guidelines, with 300 mmHg of pressure applied for 100 min. The patient had two known risk factors of male sex and old age. Additionally, preoperative dehydration, sustained postoperative hypotension, and his history of ischemic heart disease are thought to be contributing factors of the rhabdomyolysis development, as together these conditions contributed to peripheral vascular insufficiency. Moreover, postoperative shivering and fever may have limited tissue perfusion and oxygen supply, and overlapping AKI and DIC cascade further led to the rapid progression of the disease.

TKA is usually performed on older patients, many with various underlying diseases, and spinal anesthesia is preferred in lower extremity surgery for elderly patients to avoid risks of general anesthesia. However, hypotension induced by spinal block and dexmedetomidine infusion for sedation might have contributed to rhabdomyolysis by lowering perfusion pressure. Therefore, meticulous care in tourniquet use and maintaining adequate perfusion pressure are required to prevent muscle injury. We recommend the lowest effective inflation pressure with minimal inflation time in TKA because the tourniquet inflation time and pressure have additive effects.

The diagnosis of rhabdomyolysis in our patient was confirmed by elevated serum CK levels of > 1000 U/L, which is 5-times the normal upper limit. The patient also had dark urine and severe pain in the area the tourniquet was applied. Clinical suspicion is
important to make a timely decision for diagnosis, so physicians should pay attention to the clinical presentations. The symptoms of this syndrome vary, from minor and subclinical to severe and even fatal, according to the degree of skeletal muscle injury. Musculoskeletal signs are inappropriate severe pain, occasional tenderness or swelling in the affected muscle, and skin changes, indicating muscle necrosis can be present. Simple myalgia, fatigue, weakness, fever, tachycardia, nausea, and vomiting are common general manifestations, and pigmenturia can be observed in some cases. Non-specific symptoms, such as hypotension, shock and changes in mental status, might be present, requiring differential diagnosis. Complications of rhabdomyolysis are hyperkalemia, hypocalcemia, elevated AST, cardiac dysrhythmias, and cardiac arrest in early phase. AKI and DIC can develop, usually 12-72 h after insult, as late complications in serious cases.

In our patient, clotting studies detected an early DIC cascade in the postoperative period. Although fibrinolysis is activated transiently after tourniquet use itself, myocyte components can activate the coagulation pathway leading to DIC in severe rhabdomyolysis[1]. Persistent oliguria and progressive increase in creatine levels showed ongoing kidney injury. AKI is the most common serious complication of rhabdomyolysis, occurring in approximately 10%-67%. The mortality rate of rhabdomyolysis is known to about 10%, which increases with the degree of kidney injury up to 50%[19]. AKI is an independent predictor of higher mortality and more likely to develop in elderly patients and in patients with chronic comorbid disease, such as congestive heart failure, coronary artery disease, diabetes mellitus, atrial fibrillation, hyperlipidemia, and chronic kidney disease[20]. Although clear guidelines for the management of rhabdomyolysis have not yet been developed, the goals of rhabdomyolysis treatment are the same as maintaining adequate tissue perfusion and oxygenation to prevent hypoxic tissue injury and preserving renal function by maintaining urine output. Prompt fluid replacement is the keystone of treatment. Aggressive hydration should be initiated as soon as possible to control hypovolemia and maintain adequate urine output (> 200-300 mL/h in adult). High volume fluid replacement, up to 1.5 L/h or more than 6 L/d, may be needed to obtain satisfactory urine output[21,22]. Mannitol, loop diuretics, and sodium bicarbonate have been used for renal protection, but the additional benefit beyond fluid resuscitation is not known. Renal replacement therapy can be considered in deteriorating kidney function, uncontrolled hyperkalemia, metabolic acidosis, and fluid overload. In the present case, early mental changes prompted a brain MRI to rule out intracranial accident. Unfortunately, the treatment of rhabdomyolysis, such as early hydration, was delayed during the radiological study. After radiological work up, the patient was transferred to the ICU, and urine output was found to be inadequate, despite fluid replacement and pharmacological renoprotection. Higher volume expansion should have been performed in order to achieve satisfactory urine output. We thought that the unresolved dehydration and overlapping DIC cascade resulted in the devastating outcome.

CONCLUSION

Rhabdomyolysis induced by tourniquet application is very rare, but can lead to potentially lethal results if it develops. Physicians should be aware of the possibility of tourniquet-induced rhabdomyolysis after TKA, regardless of the type of anesthesia. Tourniquets should be used carefully in elderly patients with risk factors, and maintaining hemodynamic stability with adequate fluid replacement is important during the perioperative period. Regular monitoring of CK level and sufficient attention are necessary to detect this syndrome early. Once rhabdomyolysis is diagnosed, prompt aggressive treatments, including vigorous hydration, are required to save the patient, especially when accompanied by AKI or DIC.

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Left atrial appendage occlusion in a mirror-image dextrocardia: A case report and review of literature

Bei Tian, Chuang Ma, Jin-Wen Su, Jun Luo, Hong-Xia Sun, Jie Su, Zhong-Ping Ning

BACKGROUND
In mirror-image dextrocardia, the anterior-posterior position of the cardiac chambers and great vessels is maintained, but the left-right orientation of the abdominal organs is reversed. The abnormal anatomy of the heart poses surgical challenges and problems in dealing with surgical risk and monitoring complications. There are few reports on closure of the left atrial appendage (LAA) in dextrocardia and no reports on the application of enhanced recovery after surgery (ERAS) following LAA occlusion (LAAO) procedures.

CASE SUMMARY
The objective for this case was to ensure perioperative safety and accelerate postoperative recovery from LAAO in a patient with mirror-image dextrocardia. ERAS was guided by the theory and practice of nursing care. Atrial fibrillation was diagnosed in a 77-year-old male patient, in whom LAAO was performed. The 2019 guidelines for perioperative care after cardiac surgery recommend that the clinical nursing procedures for patients with LAAO should be optimized to reduce the incidence of perioperative complications and ensure patient safety. Music therapy can be used throughout perioperative treatment and nursing to improve the anxiety symptoms of patients.

CONCLUSION
The procedure was uneventful and proceeded without complications. Anxiety symptoms were improved.
Enhanced recovery after surgery (ERAS) is a multimode, interdisciplinary care model designed to improve perioperative care, including medical care before, during, and after surgery and during rehabilitation. Increasing evidence supports the use of ERAS in surgical patients. ERAS is effective in reducing gastrointestinal infections and hospital stay associated with general colon and rectum surgery. The ERAS Society has been the source of international plans for colorectal, hepatobiliary, urinary, gastric, gynecological, and cardiac surgery groups, and provided evidence-based guidelines for the perioperative treatment and nursing of patients[1-3].

In cardiac surgery, the ERAS model shows that early extubation is safe and feasible, and can significantly shorten electrocardiogram (ECG) monitoring and coronary care unit (CCU) stays. However, the application of ERAS models in cardiac surgery is still at an early stage, and reports in interventional cardiology are limited. Studies have shown that ERAS regimens are feasible and safe in minimally invasive cardiac surgery, and have the potential to significantly improve patient prognosis[4,5].

The ERAS model has characteristics specific to different clinical fields, but the basic concept is common to all fields. The 2019 guidelines for accelerating postoperative rehabilitation of heart surgery include correcting malnutrition before surgery, smoking and drinking cessation, establishing a cardiac preadaptation plan including education, nutrition optimization, sports training, social support, and reducing anxiety, infection prevention, carbohydrate loading (sugar prestorage), establishment of an electronic health platform, etc. The intraoperative care package includes local nasal treatment to eliminate staphylococcus colonization, skin preparation, defloration scheme, dressing changes, prevention of hypothermia, keeping venous access open, rigid sternum fixation, and hemostasis. Whole-process management of patients in the perioperative period includes intensive glycemic control, pain management, delirium screening, drug anticoagulation, early extubation, biomarkers for early identification of high-risk patients with acute kidney injury, and goal-directed recommendations (i.e., blood pressure, cardiac index, systemic venous oxygen saturation, and urine volume). Fluid management therapy is a cooperative multiteam effort, including nutritionists, early cardiac rehabilitation therapists, and physiotherapists.

Left atrial appendage occlusion (LAAO) is a minimally invasive intervention guided by medical imaging equipment. A device is positioned in the left atrial appendage (LAA) by percutaneous venipuncture to prevent thrombi from entering the blood circulation in patients with atrial fibrillation. Medical staff are concerned about the consequences of and low compliance with long-term use of oral anticoagulants and the high risk of bleeding. Therefore, LAAO has been applied as an alternative for stroke prevention and vascular disease management therapy; Enhanced recovery after surgery; Case report

Key Words: Atrial fibrillation; Dextrocardia; Left atrial appendage occlusion; Music therapy; Enhanced recovery after surgery; Case report

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Core Tip: Mirror dextrocardia has typical clinical characteristics. Because of the high prevalence and mortality of atrial fibrillation of patients with mirror dextrocardia, left atrial appendage occlusion has an important role in treatment, which continues to be confirmed. Left atrial appendage occlusion is an ideal choice for patients with atrial fibrillation. Moreover, music therapy can be used throughout perioperative treatment and nursing to improve the anxiety symptoms of patients.


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INTRODUCTION

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Country/Territory of origin: China
Specialty type: Cardiac and cardiovascular systems
Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind
Peer-review report's scientific quality classification
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Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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it is the most widely used LAAO closure device[9]. Studies have shown that the effectiveness of LAAO against thrombus formation is similar to that of oral warfarin, and it has advantages in preventing stroke and maintaining quality of life[10-13]. In long-term follow-up, the incidence of both bleeding and stroke decreased significantly. LAAO was also found to be suitable for patients with atrial fibrillation who cannot tolerate oral anticoagulants, have a high risk of bleeding, have anticoagulant contraindications, and for whom anticoagulation did not prevent stroke[14-16]. The Watchman device was also found to reduce the incidence of perioperative complications, hemorrhagic stroke, stroke disability and mortality, cardiovascular events, and all-cause mortality, and to improve clinical outcomes and prognosis[17-20]. With ongoing advances in perioperative care, LAAO will continue to develop as an effective alternative strategy to prevent stroke in patients with atrial fibrillation.

In dextrocardia, the apex of the heart points to or is located on the right side of the chest[21,22]. Using the longitudinal axis of the heart as a reference, dextrocardia can be seen as either situs solitus, in which the abdominal organs are in their normal positions, or situs invertus, in which the abdominal organs are horizontally reversed or “mirrored”[23]. Mirror-image dextrocardia is a rare anomaly, with an incidence of about 1:10,000 in the general population[24]. There have been few published reports of LAAO in patients with dextrocardia, which is surgically challenging because of the anatomical anomalies, surgical risk, and complication monitoring that must be considered[25,26]. There have also been no reports on the application of the ERAS model to LAAO. This case describes our experience with ERAS following the 2019 accelerated cardiac surgery rehabilitation perioperative nursing guidelines for perioperative care of a patient with dextrocardiac LAAO.

CASE PRESENTATION

Chief complaints
The patient presented to the outpatient facility with atrial fibrillation.

History of present illness
The patient reported having experienced occasional palpitations and discomfort without obvious chest tightness and pain, and presented with fluent speech, unclear articulation, hearing loss, and mild activity impairment of the left lower limb.

History of past illness
The patient had a history of cerebral infarction, hypertension, cholecystectomy, prostatic hyperplasia surgery, and fractures of both upper limbs and the left lower limb. Long-term oral aspirin was discontinued in the previous month because of hematochezia.

Personal and family history
No family history.

Physical examination
On presentation, the patient’s body temperature was 37 °C, the pulse was 89 beats/min, respiration rate was 18 breaths/min, blood pressure was 143/76 mmHg, and the numerical rating scale pain score was 0. Twelve-lead electrocardiography revealed atrial fibrillation with a change in the ST-T segment.

Imaging examinations
Twelve-lead electrocardiography revealed atrial fibrillation with a change in the ST-T segment.

FINAL DIAGNOSIS
The diagnosis was arrhythmia, paroxysmal atrial fibrillation, cardiac function New York Heart Association level II, level II very high-risk hypertension, sequelae of cerebral infarction, and visceral inversion (Figure 1).
TIAN B et al. LAAO in mirror-image dextrocardia

Figure 1 Details of the surgical procedure. A: Transesophageal echocardiography; B: Dextrocardia (45°); C: Morphology of left atrial appendage; D: Left femoral vein puncture; E: Atrial septum puncture; F: Superior pulmonary vein of guide wire; G: Sheath follow up; H: Auricle not fully exposed; I: Right anterior oblique cardiography; J: Occluder selection; K: Implantation of sealing umbrella; L: Pulling and plugging the closure umbrella; M: Release the closure umbrella; N: Multi angle compression ratio (24%-27%); O: No residual shunt (0°); P: 1.5mm residual shunt (45°); Q: No residual shunt (90°); R: No residual shunt (135°).

TREATMENT

Percutaneous LAAO was performed under general intravenous anesthesia (Figure 1).
OUTCOME AND FOLLOW-UP

After the LAAO procedure, the patient was admitted to the CCU. His vital signs were closely monitored and found to be stable following surgery. At 18 h, the heart rate was 75 beats/min, average blood pressure was 139/80 mmHg, average $O_2$ saturation was 97%, and the urine volume was 2100 mL. At 19 h, the blood pressure was 197/99 mmHg, the heart rate was 64/min, $O_2$ saturation was 92%, and the urine volume was 900 mL. Infusion of 0.9% normal saline 250 mL + 10 mg isosorbide nitrate was maintained at 10 mL/h, as advised by the doctor. At 19 h 15 min, the blood pressure was 190/85 mmHg, the heart rate was 64 beats/min, and the $O_2$ saturation was 95%. At 20 h, the blood pressure was 172/94 mmHg, heart rate was 69 beats/min, $O_2$ saturation was 97%, and the blood pressure was 135/68 mmHg.

Puncture wounds were treated by finger compression to stop bleeding. If after 20 min no bleeding had occurred, then an elastic bandage was applied for compression. A 1 kg sandbag was applied for 6 h and a right lower limb brake was applied for 12 h. The wound dressing was changed daily. TEE on the first day after the procedure showed that the position of the umbrella was good, and that the residual shunt was about 2 mm behind the lower edge of the umbrella. No procedure-associated complications occurred during hospitalization or in the 12 d after the procedure. Follow-up echocardiography on October 18, 2019, 45 d after the procedure, and November 21, 2019 found that the occluder was in a good position, with a residual shunt of 2 mm around the lower edge of the umbrella. There had been no serious arrhythmia, bleeding, or cerebrovascular accident (Figure 1).

DISCUSSION

Dextrocardia situs inversus totalis is a rare congenital cardiac anomaly[26] in which the relationship of the great arteries is normal or transposed, as in mirror dextrocardia (coordinated cardiac circulation). Uncoordinated cardiac circulation usually shows congenital transposition of great arteries[27]. In patients with mirror dextrocardia, the main challenge for surgeons is the reversal of the whole heart, and in this case, the ECG leads were placed in the mirror mode (i.e., reversed). The fluoroscopy image is reversed horizontally, and the catheter is rotated in the opposite direction from normal [28]. The risks of coronary atherosclerosis and acute myocardial infarction in those with mirror dextrocardia are not different from those in normal individuals.

Anatomical characteristics of LAA

LAA is a remnant of the primitive atrium in the embryo. It has pectinate and trabecular muscle a unique rough endocardium[11]. It usually has three anatomical regions, the mouth, neck, and leaf and a morphology usually described as chicken wing, cactus, windsock, and cauliflower, which are present in different proportions[29,30] and appear different when observed from different angles. Some studies have reported that the LAA regulates pressure and volume load, releases atrial natriuretic peptide and B-type natriuretic peptide, and regulates hemodynamics.

Capacity load

The increase of volumetric load blood pressure after cardiac interventions may be related to excess intraoperative infusion. The left ventricular cardiac ejection fraction of the patient, who weighed 79.8-80 kg, was 56%. Fluid loss was [(4 × 10) + (2 × 10) + (1 × 60)] × 9 = 1080 mL and replenishment was complete within 2 h after the start of anesthesia[31,32]. The volume of fluid replenishment at 1 h was 1080/2 + 110 = 650 mL, with an additional 650 mL at 2 h. After that, a physiological requirement of 110 mL/h was maintained. The patient was given antibiotics (0.9% normal saline 100 mL + cefuroxime 1500 mg), sodium lactate ringer injection 500 mL + 5% glucose, normal saline 500 mL + heparin 5000 U within 2 h after the start of anesthesia. The total of 2100 mL, which was more than needed, may have contributed to the postoperative elevated blood pressure. It was agreed that the total intraoperative fluid given to the patient was not likely to have exceeded 1500 mL.

Nursing guidance by ERAS recommendations

The preoperative nutritional status of the patient was good; he did not smoke or drink. His hemoglobin was 136 g/L, and he was infection-free. An electronic health platform allowed for establishment of a real-time hospital community with an application for those with coronary heart disease to participate in a cardiac preconditioning plan that
Tian B et al. LAAO in mirror-image dextrocardia

Table 1 Nursing procedures guided by the enhanced recovery after surgery model

<table>
<thead>
<tr>
<th>Phase</th>
<th>Project</th>
<th>Level of evidence</th>
<th>Recommendation</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>Hemoglobin</td>
<td>IIA, C-LD</td>
<td>Yes</td>
<td>Preoperative measurement of hemoglobin to assist risk stratification</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
<td>IIA, C-LD</td>
<td>Yes</td>
<td>Preoperative assessment of albumin contributes to risk stratification</td>
</tr>
<tr>
<td></td>
<td>Correcting malnutrition</td>
<td>IIA, C-LD</td>
<td>Yes</td>
<td>Recommend correcting nutritional deficiencies where feasible</td>
</tr>
<tr>
<td></td>
<td>Smoking and drinking</td>
<td>I, C-LD</td>
<td>Yes</td>
<td>Patients were advised to stop 4 wk prior to elective surgery</td>
</tr>
<tr>
<td></td>
<td>Carbohydrate load</td>
<td>IIIB, C-LD</td>
<td>Yes</td>
<td>Carbohydrate loading (sugar prestocking) can be performed 2-4 h before general anesthesia</td>
</tr>
<tr>
<td></td>
<td>Infection prevention</td>
<td>IA</td>
<td>Yes</td>
<td>Cephalosporins are recommended for 30-60 min before surgery</td>
</tr>
<tr>
<td></td>
<td>E-health platform</td>
<td>IIA, C-LD</td>
<td>Yes</td>
<td>Establish electronic health education platform</td>
</tr>
<tr>
<td></td>
<td>Cardiac preconditioning program</td>
<td>IIA, B-NR</td>
<td>Yes</td>
<td>These include education, nutrition optimization, sports training, social support, and mindfulness stress reduction training to reduce anxiety</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>Implementation care package</td>
<td>I, B-R</td>
<td>Yes</td>
<td>Including local intranasal therapy to eliminate staphylococcal colonization</td>
</tr>
<tr>
<td></td>
<td>Recovery temperature</td>
<td>III, B-R</td>
<td>No</td>
<td>Skin preparation, depilation plan, dressing change after every 48 h</td>
</tr>
<tr>
<td></td>
<td>Rigid sternum fraction</td>
<td>IIA, B-R</td>
<td>No</td>
<td>Rigid sternum fraction is beneficial in patients undergoing sternotomy</td>
</tr>
<tr>
<td></td>
<td>Bleeding prevention</td>
<td>I, A</td>
<td>No</td>
<td>Tranexamic acid or amino hedic acid is recommended for cardiopulmonary bypass</td>
</tr>
<tr>
<td>Postoperative</td>
<td>Enhanced glycemic control</td>
<td>IIA, B-NR</td>
<td>Yes</td>
<td>Factors of postoperative hyperglycemia: glucose toxicity, oxidative stress, prethrombotic effect, inflammation</td>
</tr>
<tr>
<td></td>
<td>Insulin infusion to treat hyperglycemia</td>
<td>IIA, B-NR</td>
<td>No</td>
<td>Insulin infusion is recommended to treat perioperative hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Pain management</td>
<td>I, B-NR</td>
<td>No</td>
<td>Prescription of acetaminophen, tramadol, dexametomidine, pregabalin, gabapentin, etc.</td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
<td>I, B-NR</td>
<td>Yes</td>
<td>Warm blankets, elevated room temperature, heat perfusion and intravenous infusion are recommended for postoperative use</td>
</tr>
<tr>
<td></td>
<td>Delirium</td>
<td>I, B-NR</td>
<td>Yes</td>
<td>At least one delirium screening is recommended for each nursing class</td>
</tr>
<tr>
<td></td>
<td>Anticoagulant drugs</td>
<td>IIA, C-LD</td>
<td>Yes</td>
<td>Drug anticoagulation is recommended to reduce the risk of thrombosis</td>
</tr>
<tr>
<td></td>
<td>Early extubation</td>
<td>IIA, B-NR</td>
<td>Yes</td>
<td>Strategies are recommended to ensure that the tube is extubated within 6 h of surgery</td>
</tr>
<tr>
<td></td>
<td>Acute renal injury</td>
<td>IIA, B-R</td>
<td>Yes</td>
<td>Biomarkers are recommended for early identification of at-risk patients early and guide the reduction of AKI</td>
</tr>
<tr>
<td></td>
<td>Goal-directed fluid therapy</td>
<td>I, B-R</td>
<td>Yes</td>
<td>Goal-directed fluid therapy is recommended to reduce postoperative complications</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Unrated</td>
<td>Yes</td>
<td>Cardiopulmonary bypass, perfusion, mechanical ventilation at low tidal volume, early postoperative enteral feeding and postoperative mobilization are recommended</td>
</tr>
</tbody>
</table>

AKI: Acute kidney injury.

The data included education, nutrition optimization, sports training, social support, and anxiety reduction. A self-rating anxiety scale was used to assess the anxiety level of the patient when he was admitted to hospital on August 29. His score was 65, indicating moderate anxiety. International studies have shown that music therapy can improve the mood of patients, promote mental health, and reduce anxiety and depression symptoms[33-35]. Chu et al[36] and others have shown that music therapy can improve anxiety and
depression in patients with Alzheimer’s disease. Studies in China have shown that five-element music therapy improved the sleep quality of patients with heart failure and anxiety and that Wuxing music combined with Baduanjin had a positive effect on the psychology of patients with poor health status.[37,38]. Music therapy was used in the care of this patient. Six pieces of music were selected and played at 8:00-8:30 in the morning and 20:00-20:30 in the evening. The volume was 40-60 DB. On September 6, the SAS score was 46, and the anxiety state had significantly improved. Music therapy was easy to provide and not limited by the venue, and was enjoyed by the patient (Table 1).

CONCLUSION

Mirror dextrocardia has typical clinical characteristics. Because of the high prevalence and mortality of atrial fibrillation of patients with mirror dextrocardia, LAAO has an important role in treatment, which continues to be confirmed[39,40]. LAAO is an ideal choice for patients with atrial fibrillation. The 2019 nursing guidelines for accelerated cardiac surgery recovery optimize the clinical nursing path of patients with LAAO and can reduce perioperative complications and ensure the patient safety. The application of music therapy can reduce patient anxiety and is suitable for the entire process of treatment and nursing care.

ACKNOWLEDGEMENTS

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Imaging presentation of biliary adenofibroma: A case report

Shao-Peng Li, Peng Wang, Ke-Xue Deng

Case Report

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Abstract

BACKGROUND
Biliary adenofibroma (BF) is a rare benign epithelial tumor with the possibility of malignant transformation. Its main pathological feature is a well-defined cystic or honeycomb mass. BF has no specific clinical manifestations or laboratory and imaging findings; thus, it is easily misdiagnosed before surgery. This report describes a case in which biliary cystadenoma was misdiagnosed preoperatively and BF was diagnosed postoperatively. The imaging features, particularly the magnetic resonance imaging (MRI) features, were analyzed and summarized.

CASE SUMMARY
A 68-year-old Chinese man was admitted to our hospital with a 2-mo history of abdominal discomfort. Following admission to our hospital, laboratory examinations showed normal tumor marker concentrations and liver function. Hepatocellular carcinoma was considered after contrast-enhanced ultrasound examination. MRI suggested the possibility of cystadenoma of the bile duct. However, postoperative pathological examination confirmed the diagnosis of BF. No local recurrence was found 1 mo after surgery.

CONCLUSION
Our objective is to highlight the imaging diagnostic value of BF, especially on an MRI enhanced scan with gadolinium ethoxybenzyl diethylenetriamine pentaaetic acid.

Key Words: Biliary adenofibroma; Magnetic resonance imaging; Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid; Misdiagnosis; Case report
Core Tip: The imaging presentation of biliary adenofibroma is complex and diverse, and the clinical history and laboratory examination were not specific. In this case, magnetic resonance imaging characteristics of biliary adenofibroma, especially enhanced scan with Gd-EOB-DTPA and an intravoxel incoherent motion diffusion-weighted imaging sequence were valuable.

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INTRODUCTION
In 1993, Tsui et al[1] were the first to describe biliary adenofibroma (BF), which is a benign, complex, tubulocystic liver tumor with a bland spindle-cell stromal component. BF is a rare disease that is usually misdiagnosed due to its nonspecific clinical symptoms and laboratory examination findings. Imaging [including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI)] usually reveal a multicystic tumor or complex mass with both solid and cystic components; these findings are very similar to cystadenoma or cystadenocarcinoma[2], intrahepatic cholangiocarcinoma[3], liver metastasis[4], and other lesions. However, the MRI findings have certain characteristics. We herein describe a case in which we analyzed the contrast-enhanced ultrasound and MRI findings of a patient with BF who was misdiagnosed with hepatocellular carcinoma by contrast-enhanced ultrasound and with hepatic cystadenoma by MRI before surgical resection of the lesion. We also summarize the imaging findings of BF in previous literature.

CASE PRESENTATION
Chief complaints
A 68-year-old man reported abdominal discomfort without obvious inducement for 2 mo.

History of present illness
The patient had no other symptoms.

History of past illness
His past medical history indicated hypertension and mild cerebral infarction for more than ten years. After regular drug treatment, these conditions were well controlled.

Personal and family history
He had no personal or family history of other diseases.

Physical examination
On physical examination, there was no tenderness or rebound pain in the abdomen, and percussion pain in the liver area was negative. His blood pressure was 121/75 mmHg, pulse rate was 67 bpm and body temperature was 36.4 ℃.

Laboratory examinations
No abnormal laboratory examinations were observed, including liver function, tumor markers, infection markers, coagulation tests and complete blood count.

Imaging examinations
A plain CT scan at a local hospital showed a space occupying lesion in the left lobe of the liver and the patient was admitted to our hospital for further treatment. Ultrasonography showed hyperechoic nodules in the left lobe of the liver. Following injection of contrast agent, early and obvious enhancement was observed (Figure 1A). Plain MRI
Figure 1 Imaging findings in a 68-year-old man with biliary adenofibroma. A: Ultrasonography showed hyperechoic nodules in the left lobe of the liver, after injection of contrast agent, it showed early and obvious enhancement; B and C: Plain magnetic resonance imaging (MRI) scan showed hypointensity on T1-weighted imaging (T1WI) and hyperintensity on T2-weighted imaging (T2WI); D and E: Diffusion-weighted imaging (DWI) showed moderate hyperintensity and isointensity on ADC; F-H: Enhanced MRI scan showed obvious enhancement of solid components and separation of lesions in the arterial phase, the degree of lesion enhancement decreased in the portal phase, in the hepatobiliary phase, enhancement of the bile duct structure was found in the lesion.

showed hypointensity on T1-weighted imaging (T1WI) and hyperintensity on T2-weighted imaging (T2WI). In this case, iterative decomposition of water and fat with echo asymmetry and least square estimation-iron quantification (IDEAL-IQ) and intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI) sequences were performed. The water phase of the IDEAL-IQ sequence showed that the signal of the lesion was higher than that of the liver. DWI showed moderate hyperintensity and isointensity according to the apparent diffusion coefficient (ADC). The ADC and pure diffusion coefficient (D) values were 2.78 and $2.12 \times 10^{-3}$ mm$^2$/s, respectively, which indicated that there was no obvious limitation in the diffusion of the lesion. There was no significant change in the signal of the lesion in the in-phase and out-phase sequence. The early and late arterial phases showed obvious enhancement of solid components and separation of lesions. The degree of lesion enhancement decreased in the portal phase and delayed scan. In the hepatobiliary phase, enhancement of the bile duct structure was found in the lesion (Figure 1B-H).
**FINAL DIAGNOSIS**

Pathology confirmed BF (a rare biliary epithelial tumor) in this patient (Figure 2). Microscopy showed irregular hyperplasia of the bile duct with varying amounts of intervening fibrous stroma and inflammatory cell infiltration. Some bile ducts were dilated and the wall thickened, cholestasis was seen in the bile duct. The cells showed no atypia, and some of them showed apocrine secretion.

**TREATMENT**

The lesion was removed by laparoscopic surgery under general anesthesia.

**OUTCOME AND FOLLOW-UP**

The patient had no signs of recurrence at the 1-mo postoperative re-examination (Figure 3).

**DISCUSSION**

Currently, although BF are classified as benign bile duct tumors and precursors by the 2019 World Health Organization tumor classification system, some cases of BF are characterized by malignant transformation, invasion, and even distant metastasis. Tsui et al. first proposed in 1993, postoperative pathology showed malignant transformation in 3 cases, 3 cases of biliary adenofibroma with invasive carcinoma, 3 cases were complicated with liver tissue invasion, 2 cases were complicated with lymph node metastasis, local recurrence occurred in 2 cases. The clinical manifestations and imaging characteristics of BF are nonspecific. A definitive diagnosis is difficult to achieve by preoperative imaging. The diagnosis mainly depends on postoperative pathological examination. Pathologically, the lesions are gray or dark red irregular masses that can show cystic, honeycomb, or solid changes and have a relatively clear boundary and no capsule.

Including the present case, 25 cases of BF have been reported to date (Tsui et al. in 1993, Parada et al. in 1997, Haberal et al. in 2001, Akin et al. in 2003, and Garduño-López et al. in 2002, Guerra et al. in 2010, Kai et al. and Nguyen et al. in 2012, Jacobs et al. in 2015, Godambe et al. in 2016, Kaminsky et al. and Arnason et al. in 2016, Esteban et al. in 2017, Esteban et al. in 2018, Sturm et al. in 2018, and the remaining patients had normal concentrations of tumor markers including alpha fetoprotein, carcinoembryonic antigen, CA19-9, and CA125. Liver function indices were within normal limits. One patient had a history of hepatitis B, but the hepatitis status was not mentioned in the remaining patients. The location of the lesion was the left lobe in 11 patients and the right lobe in 13 patients (the specific location of the liver lesion was not mentioned in the remaining patient). One patient had two lesions, and the remaining patients had single lesions. We carefully reviewed the previous literature (including the imaging findings and intraoperative descriptions of the lesion locations) and found that the most common location of BF was under the liver capsule, as was true in the present case. Thus, the lesion location has a certain particularity.

On plain CT and MRI scans, BF is mainly a cystic lesion containing septal and varied solid components. Only three lesions were described as solid tumors. In the present case, the lesion was small and mainly composed of solid components, and ultrasound showed that it was slightly hyperechoic. Plain MRI showed hypointensity on T1WI and hyperintensity on T2WI. In this case, IDEAL-IQ and IVIM-DWI sequences were performed. The water phase of the IDEAL-IQ sequence showed that the signal of the lesion was higher than that of the liver. DWI showed moderate
Figure 2 Postoperative pathology. Hematoxylin and eosin staining (100 ×) microscopy showed irregular hyperplasia of the bile duct with varying amounts of intervening fibrous stroma and inflammatory cell infiltration. Some bile ducts were dilated and the wall thickened, cholestasis can be seen in the bile duct. The cells showed no atypia, and some of them showed apocrine secretion. These results were consistent with the presentation of biliary adenofibroma.

Figure 3 Postoperative re-examination images. Ultrasound examination indicates uniform echogenicity of liver parenchyma with no obvious abnormal echogenicity and isointensity according to the ADC. The ADC and D values were 2.78 and 2.12 × 10⁻³ mm²/s, respectively, which indicated that it was more likely a benign lesion (there was no obvious limitation in the diffusion of the lesion). There was no significant change in the signal of the lesion in the in-phase and out-phase sequence. In previous cases, the bile duct epithelial components of the lesions had no secretory function, but some lesions showed a tendency to enlarge and develop cystic components during the follow-up period[21]. The diameter of the solid lesions in three cases[8,10,20] and the solid lesions in the present case were smaller (4.08 ± 1.16 cm) than the mean diameter of the cystic and solid lesions (7.00 ± 3.03 cm). Therefore, whether the bile duct epithelial components in BF have a secretory function requires further study. The intrahepatic bile duct was dilated in only one case (the lesion was located within the bile duct). Enhanced CT and MRI scans showed enhancement of the solid components and septa of the lesions; one report described a wash-in and wash-out enhancement pattern in the literature[8]. Gd-EOB-DTPA (Primovist, Bayer Schering, Pharma AG, Berlin), a hepatocyte-specific contrast agent, was used in this case. The early and late arterial phases showed obvious enhancement of the solid components and septa of the lesions; one report described a wash-in and wash-out enhancement pattern in the literature[8]. The early and late arterial phases showed obvious enhancement of the solid components and septa of the lesions; one report described a wash-in and wash-out enhancement pattern in the literature[8]. The early and late arterial phases showed obvious enhancement of the solid components and septa of the lesions; one report described a wash-in and wash-out enhancement pattern in the literature[8].
lymph nodes were found in the hepatic hilum, and postoperative pathological examination showed metastasis[15]. The remaining reports did not mention imaging signs of a malignant tumor, although pathological examination after surgical resection of the lesions showed that the lesions were combined with cytological atypia or invasive cancer and even exhibited distant metastasis.

Pathological examination revealed that the fibrous tissue matrix of the tumor showed the histological pattern of a partially cystic bile duct. The bile pigment component in the tumor duct indicated direct continuity between the lesion and the biliary system, although postoperative pathology showed that the lesion was not clearly connected with the bile duct[6,21]. Primovist is a hepatobiliary-specific contrast agent that can show the biliary system in the hepatobiliary phase. In this case, enhancement of the bile duct structure was found in the lesion in the hepatobiliary phase, suggesting that the lesion was closely related to the intrahepatic bile duct system; postoperative pathology also showed a bile duct structure and intrabiliary cholestasis. In a previous report, MRI failed to show a relationship between biliary duct adenofibroma and the intrahepatic bile duct. The author speculated that because most of the lesions were located under the liver capsule and the terminal bile duct was slender, it was difficult to show the relationship between the lesion and the bile duct by conventional MRI scanning sequences. Primovist-enhanced MRI, especially hepatobiliary phase images, was a good supplement.

CONCLUSION

BF is a rare biliary tumor that exhibits malignant transformation and usually occurs under the liver capsule. The lesions are mostly cystic and solid. On enhanced scans, the solid part can show a wash-in and wash-out enhancement pattern, and enhancement can be seen in the separation of lesions. The hepatobiliary phase of Primovist-enhanced MRI can better show the lesions and intrahepatic bile duct structure, providing more clues and value for the diagnosis. BF can be treated by surgical resection, but regular postoperative review is needed to identify recurrence or distant metastasis, such as that to the lung.

REFERENCES

Multiple gouty tophi in the head and neck with normal serum uric acid: A case report and review of literatures

Yang Song, Zi-Wei Kang, Yan Liu

Abstract

BACKGROUND
Gouty tophus is rarely reported in the head and neck areas. To the best of our knowledge, this is the first report on multiple gouty tophi in the head and neck with normal serum uric acid (SUA) levels.

CASE SUMMARY
We report a case of multiple gouty tophi in the nasal dorsal and auricle regions with normal SUA levels. The patient was admitted to the hospital with a chief complaint of recurrent nasal swelling and pain for 3 years, which was aggravated for 3 d. The patient’s SUA level had been regularly reviewed in the outpatient department and had been successfully controlled for several years. Resection of the nasal masses was performed. Cartilage from the right ear cavity was used to repair the nasal defects. The pathological report confirmed a nasal gouty tophus. No recurrence or deformity was found after a 1 year follow-up.

CONCLUSION
Normal SUA cannot completely negate the diagnosis of gouty tophus, especially in some rare regions.

Key Words: Gout; Multiple gouty tophi; Serum uric acid; Hyperuricemia; Nasal; Case report

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Core Tip: Hyperuricemia is a key factor in the formation of gouty tophus, and it is often detected on the first metatarsophalangeal or first metacarpophalangeal joints of both hands. It is rarely reported in the head and neck areas, such as the throat and auricle. We believe that clinicians should be aware of the possibility of gouty tophus in patients...
INTRODUCTION

Gout is a clinical syndrome caused by an increase in uric acid production or a weakening of renal excretion function, resulting in a continuous increase in serum uric acid (SUA) level and the deposition of urate in joints, synovium, or other tissues and organs\[1,2\]. Consequently, complications including gouty arthritis, gouty tophus, uric acid renal stones, and gouty nephropathy may develop. Gouty tophus is a sign of chronic gout, and its formation can lead to bone destruction, joint deformity, joint dysfunction, and even fracture and infection of the tophus\[3]\, which can seriously affect the quality of life of patients. The formation of gouty tophus is a complex process, and many factors can lead to and accelerate its formation. The gold standard for the diagnosis of gout is the detection of birefringent acicular urate crystals in joint fluid or gouty tophus under a polarised light microscope\[4]\.

An increased SUA level is considered as the basis for gout. When a patient presents with an SUA level > 7 mg/dL\[5,6]\, characteristic arthritis, urinary calculi, or renal colic, the clinical diagnosis of gout can be considered. However, most patients with hyperuricemia (HUA) do not develop gout\[7]\.

Several patients have normal SUA levels at gout onset and some gout patients have gouty tophus with no acute gout attack or gouty tophus before the attack\[7,8]\, potentially leading to clinical misdiagnosis and mistreatment. Herein, we report a case of multiple gouty tophi in the head and neck, specifically in the auricle and bridge of the nose, with normal SUA level.

CASE PRESENTATION

Chief complaints

A 48-year-old male patient was admitted to the hospital with a chief complaint of 'recurrent nasal swelling and pain for 3 years'.

History of present illness

Since 2016, the nasal swelling and pain were mild, without nasal congestion, runny nose, epistaxis, fever, headache, trauma, or mosquito bites. In recent years, regular outpatient reviews of SUA had been normal. Drinking alcohol and high purine diet could occasionally aggravate nasal symptoms.

History of past illness

Thirteen years ago, the patient was admitted to another hospital due to swelling and tingling of ankle joints and was diagnosed with gout and hyperuricemia. He regularly received febuxostat. The patient’s SUA level had been regularly reviewed in the outpatient department, and was well controlled for several years (Figure 1). The patient had no history of diabetes mellitus, hypertension, cystic fibrosis and metabolic disorders.

Personal and family history

The patient was a male, 48 years old, reported no history of dental surgery, facial trauma, or previous sinus surgery.
Physical examination
Skin swelling with a diameter of 2 cm on the bridge of the nose, obvious tenderness, and nasal deformity. Under the nasal endoscope, the nasal cavity was unobstructed, the nasal septum was in the centre, no obvious bulge or neoplasm was observed in the top wall of the nasal cavity (Figure 2). A new greyish-white creature with a diameter of 5 mm was observed on the outer upper edge of the right auricle.

Laboratory examinations
Laboratory examination revealed a uric acid level of 384 μmol/L (reference value range 208-428 μmol/L). The water sample secretion of rice swill was punctured from the local uplift, and general bacterial and fungal cultures showed no abnormal flora. The patient declined invasive cytological examination.

Imaging examinations
Enhanced computed tomography (CT) imaging revealed a mixed density mass shadow on the left side of the nose (Figure 3).

FINAL DIAGNOSIS
The accurate diagnosis of nasal gouty tophus was confirmed by postoperative histopathological examination (urate crystallized and granulation tissue formed around the tumour) (Figure 4).

TREATMENT
The patient underwent nasal lumpectomy and autologus cartilage graft repair under general anaesthesia. During the operation, the skin and subcutaneous tissues were incised. The deep capsule of the mass was incomplete, the left nasal bone compressed and absorbed, the bone defect obvious, and the surface of the right bone not smooth. The tumour was completely removed along the residual bone. Its contents showed yellowish silt-like changes, and 0.5 mL of yellowish viscous caseous secretions were extracted from the tumour. Nasal endoscopy detected no fistula in the nasal cavity. The operative region was flushed with normal saline, and no liquid flowed out of the nose. Cartilage from the left tragus was taken to repair the nasal bone defect, and the skin was continuously sutured subcutaneously with 4-0 absorbable protein thread and bandaged under pressure. Postoperatively, the patient received anti-infection treatment and was advised to relinquish drinking, pay attention to a gout-suitable
Figure 2 Preoperative physical examination. A: Preoperative frontal view; B: Nasal endoscope, nasal septum: obvious hypertrophy and swelling of the left upper mucosa of the nasal septum, middle turbinate, inferior turbinate. NS: Nasal septum; MT: Middle turbinate; IT: Inferior turbinate.

Figure 3 The head and neck computed tomography scan displayed a mottled radiopaque mass crossed over the nasal ridge. The boundary was clear, the size approximately 1.7 cm × 1.3 cm, the plain scan computed tomography (CT) value approximately 22-96 HU, the enhanced scan CT values approximately 25-104 HU and 14-109 HU, and the left nasal bone locally discontinuous.

Figure 4 Postoperative histopathological examination.

diet, and engage in active follow-up at the internal medicine department for the regulation of SUA levels.
OUTCOME AND FOLLOW-UP

There was no recurrence in nearly 2 years after operation (Figure 5).

DISCUSSION

The essence of gout inflammation is the deposition of monosodium urate (MSU) in bone, joint, kidney, and subcutaneous tissue, which leads to tissue damage and inflammation[9]. The development of inflammation depends on changes in the surface protein for MSU crystals. Repeated inflammation depends on the innate immune response mediated by the MSU crystal. Gouty tophus is a granulomatous substance formed by urate crystals encapsulated by monocytes and multinucleated giant cells. Gouty tophus is mainly composed of three layers[3]: (1) MSU crystals forming the centre of the gouty tophus; (2) Monocytes and multinucleated macrophages that are wrapped around the MSU crystal; and (3) Dense connective tissue constituting the outermost layer. Age, sex, genetic susceptibility, SUA level, disease duration, metabolic syndrome, lifestyle, drugs, high purine diet, and drinking are risk factors for gout[10-12]. Gouty tophus is a sign of chronic gout. The formation of gouty tophus can lead to bone destruction, joint deformity, joint dysfunction, fracture, and infection of gouty tophus, seriously affects the quality of life of patients.

The gold standard for the diagnosis of gout is the detection of birefringent acicular urate crystals in joint fluid or gouty tophus under a polarised light microscope. In China, HUA is defined as the condition of a normal purine diet, in which the fasting SUA level is higher than 420 μmol/L (7 mg/dL) in men and 360 μmol/L (6 mg/dL) in women. Nonetheless, the definition of HUA varies widely across published studies in different countries, ranging from 6 to 7 mg/dL[13], and the clinical diagnosis of gout should be considered with the onset of characteristic arthritis, urinary calculi, or renal colic occurrence. In the chronic stage of gout, X-ray and conventional CT examinations can better reveal bone and joint destruction in patients, and can show the characteristic chisel-like and worm-like changes with high specificity; however, they are only suitable for the evaluation of bone destruction in patients with late gout. Magnetic resonance imaging (MRI) has shown that in the early stages of gout, though crystal deposition cannot be observed with the naked eye, the display level is clear, diagnostic sensitivity is high, and the diagnostic value is favourable on MRI. However, because of the high cost and long appointment period, MRI is rarely used in clinical practice. In recent years, the application of dual-energy CT (DECT) in the diagnosis and treatment of gout has become a popular research topic[14-16]. It can identify the chemical composition of urate crystals and the deposition of urate in deep tissues, which can be applied to a patient’s whole body. With the improvement in ultrasound resolution, ultrasound can be used to observe urate crystals, gouty tophus, and bone erosion damage as well as evaluate joint inflammation[17,18]. It has become an effective means of diagnosing gout and monitoring the effect of reducing uric acid levels.

The current patient’s SUA level was 384 μmol/L (in China, the reference value is 208–428 μmol/L). He took febuxostat regularly for ten years, and his SUA level was regularly reviewed in the outpatient department. The uric acid level was well under control for several years. When he was diagnosed with gout 13 years ago, gouty tophi appeared in his lower limbs, feet, and ankles. Although his SUA level was reduced to normal by drug treatment, he drank alcohol for a prolonged period and enjoyed consuming seafood with high purine. The patient was convinced that the gout condition was well under control, in recent years, the symptoms of foot and ankle gouty tophus had not been aggravatated, and because the occurrence of gouty tophus in the head and neck is extremely rare, the nasal gouty tophus was not considered the main diagnosis before the operation. Nasal ultrasound examination was not performed before the operation, and the patient refused the puncture cytology examination; therefore, it was impossible to make a definite diagnosis before the operation. A CT scan of the nose revealed bone erosion of the tumour, and considering the possibility of a malignant tumour of the nose[19], we did not perform an external inverted-V incision along the columella, in case of residual tumour. Subsequent to complete exposure of the tumour during the operation, the capsule could be observed surrounding the tumour. There was sand-like filling and rice swill water liquid in the tumour; we considered it a gouty tophus infection that caused exudate formation, although the bacterial and fungal cultures were negative[10]. The diagnosis of gouty tophus lesions was confirmed during the operation and by postoperative pathology. The auricle lesions were mild, and surgery was not performed. Therefore, attention
One year after operation, there was no deformity of nasal bridge and no recurrence of gouty tophus.

should be directed to the formation of tumours in atypical parts of the body and atypical chondritis in gout patients without HUA as well as to the establishment of a clinical understanding of gouty tophus to prevent misdiagnosis[20].

Gouty tophus can be deposited in different parts of the human body, which can be categorised into typical and atypical parts[21]. Gouty tophus in the head and neck is atypical and rarely observed in the bridge of the nose[22]. In addition, gout often mimics the process of malignant tumours, infections, or other unrelated diseases. A few reports have described the deposition of gout in unusual body parts[23-26]. Therefore, a more systematic, scientific, and comprehensive diagnosis of gout is necessary. In 2015, the American College of Rheumatology/European Alliance Against Rheumatology developed new classification criteria for gout[27]; ultrasound and DECT were included in the gout classification for the first time. If patients met the diagnostic criteria of clinical, laboratory, and imaging examinations, the sensitivity and specificity of diagnosis could be as high as 92%, which also stratified the level of SUA, taking into account that SUA level may not be high during a gout attack. After a definite diagnosis, we further emphasise that drug treatment of patients with gout is particularly important[28-30]. The recommended serum uric acid level is below 6 mg/dL in all gouty patients or 5 mg/dL in severe gout patients to allow more rapid dissolution of the crystals[23].

Why a multiple gouty tophi in the head and neck with normal serum uric acid have been developed in this patient? The possible reason is that although the blood uric acid decreased to normal through drug treatment, the gouty tophus symptoms did not stop developing with the normal blood uric acid due to long-term drinking and eating seafood high purine diet, and gradually occurred in the auricle and nasal, which did not attract enough attention from the patient. Another important reason is that although the patient's blood uric acid is in the normal range, it is still not low enough. The blood uric acid of patients with gout stone should be controlled at 5 mg/dL.

CONCLUSION

This report describes a case of gouty tophus with normal SUA in an atypical location and atypical symptoms. In clinical settings, especially for patients with normal SUA, the possibility of atypical symptoms and atypical parts of gouty tophus should be considered. Strict control of diet, drinking habits, and SUA levels are needed to avoid the progression of gouty tophus and the development of more serious complications. Surgery is an effective treatment method for gouty tophus.

ACKNOWLEDGEMENTS

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Toxic epidermal necrolysis induced by ritodrine in pregnancy: A case report

Wen-Yu Liu, Jia-Rong Zhang, Xian-Ming Xu, Tian-Yi Ye

Abstract

BACKGROUND
Preterm birth accounts for about 12% of all pregnancies worldwide and is the leading cause of neonatal morbidity and mortality. In order to avoid premature birth and prolong gestational age, tocolytics are the first and the best choice. Ritodrine is the most commonly used tocolytic medication. However, side effects such as pulmonary edema, hypokalemia, and hyperglycemia are known. Here we report a rare but serious side effect—toxic epidermal necrolysis (TEN)—caused by ritodrine.

CASE SUMMARY
A woman (31 years, gravida 4, para 2) was hospitalized because of premature contractions at 27 + 6 wk of gestation. A skin rash with pruritus appeared at 32 + 3 wk of gestation after administration of ritodrine, indomethacin, and dexamethasone, and it spread throughout the whole body in 3 d, particularly the four limbs. After 11 d’ treatment, she was diagnosed with TEN. An emergency cesarean section was performed immediately to deliver the baby and intensive symptomatic treatment was promptly commenced after delivery. She recovered from the severe condition without any sequelae except for slight pigmentation after symptomatic treatment.

CONCLUSION
When a skin rash appears during the administration of ritodrine, we are supposed to consider the risk of TEN.

Key Words: Preterm birth; Ritodrine; Side effect; Tocolytics; Toxic epidermal necrolysis; Case report
INTRODUCTION

Every year, approximately 15 million babies are born prematurely worldwide (<37 completed weeks of gestation)[1], and 99% of the related morbidity and mortality occurs at <35 wk of gestation[2]. Tocolytics are essential for the suppression of uterine contractions, but they also bring a series of side effects such as palpitations, pulmonary edema, hypokalemia, and hyperglycemia. In this case, we discuss a rare but fatal side effect–toxic epidermal necrolysis (TEN)–induced by ritodrine in pregnancy. TEN is an often fatal severe mucocutaneous reaction, most commonly triggered by drugs, characterized by extensive necrosis and exfoliation of the epidermis. TEN is a rare disease with an annual incidence of approximately 1.9 cases per million inhabitants[3], while the mortality rate is approximately 30%–35%[4]. Hence, early identification leading to an early diagnosis and the withdrawal of all potential pathogenic drugs is essential for achieving good treatment results. In this case, we present a patient who had diabetes mellitus and threatened premature labor during the second trimester; she got TEN after administration of insulin, dexamethasone, ritodrine hydrochloride and indomethacin.

CASE PRESENTATION

Chief complaints

A 31-year-old Chinese woman was hospitalized because of premature contractions at 27 + 6 wk of gestation.

History of present illness

The patient had conceived spontaneously, her blood pressure during pregnancy was normal but her serum glucose was found high at 24 wk of gestation. She had been controlling her blood sugar by injecting insulin subcutaneously, along with diet and exercise. She came to our hospital because of the frequent contraction at 27 + 6 wk of gestation.

History of past illness

The patient (gravida 4, para 2) had no history of coronary heart disease, hypertension, hepatitis or tuberculosis, or food and drug allergies.

Personal and family history

The patient had no history of drug abuse, smoking, or drinking. There was no family history of genetic disease or cancer.

Physical examination

Body temperature 36.7 °C, pulse rate 86 bpm, blood pressure 121/78 mmHg, respiratory rate 18 per minute, indoor oxygen saturation 99%. Fetal heart rate was 147
Laboratory examinations

Laboratory examinations revealed a white blood cell count of $6.34 \times 10^9/\text{l}$ (70.1% neutrophils), and an elevated C-reactive protein level of 29.3 mg/L. Liver and kidney function, electrolytes, creatinine, and cholestatic liver enzymes were all within normal limits. Extensive serological tests such as Epstein-Barr virus, cytomegalovirus, rubella, and Coxsackie proved to be negative. Tests for hepatitis B, chlamydial antigens and human immunodeficiency virus were negative, as well as the bacterial culture of skin, blood, urine, and genital lesions.

Imaging examinations

Ultrasound: The heart, liver, and kidneys showed no obvious abnormalities.

Fetal ultrasound: Ultrasound examination at 30 wk of gestation showed a single live fetus of 29 wk and the amniotic fluid was normal.

Further diagnostic work-up

Continuous ritodrine (for 5 wk until her skin issues appeared) and indomethacin rectally (6 times) were used to suppress premature labor whereas dexamethasone (twice, 2 d every time) was given to reduce the severity of respiratory distress syndrome and offspring mortality. The patient began to complain of itching and abdominal rash at 32 + 3 wk of gestation, which spread fast to her back and all extremities (Figure 1A). After 3 d, a fine maculopapular rash resembling erythema multiforme cover the whole body but over the face, neck, and chest. Her skin condition was diagnosed as allergic dermatitis; therefore, calamine lotion and mometasone furoate cream were topically applied when she was 32 + 6 wk pregnant. She started taking prednisone (20 mg/d) and was advised to terminate the pregnancy if contractions could not be suppressed when she was 33 + 1 wk pregnant. At 33 + 3 wk of pregnancy, erythema and bullous rashes had spread throughout the body (Figure 1B) and was particularly prominent on the upper limbs, the dorsum of the hands, back, and breech. As the lesions became confluent, hydrocortisone (200 mg/d i.v.) was used. Since starting with the rash, indomethacin and dexamethasone had been no longer used. Due to increased uterine contraction and the patient’s refusal to terminate the pregnancy, intravenous ritodrine to prevent preterm delivery was not stopped and the dose of ritodrine had been increased despite the skin rash. At 34 wk of pregnancy, she had been on treatment for 10 d but her condition was progressing; her skin rash on the upper extremities turned dark and gray with small blisters, and the skin of the patient’s elbows became broken, blisters enlarged, and the whole body rashes were accompanied by blisters (Figure 1C); several white spots were seen on the tip of the tongue, and there was obvious pain when eating. After a multidisciplinary team discussion, involving a dermatologist, intensivist, pharmacist, obstetrician, nutritionist, and pediatrician, we considered these phenomena likely to be a severe drug eruption. Intravenous methylprednisolone (60 mg) and immunoglobulin were administered immediately. After a comprehensive analysis of the history of medication, clinical symptoms, and auxiliary inspection, we suspected TEN induced by the ritodrine (Symptoms and treatment of the patient during different periods is listed in Table 1).

FINAL DIAGNOSIS

The final diagnosis of the presented case was TEN induced by tocolytics.

TREATMENT

In order to prevent deterioration and save the woman’s life, the medical panel decided to immediately stop using ritodrine and terminate the pregnancy. A male infant weighing 2400 g was delivered with Apgar scores of 2 and 7 at 1 and 5 min, respectively. The baby showed neither signs of skin abnormalities nor sequelae caused by the mother’s TEN and the prolonged therapy.
Table 1 Symptoms and treatments of the patient in different periods

<table>
<thead>
<tr>
<th>Date</th>
<th>Gestational week</th>
<th>Symptoms</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>November 1, 2017</td>
<td>32 + 3 wk</td>
<td>Red skin rash on both lower limbs, accompanied by itching, no pain</td>
<td>None</td>
</tr>
<tr>
<td>November 4, 2017</td>
<td>32 + 6 wk</td>
<td>Red skin rash, lumps, and itching all over the body</td>
<td>Calamine lotion until recovery and mometasone furoate cream for 3 d externally</td>
</tr>
<tr>
<td>November 6, 2017</td>
<td>33 + 1 wk</td>
<td>Scattered red rash all over the body with itching</td>
<td>Prednisone 60 mg a day for 2 d p.o.</td>
</tr>
<tr>
<td>November 8, 2017</td>
<td>33 + 3 wk</td>
<td>Erythematous and bullous rashes spread to the entire body</td>
<td>Hydrocortisone 200 mg a day until delivery i.v.</td>
</tr>
<tr>
<td>November 9, 2017</td>
<td>33 + 4 wk</td>
<td>Rash on the right upper arm turned dark gray</td>
<td>Calcium gluconate 10 mL once i.v.</td>
</tr>
<tr>
<td>November 11, 2017</td>
<td>33 + 5 wk</td>
<td>Red skin rash, lumps, and itching all over the body, skin tingling</td>
<td>As above</td>
</tr>
<tr>
<td>November 12, 2017</td>
<td>34 wk</td>
<td>Skin rash on the upper extremities turned dark and gray with small blisters; the skin of the elbows was broken, the blisters became larger, and the body-wide rashes were accompanied by blisters; several white spots were seen on the tip of the tongue</td>
<td>Methylprednisolone 60 mg i.v.g once + immunoglobulin for 5 d + mupirocin ointment until recovery externally</td>
</tr>
<tr>
<td>November 13, 2017</td>
<td>34 + 1 wk</td>
<td>Symmetrical edema of the skin all over the body with dark red patches; unclear, tender, tongue mucosal ulcer</td>
<td>Cesarean section, methylprednisolone 40 mg i.v. twice a day for 1 wk</td>
</tr>
</tbody>
</table>

OUTCOME AND FOLLOW-UP

After the operation, the patient was transferred to the intensive care unit and treated with intravenous fluids, intravenous methylprednisolone (40 mg twice daily) and a massive intravenous dose of immunoglobulin once daily. Furthermore, supportive care was essential, including wound care, fluid and nutritional supplements, pain control, and the prevention or treatment of infections. Bullae on the shoulder, breech, and upper limbs began to rupture, which led to epidermal detachment on postoperative day 3; at this time, the course of immunoglobulin treatment had ended. After active anti-allergic skin care and other symptomatic treatments, part of the patient's skin became loosened, the ulcerated area was covered with Vaseline gauze, the extremities and torso displayed dark red rashes, sloughing of skin was visible, and the new skin appeared healthy (Figure 1D). One week after surgery, methylprednisolone was decreased to 60 mg/d, and was further decreased to 40 mg/d at two week after surgery. Three weeks after surgery, all necrotic skin that had covered large areas of the patient's body had sloughed off; some of the involved parts were pigmented and the new skin appeared healthy (Figure 1E). The patient was administered 20 mg of prednisone twice a day and was discharged from the hospital. A month after surgery, her skin was completely dry and there was no crust or desquamation. Six months later, her skin appeared normal, only a little pigmented, but she had no visible skin disorder, and her child was healthy.

DISCUSSION

As a rare and potentially lethal skin drug reaction, TEN is accompanied by skin and mucous membrane involvement, which is considered to be a pedigree of the same disease. TEN may be a threat to normal delivery during pregnancy. According to the limited data available, mortality rate of pregnancy-related TEN is lower than that of the general population. Fetal manifestation of TEN is rare during pregnancy[5], the worst effect on the unborn fetus is an increased risk of preterm delivery owing to fetal distress[6]. It is unclear whether this increased risk is due to underlying maternal illness, fever, or placental dysfunction. Medications are the main inducement of TEN, and the most commonly associated medications are antiepileptic drugs, allopurinol, nevirapine, antibacterial sulfonamides, and oxicam nonsteroidal anti-inflammatory drugs both in neonates and adults[7]. The risk of TEN seems to be limited to the first 8 wk of treatment and the typical onset time is between 4 d and 4 wk of continuous use [8]. In the current case, the insulin that the patient had been using for a long time was
Figure 1 Skin change record. A: Maculopapular rash in the leg; B: Erythematous and bullous rashes spread over the entire body at 33 + 3 wk of gestation; C: The skin of the patient’s abdomen became broken; D: The extremities and torso displayed dark red rashes, sloughing of skin was visible; E: The new skin has partial pigmentation and looks healthy.

not considered to be the trigger. Corticosteroids may be a risk factor for developing TEN[9] and there are no randomized clinical trials of corticosteroids in the treatment of TEN. In our current case, systemic corticosteroids were used effectively until recovery and we suggested that this promoted the patient’s recovery. So only indomethacin that was administered for 5 consecutive days and ritodrine for 5 wk met the standard. Although drug reactivation is a useful diagnostic test, we cannot test it on individuals because of safety and ethical concerns; therefore, the relationship between eruption and drugs could only be inferred. Indomethacin has been reported to be a cause of TEN[10], but the risk is reported to be low[11]. In the current case, the latest indomethacin was used at 31 wk of gestation and the dermatological signs first appeared at 32 + 3 wk. One criterion to implicate a drug as the cause of the rash is the recovery after stopping using the drug. In our patients, the rash began to appear after discontinuation of the indomethacin for 10 d and the symptoms continued to worsen after 3 wk. We speculate that the rash was nearly impossible to be caused by indomethacin but the reasons were not sufficient. One case of TEN was found in English literature, which indicated that it may be caused by ritodrine hydrochloride[12]. In our case, ritodrine hydrochloride had been used until the day of surgery as she had experienced frequent contractions while her condition worsened with time. In contrast, after surgery, her condition began to improve when the ritodrine was removed. So ritodrine hydrochloride appeared to be the cause of TEN in this case. In addition, consideration should be given to the combined effect of the use of ritodrine and indomethacin as the combined use of two or more tocolytics may increase the occurrence of adverse reactions[13].
In the current case, we adopted a multi-disciplinary treatment strategy. The obstetricians terminated the pregnancy immediately and intensive dermatological treatment was commenced promptly after delivery, which helped the patient recover from the severe condition without any sequela except for mild pigmentation. Because of the high mortality rate and the terrible impact on the mother and fetus, the pregnant patients with TEN requires prompt diagnosis, identification, and blocking of the sensitizing medicines, followed by specialized supportive treatment in the intensive care unit, and consideration of immunomodulatory agents such as high-dose intravenous immunoglobulin[14].

Our study has several limitations. First of all, we were unable to get a definite diagnosis of TEN as we did not perform skin biopsies. Furthermore, it was difficult to consider ritodrine to be a new culprit drug for TEN because it was administered over the same time as indomethacin. It may even be possible that the combination of the two drugs caused TEN. However, since TEN is a life-threatening disease, awareness of the possible association between ritodrine and TEN is warranted. Only a limited yeast solubilizers are available. It is well known that prostaglandin inhibitors are effective in inhibiting uterine contraction and prolonging pregnancy.

What makes us feel shame is that only limited number of tocolytic agents are currently available. It is well known that prostaglandin inhibitors are effective at inhibiting uterine contractions and prolonging gestation[15]. However, they may cause the periventricular leukomalacia, severe intraventricular hemorrhage and necrotizing enterocolitis[16]. Ritodrine may be useful for short-term prolongation of pregnancy, but it has caused increased incidence of palpitation and chest pain. It is also known that it may induce either severe pulmonary edema or rhabdomyolysis[17]. In addition, exposure to ritodrine for a long time is known to desensitize the function of beta 2-adrenergic receptor. Atosiban is the only tocolytic that has demonstrated superiority as maintenance therapy in prolonging pregnancy[18] with few side-effects[19] but it is very expensive. As a result, there is a tendency to continue to use ritodrine to prevent preterm delivery even when the side effects are obvious. The use of tocolytics should be individualized and depends on potential adverse events and maternal condition. Moreover, the combined use of tocolytics should be avoided as far as possible.

CONCLUSION

Ritodrine hydrochloride must be considered when TEN is diagnosed. With this in mind, it is essential to re-evaluate the effectiveness and safety of ritodrine when a risk-benefit analysis of the continuous use of tocolytics is conducted. When a patient develop a rash during the use of ritodrine, the doctor must take into account TEN caused by the drug and stop using it immediately.

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Direct antiglobulin test-negative autoimmune hemolytic anemia in a patient with β-thalassemia minor during pregnancy: A case report

Yang Zhou, Yi-Ling Ding, Li-Juan Zhang, Mei Peng, Jian Huang

Abstract

BACKGROUND
Severe refractory anemia during pregnancy can cause serious maternal and fetal complications. If the cause cannot be identified in time and accurately, blind symptomatic support treatment may cause serious economic burden. Thalassemia minor pregnancy is commonly considered uneventful, and the condition of anemia rarely progresses during pregnancy. Autoimmune hemolytic anemia (AIHA) is rare during pregnancy with no exact incidence available.

CASE SUMMARY
We report the case of a 30-year-old β-thalassemia minor multiparous patient experiencing severe refractory anemia throughout pregnancy. We monitored the patient closely, carried out a full differential diagnosis, made a diagnosis of direct antiglobulin test-negative AIHA, and treated her with prednisone and intravenous immunoglobulin. The patient gave birth to a healthy full-term baby.

CONCLUSION
Coombs-negative AIHA should be suspected in cases of severe hemolytic anemia in pregnant patients with and without other hematological diseases.

Key Words: Maternal anemia; β-thalassemia minor; Autoimmune hemolytic anemia; Direct antiglobulin test; Pregnancy; Case report

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Zhou Y et al. AIHA in a thalassemia carrier during pregnancy

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INTRODUCTION
As an autosomal inherited hemoglobin (Hb) disorder, due to the absence or reduced synthesis of the globin chains of Hb, thalassemia has two main types, α- and β-thalassemia. Over 300 types of β-globin gene mutations have been reported causing varying degrees of reduced β-globin synthesis, usually categorized as minor, intermedia, or major on the basis of their clinical manifestations and dependence on blood transfusion[1]. China has a high prevalence of thalassemia, especially in the south of the Yangtze River. From epidemiological data, the thalassemia carrier population in China is over 30 million, among which over 1% has the major or intermedia type[2]. Patients with asymptomatic β-thalassemia minor, also known as silent carriers, who have mild microcytic, hypochromic anemia or even a normal Hb level, usually require little medical care.

Pregnancy complications are considered uncommon among β-thalassemia minor patients[3]. Aside from accurate and timely antenatal counseling, β-thalassemia minor patients do not require more frequent antenatal check-ups than normal, as this type of anemia during pregnancy rarely progresses to a serious condition that can cause significant adverse effects with a high risk of maternal mortality.

We report the case of a 30-year-old multipara with β-thalassemia minor who experienced severe hemolytic anemia throughout pregnancy. Fortunately, the maternal and fetal outcome was favorable following diagnosis and treatment. To our knowledge, this is the first report of such a case.

CASE PRESENTATION

Chief complaints
A 30-year-old woman, gravida 2 para 1, presented with fatigue, chest tightness, and shortness of breath for over 1 mo after activities at the 17-wk gestation.

History of present illness
The patient was diagnosed with severe anemia at a local hospital. Her Hb level was 40 g/L and she had several blood transfusions, but her Hb did not increase as expected and began to drop when the transfusion stopped.

History of past illness
Signs of anemia had not been taken seriously until the patient was hospitalized for pleuritis in 2019, when she was found to be an IVS-II-654(C>T) carrier. Her husband is not a carrier of thalassemia trait. Special medication history (other than Vitamin Complex Tablets) and transfusion history before this pregnancy were denied.

Personal and family history
No contributory personal history or similar family history.

Physical examination
The patient’s vital signs were normal. She had a pale appearance, her uterus size matched the gestational age, and fetal heart rate was normal.
Laboratory examinations
The patient was referred to our hospital at the 25-wk gestation. Laboratory investigations showed severe anemia, with an Hb level of 39 g/L, mean corpuscular Hb of 22.5 pg, mean corpuscular volume of 74.6 fl, and fraction of Hb A2 of 4.7%, as well as a raised bilirubin level of 34.8 μmol/L, direct bilirubin level of 15.9 μmol/L, raised lactate dehydrogenase (LDH) level of 392.5 U/L, reticulocyte count of 3.15%, and haptoglobin below the detection limit. The ferritin level was 291.57 ng/mL, and B12 and folate levels were normal. Oral glucose tolerance test and other routine prenatal blood test results were within the normal range. We performed TORCH (comprising toxoplasmosis, Treponema pallidum, rubella, cytomegalovirus, herpes virus, and hepatitis viruses) serology to rule out preceding infection. Signs of intravascular hemolysis that could not be ascribed to β-thalassemia minor were observed.

Imaging examinations
Abdominal ultrasound showed a spleen diameter of 68 mm. Echocardiography demonstrated a left atrial diameter of 40 mm and mild mitral, tricuspid, and aortic regurgitation.

Further diagnostic work-up
We carried out a multidisciplinary consultation on the third day after the patient’s admission. Taking expert opinions from a hematologist and rheumatologist, we performed further examinations. Bone marrow cytology suggested active proliferation of erythrocytes. Flow cytometry showed normal erythrocyte levels of CD55 and CD59. Connective tissue screening including antinuclear antibody and extractable nuclear antigen was also negative. A normal complement C3 level and slightly decreased C4 level were detected. We performed the direct antiglobulin test (DAT; also referred to as the “Coombs” test) including IgG and C3 several times; however, the results were negative. According to the principle of exclusion, the patient’s severe hemolytic anemia could be due to autoimmune reasons. On the other hand, the patient’s intermediate Down’s screening indicated a high risk of trisomy 21; thus, a prenatal diagnosis was performed. The karyotype of the fetus was normal and copy number variation-sequencing did not find any disease-causing gene mutations.

MULTIDISCIPLINARY EXPERT CONSULTATION
Ming-Yang Deng, MD, PhD, Assistant Professor, Department of Hematopathology, The Second Xiangya Hospital, Central South University
According to the patient’s test results, the presence of intravascular hemolysis was basically established; however, the gene sequencing did not match thalassemia major. Erythrocyte CD55 and CD59 should be analyzed to rule out paroxysmal nocturnal hemoglobinuria.

Jing Tian, MD, PhD, Assistant Professor, Department of Rheumatology and Immunology, The Second Xiangya Hospital, Central South University
The evidence for connective tissue disease was insufficient.

FINAL DIAGNOSIS
DAT-negative autoimmune hemolytic anemia (AIHA) during pregnancy.

TREATMENT
The patient was given red blood cell (RBC) transfusions with other symptomatic and supportive treatment, and the growth parameters and middle cerebral artery peak systolic velocity (MCA-PSV) of the fetus were monitored. Fortunately, fetal growth and development matched the gestational age and the MCA-PSV did not increase. The patient was discharged 2 wk later and underwent strict follow-up. She returned to her hometown for 1 mo, and at the 31-wk gestation, she underwent echocardiographic re-examination at the local hospital, which showed an atrial septal aneurysm 35 mm × 14
mm in size, indicating anemic cardiomyopathy. She was admitted to our hospital for the second time. Her blood tests still suggested severe hemolytic anemia, but this time we were very cautious regarding blood transfusion in order to avoid heart overload. We suspected that the hemolysis was due to autoimmune factors, and after discussions with the patient and her family, she was given corticosteroid and immunoglobulin therapy. She received prednisone 30 mg orally qd and intravenous immunoglobulin (IVIG) 20 g/d for 3 d. Her Hb level rose to > 80 g/L. The patient’s Hb and LDH values throughout pregnancy in relation to medication administration and RBC transfusion are shown in Figure 1. At 38+ wk gestation, she was given vaginal misoprostol to induce labor, following echocardiography which found no abnormalities.

OUTCOME AND FOLLOW-UP

A live 3255-g boy was born by normal vaginal delivery. The neonate was transferred to the Neonatology Department 35 h after birth due to hyperbilirubinemia. Blood test results showed no sign of hemolysis; however, Hb was 136 g/L, white blood cell count was 9.07 × 10^9/L, platelet count was 314 × 10^9/L, and inflammatory indicators were elevated, indicating neonatal infection, and he had inherited the same IVS-II-654(C>T) mutation from his mother. The neonate was discharged after antibiotic treatment and phototherapy 10 d later. The mother discontinued oral corticosteroid postnatally, and maintained an Hb level above 90 g/L.

DISCUSSION

β-thalassemia carriers are asymptomatic; however, little research is available on the pregnancy outcome of β-thalassemia carriers, although it has been reported that the incidence of intrauterine growth retardation and oligohydramnios is higher[3-5]. It is recommended that pregnant women with mild thalassemia should follow the health care guidelines for normal pregnancy[6]. Thalassemia carriers tend to become more anemic during pregnancy, and it is commonly believed that this is due to physiological hemodilution[3]. It has been reported that only 3% of pregnant β-thalassemia carriers have an Hb level lower than 80 g/L, which can be associated with maternal clinical symptoms of anemia and adverse neonatal outcomes[3]. In this case, hemoglobinopathy itself might be a cause of hemolysis anemia, but it is difficult to ascribe severe and acute hemolytic anemia to simply β-thalassemia minor.

AIHA is characterized by the production of RBC autoantibodies, accelerating their destruction[7]. The incidence of AIHA in the general population is 1/100,000[8]. AIHA is rare during pregnancy, and the exact incidence has not been reported[9,10]. It has been reported that ovarian teratomas were suggested as a possible trigger of AIHA in pregnant and non-pregnant patients[11]. The diagnosis is generally based on the presence of anemia along with signs of hemolysis such as reticulocytosis, low haptoglobin, increased LDH, elevated indirect bilirubin, and a positive DAT. DAT-negative AIHA, as in our patient, only occurs in 5%-10% of all cases, and requires more specific detection with new diagnostic tools[7,9]. Due to insufficient knowledge and conditions, we did not perform a more sensitive DAT test such as anti-IgA and IgM antiserum[12], and there is still room for improvement in this area. The prognosis is usually favorable once an accurate diagnosis of AIHA has been made, patients usually respond to first-line corticosteroids, and AIHA resolves after delivery[13]. Other treatments include RBC transfusions and IVIG. It was reported that cyclosporine A was safe and effective in a case of β-thalassemia major, AIHA, and insulin treated diabetes mellitus when first-line corticosteroids were unsuitable[14]. Research focused on AIHA in patients with thalassemia is very limited. Available reports are usually on alloimmunization in thalassemia major patients after receiving multiple blood transfusions. A multicenter study showed that erythrocyte autoantibodies occurred in 6.5% of chronically or intermittently transfused thalassemia patients[15]. As reported, the presence of underlying RBC autoantibodies may be predictors of AIHA in β-thalassemia patients[16]. Our thalassemia patient was not transfusion dependent, and as pregnancy is a semi-allogeneic process, we thought that there might be potential links between these three pathological processes.
CONCLUSION
We report a rare case of severe refractory anemia during pregnancy. Following various examinations, the underlying cause of the anemia was finally identified, and the patient received timely treatment. Very little research has been carried out on AIHA in pregnant patients with thalassemia. Little is known about possible pathologic process and ignoring it can lead to delays in treatment and adverse pregnancy outcome. We suggested that DAT-negative AIHA should be suspected in cases of severe hemolytic anemia in pregnant patients with and without other hematological diseases. Hopefully, there will be more detailed and in-depth studies carried out on this issue in the future.

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External penetrating laryngeal trauma caused by a metal fragment: A Case Report

Zi-Han Qiu, Jin Zeng, Qiang Zuo, Zhong-Qi Liu

Abstract

BACKGROUND
Although external penetrating laryngeal trauma is rare in the clinic, such cases often result in a high mortality rate. The early recognition of injury, protection of the airway, one-stage laryngeal reconstruction with miniplates and inter-disciplinary cooperation are important in the treatment of such patients.

CASE SUMMARY
A 58-year-old male worker sustained a penetrating injury in the left neck. After computed tomography scanning at a local hospital, he was transferred to our hospital, where he underwent tracheotomy, neck exploration, extraction of the foreign object, debridement and repair of the thyroid cartilage using titanium miniplates. An endo laryngeal stent was inserted, which was removed 12 days later. The patient recovered well and his voice rapidly improved after surgery.

CONCLUSION
Penetrating laryngeal trauma is uncommon. We successfully treated a patient with early laryngeal reconstruction and management by interdisciplinary cooperation.

Key Words: Laryngeal trauma; Reconstructive operation; Miniplate; Multi-discipline cooperation; Computed tomography; Case report

Core Tip: External penetrating laryngeal trauma is rare, and is associated with a high
INTRODUCTION
External penetrating laryngeal trauma is rare, but is a potentially life-threatening injury. It is mostly caused by sharp objects or great destructive force, similar to a gunshot wound and explosion injury[1-3]. Damage to the larynx may result in severe consequences, such as massive hemorrhage, cartilage fracture and airway collapse[4,5]. It presents with a spectrum of symptoms and signs that range from changes in voice quality to cardiopulmonary arrest due to airway obstruction[6]. Severe penetrating laryngeal trauma may be accompanied by injury to cervical great vessels, esophagus, trachea and chest[7]. Correct diagnosis and timely treatment are vital for improving patient survival and reducing the loss of organ function. When severe consequences occur, such as shock, bleeding and asphyxia, they should be treated immediately according to the general surgical principles for rescue, and tracheotomy should be performed[8-10]. In addition, early reconstruction of the larynx is important for vocal function reconstruction and recovery of patients with laryngeal cartilage fracture[7,8,11,12].

We here present a case of a 58-year-old male worker who suffered from an external penetrating laryngeal trauma and underwent timely management with one-stage laryngeal reconstruction, and achieved good functional results.

CASE PRESENTATION
Chief complaints
A 58-year-old Chinese male worker was walking in a construction site in Inner Mongolia when a metal rope suddenly broke. He was hit by a metal fragment due to the force of the metal rope. The fragment resulted in an injury to his left neck.

History of present illness
Due to this serious injury and the importance of the injured area, he was immediately transferred to a tertiary hospital in Beijing with a cervical collar for spinal immobilization.

History of past illness
The patient had no specific history of past illness.

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

Physical examination
Physical examination found an irregular and dirty wound of approximately 2 cm in his left neck.

Laboratory examinations
The patient had no specific laboratory examination.
Imaging examinations
Upon admission, computed tomography (CT) was performed using a 64-row CT scanner (LightSpeed VCT, GE Medical Systems), with the following scanning parameters: 3.250 mm section thickness, 120 kVp, 498 mA, and 0.6 s rotation time. The patient underwent a standard diagnostic CT in the craniocaudal direction at a local hospital. CT scanning confirmed significant thyroid cartilage fracture, cervical emphysema, fracture of the C4 vertebra and right vertebral arch and a metal foreign object in front of the C4 vertebra (Figures 1A and 1B).

FINAL DIAGNOSIS
The final diagnosis was external penetrating laryngeal trauma of Schaefer-Fuhrman classification group 4 (Table 1).

TREATMENT
After an artificial airway was established by tracheotomy, the neck was explored. There was an irregular injury of approximately 2 cm in the left neck. The wound was dirty, and multiple fine black foreign objects were seen in the wound. The sinus tract formed by the trauma passed through the skin wound, the left thyroid cartilage and the pharynx to the front of the C4 vertebra. The left thyroid cartilage was broken into several fragments, while the right was largely intact. The structure of the left vocal cord, ventricular band and laryngeal ventricle was disordered, and the residual local mucosa was swollen and congested (Figure 2A). The anterior commissure, the right vocal cord, ventricular band and laryngeal ventricle were structurally clear, and the mucous membrane of the vocal cord and ventricular band was slightly swollen. A cylindrical metal foreign object of 1 cm × 1 cm × 1 cm was seen which was partially lodged in the C4 vertebra (Figure 2B). The metal foreign object was removed by orthopedists (Figure 2C).

After adequate debridement, an endolaryngeal stent was inserted in order to support the laryngeal structure. The fragments of thyroid cartilage were repaired with two titanium miniplates (Figure 2D). A drainage tube was used to drain the hematoma and pneumatosis of the neck. The patient was able to breath via the tracheostomy cannula after surgery, and post-operative feeding was via a nasogastric tube. Because of the unstable C4 vertebra fracture, the orthopedist, after ensuring that there was no spinal cord injury, ordered absolute bed rest for at least one month.

OUTCOME AND FOLLOW-UP
Post-operative radiography showed that the two plates were in a satisfactory position and no replacement was needed (Figure 3A and 3B). On the 14th day, fibrolaryngoscopy showed that the laryngeal structure was intact; there was hyperemia and swelling in the left vocal cord, some granulation tissues could be seen in the left vocal cord, ventricular band and laryngeal ventricle; the activity of the left vocal cord was poor, and both hyperemia and hypertrophy were observed in the right vocal cord (Figure 3C). Six months later, the patient returned for review, and dynamic laryngoscopy showed that vocal fold movement had improved and the wound had healed well without obvious laryngostenosis (Figure 3D).

DISCUSSION
Surgery for penetrating laryngeal trauma caused by a metal fragment is worth studying to avoid death among workers in the construction industry. Although external penetrating laryngeal trauma is uncommon, attention should be paid to such injuries. The clinical treatment of the patient in this report highlights several important aspects of the management of this injury. Rapid transportation of patients is essential, and the necessary examinations and treatment should be carried out as soon as possible.
Table 1 Schaefer-Fuhrman classification of laryngeal trauma[4,13]

<table>
<thead>
<tr>
<th>Group</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Minor endolaryngeal hematomas or lacerations; no detectable fracture</td>
</tr>
<tr>
<td>Group 2</td>
<td>Edema, hematoma, minor mucosal disruption without exposed cartilage; nondisplaced fracture; varying degrees of airway compromise</td>
</tr>
<tr>
<td>Group 3</td>
<td>Massive edema, large mucosal lacerations, exposed cartilage; displaced fracture(s); vocal cord immobility</td>
</tr>
<tr>
<td>Group 4</td>
<td>Same as group 3 but more severe with: mucosal disruption; disruption of the anterior commissure; unstable fracture, two or more fracture line</td>
</tr>
<tr>
<td>Group 5</td>
<td>Complete laryngotracheal separation</td>
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Figure 1 Axial computed tomography scan of the neck. A: Laryngeal injury; B: Metal fragment.

Figure 2 Intra-operative images. A: Laryngeal injury; B: Fragment lodged in the C4 vertebra; C: Fragment was removed; D: Miniplate fixation.

Laryngeal trauma was classified into four groups by Schaefer[4]. In 1990, Fuhrman added a fifth group (Table 1)[13]. The case described here was classified into group 4.

The choice of examination is important for diagnosing injuries and optimal treatment planning. In this case, CT findings helped us make the primary diagnosis and determine the surgical plan. CT is more sensitive than flexible laryngoscopy for...
identifying laryngeal injury because it can show minimal cartilage fracture and other details[14,15]. In addition, distorted anatomy, bleeding and poor visualization may result in difficulties in laryngoscopy[7]. When plain CT cannot show radiological signs of potential vascular injuries, which may delay patients' diagnoses, contrast-enhanced CT is more sensitive for vascular injuries[16]. In an emergency, contrast-enhanced CT is helpful in revealing details regarding the vessels and surrounding structures, such as angiorrhaxis and hematoma[7,18]. In a retrospective study of 67 patients with penetrating neck injuries, combining clinical signs and radiological evidence improved the accuracy of exploration of injured vessels to 97.7%[19]. Therefore, contrast-enhanced CT is an essential examination for the diagnosis of injuries because of its high sensitivity in evaluating soft tissues, specifically vascular structures, in addition to fractures.

In patients with laryngeal trauma, the overriding priority is to maintain airway patency. Endotracheal intubation and tracheotomy have been recommended to establish a safe airway. However, intubating patients who have laryngeal injuries may be difficult or can fail, due to disordered anatomy, limited visualization and poor condition of the patients[8,9,10,20]. In our case, in order to avoid worsening the situation, we chose tracheotomy but not endotracheal intubation because of the severe laryngeal cartilage fracture with displacement of fragments and the unstable C4 vertebra fracture. Other reports have also shown that cricothyroidotomy may be a helpful temporary measure in emergency situations[20,21].

The optimal method and timing of surgery are controversial. A review of 77 patients revealed that expeditious repair of laryngeal injuries within 48 h could reduce the incidence of poor voice and/or airway outcomes[8]. In some retrospective studies, frequently, the airway repair was carried out within 8 h of the original injury[11,12]. Steven et al[7] suggested that patients with acute laryngeal trauma should undergo surgery within 24 h, or as soon as the patient can be brought to the operating room. Thanks to the short distance and rapid transportation, our patient received timely surgery within the window period.

In previous studies, several methods of repair and fixation were introduced. In a cadaveric study, miniplate fixation provided an easy procedure, tolerability, and superiority for thyroid cartilage fractures compared to wire fixation[22]. de Mello-Filho and Carrau reviewed 20 cases of laryngeal fractures repaired with miniplates, and most of them had good recovery of respiration, phonation and deglutition[23]. In
the present case, the choice of repair was miniplate fixation, with good prognosis of various laryngeal functions.

Interdisciplinary cooperation is important because the force of high velocity damage usually causes multiple injuries, such as thyroid cartilage fracture and cervical injury. Emergent life-saving airway or hemodynamically stabilizing procedures have priority over spinal precautions[24]. Prehospital spinal immobilization is necessary in patients who have unstable fractures without an initial neurologic deficit[25]. In this case, good outcome was also attributed to spinal immobilization with a cervical collar and post-operative bed rest, which reduced the adverse effects of transportation and activity. Undoubtedly, a healthy physical condition before injury and high degree of compliance with treatment also played a role in achieving a good outcome.

CONCLUSION
External laryngeal trauma is rare but potentially fatal, which may be accompanied by injuries to other areas. Contrast-enhanced CT scanning is important for judging the severity of injuries. Maintaining airway patency is the key to patient management. Timely and appropriate treatment with interdisciplinary cooperation is essential for subsequent rehabilitation.

REFERENCES


Antegrade in situ laser fenestration of aortic stent graft during endovascular aortic repair: A case report

Zhi-Wei Wang, Zhen-Tao Qiao, Ming-Xing Li, Hua-Long Bai, Yuan-Feng Liu, Tao Bai

BACKGROUND
The endovascular repair of juxtarenal abdominal aortic aneurysms (JAAA) usually requires combination treatment with various stent graft modifications to preserve side branch patency. As a feasible technique, according to the situation, antegrade in situ laser fenestration still needs to be improved.

CASE SUMMARY
This report describes a case that was successfully treated with endovascular repair facilitated by antegrade in situ laser fenestration while maintaining renal arterial flow. Laser fenestration was performed using a steerable sheath positioned in the stent graft lumen in front of the renal artery ostium. With the bare stent region unreleased, renal artery perfusion could be maintained and accurate positioning could be achieved by angiography in real time.

CONCLUSION
This study suggests the feasibility and short-term safety of this novel antegrade in situ laser fenestration technique for select JAAA patients.

Key Words: Juxtarenal abdominal aortic aneurysm; In situ fenestration; Thoracic endovascular aortic repair; Antegrade; Case report

Core Tip: This report describes the feasibility and short-term safety of a novel antegrade in situ laser fenestration technique. During the operation, laser fenestration was performed using a steerable sheath positioned in the stent graft lumen in front of the renal artery ostium. With the bare stent region unreleased, renal artery perfusion could
be maintained and accurate positioning could be achieved by angiography in real time. The technique is uncomplicated and has potential as an alternative approach when dealing with a hostile proximal aortic neck during endovascular aortic repair.

INTRODUCTION

An inadequate proximal neck is the most common anatomical challenge during the endovascular repair of juxtarenal abdominal aortic aneurysms (JAAAs)\(^1\). Retrograde in situ fenestration (ISF) has been reported to preserve the major aortic branches during thoracic endovascular aortic repair (TEVAR) effectively and safely\(^2\); however, because of the lack of downstream branch artery access, retrograde revascularization cannot be achieved easily in EVAR without a laparotomy or retroperitoneal incision\(^3\)-\(^5\). If endovascular therapy is deemed to be the best treatment option, antegrade ISF may be an ideal method to preserve the patency of visceral arteries. Many animal experiments\(^6\)-\(^9\), benchtop studies\(^10\)-\(^12\), and clinical studies\(^13\)-\(^17\) have demonstrated that the antegrade ISF of aortic stent grafts during EVAR is technically feasible. The following report describes a novel approach of antegrade in situ laser fenestration (ISLF) during EVAR. We found that the ostium of the right renal artery (RRA) could be accurately positioned by angiography in real time. Moreover, RRA perfusion could be maintained during the procedure.

CASE PRESENTATION

**Chief complaints**

A 55-year-old man presented to the emergency department of our hospital complaining of worsening lower abdomen pain.

**History of present illness**

The patient’s symptoms started a week prior with recurrent episodes of lower abdomen pain and distention, which had worsened in the last 4 h. The patient had no fever or diarrhea. Color Doppler ultrasound in a community hospital showed an abdominal aortic aneurysm (AAA).

**History of past illness**

The patient had a clear previous medical history.

**Personal and family history**

However, he had smoked at least five cigarettes a day for ten years.

**Physical examination**

The abdomen was soft, with mild periumbilical tenderness and no rebound tenderness. A pulsatile abdominal mass could be palpated. The liver and spleen were impalpable.

**Laboratory examinations**

The patient’s blood pressure was approximately 108/80 mmHg. The blood routine examination findings were normal. The prothrombin and partial thromboplastin times were normal, and the D-dimer level was slightly increased, at 0.47 mg/L. The serum C-reactive protein level was increased, at 66.48 mg/dL (normal range: < 5 mg/dL), and the erythrocyte sedimentation rate was 23 mm/h. The results of blood biochemistry, urinalysis, electrocardiography and arterial blood gas analysis were also

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normal.

**Imaging examinations**

Preoperative computed tomography angiography (CTA) showed a JAAA with a diameter of 50.4 mm, a thick hematoma and multiple penetrating aortic ulcers (PAUs). Preoperative sizing showed an aortic ulcer with a hematoma below the right renal ostium, a short (4-mm-long) infrarenal aortic neck, and a proximal healthy landing zone of approximately 16.0 mm between the two renal arteries. The diameter of RRA was 6.1 mm. The diameter of the aortic bifurcation was 32 mm. The diameter of the vessel at the lower edge of the left renal artery was 20.9 mm. The diameter of the vessel at the lower edge of the RRA was 20.5 mm. The distance from the lower edge of the RRA to the aortic bifurcation was 91.2 mm. The distance from the lower edge of the RRA to the bifurcation of the right iliac artery was 124.3 mm (Figure 1A-D).

**MULTIDISCIPLINARY EXPERT CONSULTATION**

After a thorough patient evaluation, we discussed the possible treatment alternatives. The PAUs involved the RRA, so open surgery was likely to be more traumatic and technically complex than traditional infrarenal repair [18]. EVAR has been widely accepted as the treatment of choice for patients who are unfit for open surgery. To achieve an adequate proximal seal, the RRA might need to be covered and then revascularized. "Off-the-shelf" techniques (such as chimney, periscope, and sandwich techniques) have a high risk of type IA endoleakage and reintervention and are thus not preferred. Customized fenestrated and branched endografts are expensive and not available for the treatment of acute syndromes. Even physician-modified stent grafts still need to be rotated and moved as needed for cannulation of the visceral vessels. In this case, the enhanced abdominal pain and thick perivascular hematoma suggested that the risk of aneurysm rupture was high. Therefore, for early and minimally invasive treatment, after obtaining informed consent, EVAR with antegrade ISF was planned.

**FINAL DIAGNOSIS**

Confirmed JAAA combined with PAUs.

**TREATMENT**

Emergency surgery was performed 24 h after admission. The surgical procedure was as follows. A sizing catheter was advanced via left femoral access, allowing for angiography and pertinent measurements to be achieved (Figure 1E). A long sheath (Flexor, Cook Medical) was used to deploy a guidewire and a balloon catheter into the RRA via brachial access to allow RRA salvage in case of fenestration failure. First, the right internal iliac artery was embolized. An Endurant II stent graft (25 mm × 13 mm × 166 mm, Medtronic Vascular, Inc.) was advanced through the right femoral sheath and deployed just below the left renal artery. The short leg of the stent graft was released while leaving the bare stent in place. Thereafter, a 10-F steerable sheath (FuStar, Lifetech Scientific Corp.) was inserted into the stent graft from the left groin through the short leg. The ostium of the RRA was displayed in real time by contrast injection from the brachial access point. Meanwhile, the tip of the steerable sheath was adjusted to align with the ostium of the RRA (Figure 2A), and the site of perforation was determined via 2 different fluoroscopic projections. A 4-mm balloon catheter (Bard Rival, Bard Peripheral Vascular) was passed via the sheath followed by a laser fiber (GIGAA Laser, Wuhan, China), which was calibrated to deliver energy pulses of 18 W in 3 s, to fenestrate the membrane of the thoracic aortic stent graft [2]. After fenestration, the laser was removed and replaced with a 0.035-inch guide wire that was advanced into the proximal abdominal aorta. A 4-mm balloon was passed along the wire across the opening, and balloon dilation was achieved (Figure 2B). Due to the straight angle, after trying a variety of catheters, we finally used a trimmed pigtail catheter (Merit Medical Systems, Inc.) to reach the RRA (Figure 2C). An angioplasty balloon (5 mm × 10 mm, Mustang, Boston Scientific Corp.) was passed from the opening into the renal artery, followed by balloon dilation. Then, the balloon was
deflated to 2 atmospheres, with no residual waist, while the bare stent was fully released. The stent was opened smoothly, without any balloon kinking (Figure 2D). Thereafter, a covered stent (8 mm × 50 mm, Gore VIABAHN) was deployed. Then, a 7-mm angioplasty balloon was used to “flare” the RRA stent (Figure 2E). Angiography demonstrated that the RRA was patent, with no endoleakage (Figure 2F). Then, the contralateral iliac limb was placed, with no issues. Repeat ballooning of the regions of stent overlap was performed with a Coda® balloon (Cook Medical). Imaging on completion demonstrated good renal perfusion, with no evidence of endoleakage or stenosis (Figure 3A).

OUTCOME AND FOLLOW-UP

The patient had an uneventful recovery and was continued on aspirin daily. The total procedure time was 2 h. The fluoroscopy time was 45 min, and the total amount of contrast used was 100 mL. The estimated blood loss was 20 cc. Because the left renal artery was not involved, RRA perfusion was maintained during the operation. Postoperatively, there was no abnormal renal function, and the patient was discharged home on postoperative day 7. The 1-year follow-up CTA confirmed patency the of both renal arteries and the absence of endoleakage (Figure 3B).

DISCUSSION

The endovascular repair of complex aortic aneurysms involving renal and/or visceral branches usually requires combination treatment with various types of stent graft modifications to preserve side branch patency. These techniques feature devices with parallel grafts, fenestrations, or branches. The parallel graft technique has a high risk of type 1A endoleakage, especially when multiple arteries require reconstruction[17]. The use of such customized systems, including those involving fenestrated grafts and branched endografts, requires accurate preoperative imaging and planning. During
Figure 2 Steps for fenestrations. A: The tip of the steerable sheath was adjusted to align with the ostium of the right renal artery (RRA); B: Progressive enlargement of the fenestration was performed using balloons; C: A trimmed pigtail catheter was used to guide the guidewire to the RRA; D: The bare stent region was released with a balloon anchored at the RRA; E: The covered bridging stent was deployed; F: Angiography demonstrated that the RRA was patent, with no endoleakage.

the procedure, alignment of the vessel ostia with the fenestrations or branches can be difficult[3-5,19]. In addition, the high cost and long waiting time reduce the accessibility of these technologies to patients, particularly in emergent cases. In retrograde ISF, as the site is approached from within the target vessel, it is easy to place the stent graft at the correct site, and this method has been confirmed to be effective and safe for use in major aortic branches[2]. Unfortunately, retrograde endovascular revascularization cannot be easily achieved in visceral arteries[3,4,20]. Since Tse et al[6] first reported the feasibility of antegrade ISF in the placement of abdominal aortic stent grafts to preserve the patency of the renal arteries in a canine model, many studies have explored this technique (Tables 1 and 2).

Fenestration devices are important components of antegrade ISF. Graft perforation is achieved easily with most devices, including mechanical and energetic fenestration devices. Mechanical fenestration requires rigidity to transfer force from the operator’s hands to the graft. If the angulation of the needle is not sufficiently acute, target vessel cannulation becomes difficult[6,9]. Additionally, the rigidity of the needle may make it difficult to cross the typically tortuous and diseased iliac vessels. However, the occurrence of complications, such as retroperitoneal hematoma, has been rarely reported in previous studies[6,7,9]. Compared with needles, radiofrequency probes and laser fibers have been found to be sufficiently compliant for perforation[8]. Therefore, we decided to perform ISLF in this case.

When using an antegrade approach in visceral arteries, finding the right puncture site can be challenging. To allow for fluoroscopic visualization, various landmarks can be deployed in target arteries prior to endograft deployment. In Tse et al[6]’s first report, bare stents were deployed in both renal arteries; however, stent fractures were observed bilaterally. No renal stent fractures were observed in a second study by the same team[8], in which the modified stent grafts had an unsupported portion in the fenestration area. In this study, they marked target vessels with detachable coils or hydrophilic catheters. However, thrombosis of the renal artery was observed after the
procedure, which was likely related to partial coil deployment. Le Houérou et al.[14] confirmed the feasibility of preliminarily stenting each target artery in a large clinical study[14]. Hsiao et al.[21] found that overlapping stents exhibited lower fatigue resistance during respiration than a single stent. In Saari et al.[9]'s study, deflation of the balloon in the renal artery indicated successful puncture, but a long warm ischemia time for the left kidney caused infarction. Furthermore, stents, balloons, and coils result in additional costs.

To avoid using invasive landmarks, Riga et al.[7] marked target vessels on a fluoroscopy screen on a fixed projection with robot-assisted antegrade ISF. Leger et al.[15] and Salib et al.[17] succeeded under fused CT guidance. However, the configuration of the aorta may change after stent graft insertion[5]. To accurately position stent grafts in real time, various navigation devices have been tested for guidance during antegrade ISF. Intravascular ultrasound probes were not able to visualize the renal orifices for fenestration both within the stent graft and within the inferior vena cava[6]. However, electromagnetically guided endovascular instrumentation was successful in in vitro trials[11,12]. Therefore, in our case, fenestration was performed while the stent graft was positioned well with the bare stent region unreleased, allowing real-time positioning by angiography.

Blocking a visceral artery may cause visceral ischemia[9]. Le Houérou et al.[14] implanted an undersized stent graft at the level of the visceral aorta to avoid temporary visceral ischemia. Tse et al.[8] thought that, in theory, the marking catheter could serve to cold-perfuse renal arteries during the fenestration procedure. Bismuth et al.[13] performed antegrade ISF with a constrained stent graft. In our case, fenestration was performed while the bare stent region was unreleased, and RRA perfusion was maintained during the procedure.

The stability of supporting devices is also important for correct positioning of the perforation site. Tse et al.[6] described that support for the needle was provided by inflating a balloon catheter against the contralateral aortic wall. However, this catheter does not provide sufficient needle angulation. In most studies, a steerable catheter or sheath has been used to support fenestration devices. Riga et al.[7] used a remotely controlled robotic steerable catheter system to improve accuracy and stability. Piazza et al.[11] also proposed some design solutions for catheter stabilization. In this study, a FuStar steerable sheath was used. In addition, the main body of the stent graft was fixed, and the space in the proximal part was limited, which improved the stability of

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**Table 1 Summary of published antegrade in situ fenestration animal and benchtop studies**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Model</th>
<th>Fenestration device</th>
<th>Guidance/landmarks of visceral arteries</th>
<th>Stent graft</th>
<th>Technical success rate</th>
<th>Experimental results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tse et al[6]</td>
<td>2007</td>
<td>Canine</td>
<td>Needle</td>
<td>(1) Intravascular ultrasound; and (2) Preliminary stenting of all visceral arteries</td>
<td>Endurant</td>
<td>(1) 0/2; and (2) 2/2</td>
<td>(1) The experiment was terminated; and (2) At the 1-mo follow-up, both renal arteries were patent. Stent fractures were observed bilaterally</td>
</tr>
<tr>
<td>Riga et al[7]</td>
<td>2009</td>
<td>Porcine</td>
<td>Needle</td>
<td>On a fixed fluoroscopic projection, the position of these target vessels was marked on the fluoroscopy screen</td>
<td>Valiant</td>
<td>2/2</td>
<td>There were no immediate complications. Both renal arteries were patent</td>
</tr>
<tr>
<td>Tse et al[5]</td>
<td>2010</td>
<td>Canine</td>
<td>Radiofrequency</td>
<td>Target vessels were marked with detachable coils or with hydrophilic catheters</td>
<td>Zenith</td>
<td>2/3</td>
<td>Thrombosis was seen in one stent during 1 mo of follow-up, while the other fenestrated artery remained patent</td>
</tr>
<tr>
<td>Saari et al[9]</td>
<td>2012</td>
<td>Porcine</td>
<td>Needle</td>
<td>Target vessels were marked with balloon catheters</td>
<td>Endurant, Talent</td>
<td>2/6</td>
<td>In one pig, the kidney showed clear signs of ischemic injury when autopsied</td>
</tr>
</tbody>
</table>

1Number of successful fenestrations/number of target vessels.
NA: Not applicable; EM: Electromagnetic.
### Table 2 Summary of published antegrade in situ fenestration clinical studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>No. of patients</th>
<th>Puncture method</th>
<th>Guidance/landmarks</th>
<th>Stent graft</th>
<th>Technical success rate</th>
<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth et al</td>
<td>2012</td>
<td>1</td>
<td>Needle</td>
<td>NA</td>
<td>C3 Excluder</td>
<td>1/1</td>
<td>At the 1-mo follow-up, the patient remained without complications. There was no evidence of endoleakage, migration or stent occlusion, and the bilateral renal arteries remained patent</td>
</tr>
<tr>
<td>Köbel et al</td>
<td>2013</td>
<td>1</td>
<td>Needle</td>
<td>Angiography and the marker at the proximal graft edge</td>
<td>Zenith</td>
<td>1/1</td>
<td>On CTA 4 d postoperatively, all side branches were fully preserved. Renal function was completely restored</td>
</tr>
<tr>
<td>Le Houérou et al</td>
<td>2018</td>
<td>16</td>
<td>Laser</td>
<td>Preliminary stenting of all visceral arteries</td>
<td>Valiant, Endurant, Zenith</td>
<td>33/35</td>
<td>During a mean follow up of 17 mo, no deaths occurred. Four secondary procedures were required: Two related to fenestrations; one for stent dislocation; and one for stent stenosis. The follow up CTA demonstrated 97% primary patency</td>
</tr>
<tr>
<td>Leger et al</td>
<td>2019</td>
<td>20</td>
<td>Laser</td>
<td>Image fusion guidance</td>
<td>Endurant</td>
<td>48/50</td>
<td>The 30-d safety rate was 90% (n = 2 deaths). At the one-week follow-up, all target vessels were patents, and two patients (15%) required a secondary procedure for endoleakage</td>
</tr>
<tr>
<td>Zhang et al</td>
<td>2020</td>
<td>1</td>
<td>Laser</td>
<td>Preliminary stenting of all visceral arteries</td>
<td>Valiant</td>
<td>4/4</td>
<td>The 3-mo CTA demonstrated a decreased aneurysm sac, patent stent branches, and no endoleakage</td>
</tr>
<tr>
<td>Salib et al</td>
<td>2021</td>
<td>1</td>
<td>Laser</td>
<td>Image fusion guidance</td>
<td>Endurant</td>
<td>3/3</td>
<td>The postoperative course was uneventful. The 6-mo CTA demonstrated an excluded aneurysm, patent stent branches, and no endoleakage</td>
</tr>
</tbody>
</table>

1 Number of successful fenestrations/number of target vessels. NA: Not applicable; CTA: Computed tomography angiography.

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**Figure 3 Postoperative imaging.** A: Final angiogram; B: Computed tomography reconstruction at 1 year demonstrated graft patency.

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Other aspects, such as fatigue resistance,[21] are also important issues in antegrade ISF. Our technique may be suitable for use in select JAAA patients with the involvement of only one renal artery. Due to the length limitation of the bare area, whether other visceral arteries can be cannulated in the same fashion needs further study.
CONCLUSION

This study suggests the feasibility and short-term safety of this novel antegrade ISF technique as an off-label technique for use in select JAAA patients. Renal artery perfusion was maintained during the procedure, and accurate positioning was achieved using angiography. This technique could serve as an alternative approach for the management of hostile proximal aortic necks during EVAR. However, the long-term effects of this method require further study in a larger cohort with long-term follow-up.

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Hoffa’s fracture in an adolescent treated with an innovative surgical procedure: A case report

Zu-Xin Jiang, Pan Wang, Shun-Xin Ye, Xiao-Ping Xie, Chun-Xiu Wang, Yue Wang

BACKGROUND
Hoffa fracture is rare, especially in adolescents, and has a high rate of complications such as avascular necrosis and osteoarthritis; moreover, there are no definitive guidelines for its treatment. This report could provide a new potential treatment for Hoffa fracture.

CASE SUMMARY
A 16-year-old girl presented to the orthopedic emergency department of No. 2 People’s Hospital of Yibin City with persistent pain following a right knee injury sustained during a sprint race. Her knee was swollen and tender, and the range of motion was restricted by the pain. X-ray and computed tomography revealed a Hoffa fracture in the right knee. After consultation, surgical treatment was performed, and the fracture was fixed with three 3.5-mm cannulated cancellous screws; osteochondral plugs that were harvested from the screw insertion site were re-implanted to cover the screw head. The patient’s fracture and osteochondral plug healed 6 mo postoperatively, and she presented a knee range of motion of 0–135 without pain, and was walking without support with a normal gait.

CONCLUSION
Here, we describe an innovative surgical procedure for Hoffa fracture that could provide a new possibility for the treatment of similar fractures, and further improve their management.

Key Words: Hoffa fracture; Osteochondral plug; Open reduction; Internal fixation; Case
A 16-year-old girl presented to our orthopedic emergency department with persistent pain following a right knee injury sustained during a sprint race. On examination, the right knee was swollen and tender with decreased range of motion. Laboratory examination revealed no obvious abnormality. She was treated by open reduction and internal fixation with osteochondral plug re-implantation, and had no postoperative complications. The fracture and osteochondral plug had completely healed, 6 mo postoperatively.

Core Tip: A 16-year-old girl presented to our orthopedic emergency department with persistent pain following a right knee injury sustained during a sprint race. On examination, the right knee was swollen and tender with decreased range of motion. Laboratory examination revealed no obvious abnormality. She was treated by open reduction and internal fixation with osteochondral plug re-implantation, and had no postoperative complications. The fracture and osteochondral plug had completely healed, 6 mo postoperatively.

INTRODUCTION

Hoffa fracture, a fracture of the femoral condyle in the coronal plane involving one or both of the condyles, was first described in 1904 by Hoffa[1]. The conventional classification system includes the three subtypes proposed by Letenneur et al[2]. The diagnosis of these fractures is challenging, since they are easily misdiagnosed and missed in anteroposterior X-rays, because the unfractured condylar part of the femur can obscure the fractured condyle[3]. Therefore, when Hoffa's fracture is suspected, further computed tomography (CT) is necessary. This is an uncommon injury in adults, which is even rarer in adolescents. It accounts for 8.7% to 13% of distal femoral fractures[4]. There are no data on the potential injury mechanism. Although in children and individuals with osteoporosis, low-energy trauma can produce the lesion, the main cause of a Hoffa fracture is a high-energy injury (e.g., a traffic collisions or a fall)[5,6]. Surgical treatment, anatomical reduction, and stable fixation are recommended to reduce the rate of complications, such as arthritis, nonunion, and osteonecrosis[7]. However, as far as the literature reports, there is no optimal surgical approach and fixation method[3]. Hence, we present the case of an adolescent girl with a medial condyle fracture (type III) of the distal femur, which was successfully managed with an innovative surgical procedure. We hope to provide a new possibility for the treatment of similar fractures, and further improve their management.

CASE PRESENTATION

Chief complaints
A 16-year-old girl presented to our orthopedic emergency department with sustained pain following a right knee injury in a sprint race.

History of present illness
She felt persistent pain in her right knee and was unable to walk normally. She had no other symptoms, including dizziness, headache, chest tightness, and abdominal pain.

History of past illness
She had no other history of past illnesses.

Personal and family history
She had no genetic or familial disease history.
Physical examination
On examination, the patient's vital signs were stable. Right knee was swollen and tender with bone crepitation and decreased range of motion. There were no open wounds or distal neurovascular deficits.

Laboratory examinations
Laboratory examination revealed no obvious abnormality.

Imaging examinations
Knee radiographs and CT images confirmed a coronal plane fracture of the posterior part of the medial femoral condyle with epiphyseal injury (Figure 1).

FINAL DIAGNOSIS
Hoffa fracture.

TREATMENT
Following examination and under anesthesia, the patient was placed in the prone position, with the knee stabilized and locked in a flexed 30° position. The fracture was accessed through a posteromedial incision to the knee. Under X-ray guidance, the medial femoral condyle fragment was reduced and temporarily fixed with Kirschner wires. A 5.0 mm annular drill (Wellbone, Suzhou, China) was used to remove the 5.0 mm × 5.0 mm cylindrical articular cartilage and subchondral bone. After fixing the fragment with three 3.5 mm partially threaded cancellous screws (inserted in a posterior-to-anterior direction), the articular cartilage and subchondral bone were re-implanted in situ and the screw heads were covered (Figure 2) to ensure stability and ease upon pressure. Postoperatively, the limb was maintained on a long-leg back slab with the knee in a 30° flexion position for approximately 2 wk. Active isometric muscle contractions were permitted during this period. Subsequently, the slab was removed, and passive flexion and extension exercises were initiated.

OUTCOME AND FOLLOW-UP
Upon radiographic monitoring, weight-bearing was gradually permitted at 2 mo. At the 6-mo follow-up, the patient presented a knee range of motion of 0°–135° without pain, and was walking without support with a normal gait (Figure 3). The fracture and osteochondral plug had completely healed. There were no signs of avascular necrosis of the femoral condyle or knee osteoarthritis (Figure 4). The patient and her parents provided consent for the publication of the images.

DISCUSSION
A coronal fracture of the distal femur is termed as Hoffa fracture; Letenneur et al[2] divided it into three types according to the relationship between the fracture line and the posterior cortex of the femoral shaft in 1978[2]. Type I is a fracture in the posterior cortical extension of the distal femur. Type II fracture is similar to type I fracture, but the fracture line is closer to the posterior condyle, and is further divided into A, B, and C subtypes based on the distance. Type III is a fracture oblique to the femur condyle, and can be divided into the medial, lateral, or conjoint bicondylar fracture according to the fracture site[1,8,9]. A summary of the main surgical approaches and fixation methods for different Hoffa fracture types is provided in Table 1[10-16]. There is no optimal surgical approach and fixation method for Hoffa fractures as described in Table 1. Direct lateral/medial and posterolateral approaches can expose small Hoffa fragments and employ the more biologically advantageous posterior-anterior direction screws, as well as a plate if necessary, but with a risk of neurovascular injury; lateral/medial parapatellar approaches are suitable for large Hoffa fragments and can expose both the femoral condyles, but small Hoffa fragments are difficult to expose and reduce, and posterior-anterior direction screws are not feasible[17]. Other studies
Table 1 Summary of main surgical approaches and fixation methods for different Hoffa fracture types

<table>
<thead>
<tr>
<th>Condyle</th>
<th>Approach</th>
<th>Fixation technique</th>
<th>Letenneur classification</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral</td>
<td>LPPA</td>
<td>A-P screw</td>
<td>I, III</td>
<td>Singh et al[10]</td>
</tr>
<tr>
<td></td>
<td>Posterolateral</td>
<td>Suture</td>
<td>IIC</td>
<td>Tan et al[11]</td>
</tr>
<tr>
<td></td>
<td>Direct lateral</td>
<td>P-A screw</td>
<td>II B</td>
<td>Egol et al[12]</td>
</tr>
<tr>
<td>Medial</td>
<td>MPPA</td>
<td>A-P screw</td>
<td>III</td>
<td>Dhillon et al[13]</td>
</tr>
<tr>
<td></td>
<td>Direct medial</td>
<td>P-A screw</td>
<td>III</td>
<td>Borse et al[14]</td>
</tr>
<tr>
<td>Bicondylar</td>
<td>Lateral incision</td>
<td>Screw plus plate</td>
<td>Not mentioned</td>
<td>Agarwal et al[15]</td>
</tr>
<tr>
<td></td>
<td>Swashbuckler approach</td>
<td>A-P screw</td>
<td>Not mentioned</td>
<td>Ul Haq et al[16]</td>
</tr>
</tbody>
</table>

A-P: Anterior to posterior screw trajectory; P-A: Posterior to anterior screw trajectory; LPPA/MPPA: Lateral/Medial parapatellar approach.

Figure 1 Image data before operative treatment showing a distal femoral medial condylar fracture. A and B: Anteroposterior and lateral radiographs images before operative treatment; C and D: Computed tomography images before operative treatment (arrow); E: Computed tomography three dimensional reconstruction images before operative treatment (arrow).

[18-21] reported the treatment of the nonunion of Hoffa fracture, suggesting bone grafting following debridement and fixation with screws and bone plates, and finally achieved satisfactory results. Currently, there is no optimal surgical approach and fixation method[3]; hence, the treatment of the different types of Hoffa fractures are mainly determined by the experience and skill of the surgeon. Studies have demonstrated that the biomechanics of the screws in the posterior-anterior direction are superior to the screws in the anterior-posterior direction[22,23]. Furthermore, if the fracture is small, such as a type II fracture, posterior-anterior direction screws are strongly recommended except for the type II C fracture[11]. Therefore, the posterior-anterior direction screws should be preferred for Hoffa fractures. However, this will
Intraoperative images. A: Image after screws fixation and countersunk; B: Image after osteochondral plugs covering the screw heads.

Images of the affected joint, 6 mo postoperatively. A: Complete extension of the right knee joint; B: Complete flexion of the right knee joint; C: Posteromedial approach.

inevitably damage the articular cartilage when holes are punched in the articular surface. Even though Borse et al[14] attempted to avoid damage to the articular cartilage by using headless screws, the cartilage was still damaged to a certain extent. However, the method we provide solves this problem well. Our paper reports a rare case; although open isolated Hoffa fractures of the medial femoral condyle have been reported in children[24], no study has reported a similar case treated by open reduction and internal fixation with osteochondral plug re-implantation.

This type of fracture has a high rate of complications, such as avascular necrosis and osteoarthritis, owing to the subsequent reduction of blood supply to the area and the absence of soft tissue attachment. Surgical stabilization is the preferred treatment for Hoffa’s fractures to achieve satisfactory long-term functional results[25]. In our case, we chose the posteromedial approach to access the knee and used the screws to fix the fragment. The articular cartilage and subchondral bone at the location of the screw were removed in advance, and the head of the screw lowered following its fixation; the articular cartilage and subchondral bone were re-implanted and used to cover the screw heads. Similar to osteochondral autograft implantation, osteochondral plug re-implantation in situ can reduce the extent of cartilage damage. Osteochondral autograft implantation is commonly used in articular cartilage defects, and excellent results have been achieved[26]. This report offers similar methods. The osteochondral plug healed successfully, because fragmentation of healthy cartilage is meant to activate the mitogenic activity of chondrocytes, which proliferate and secrete extracellular matrix to repair damaged cartilage tissue in vivo[27]. We obtained sufficient stability between the fragments, and minimized the damage to the articular cartilage attributed to the surgical procedure. The fracture and osteochondral plug healed, and joint function improved 6 mo postoperatively.
The potential risks, the non-healing and failure of the osteochondral plugs, and minor difficulties in removing the internal fixation when necessary are the potential problems that need to be resolved.

CONCLUSION

To date, a similar surgical treatment has not been reported in the literature. We believe that this innovative surgical procedure could provide a new possibility for the treatment of Hoffa fracture, and further improve the treatment system in patients with similar conditions; however, more cases are warranted to confirm our claims.

ACKNOWLEDGEMENTS

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Hemizygous deletion in the OTC gene results in ornithine transcarbamylase deficiency: A case report

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Author contributions: Wang LP, Cao YT, and Chen J jointly conceived the study and contributed to the study design, initial writing, and revision of the manuscript; Luo HZ collected the patient data; Wang LP and Song M performed the molecular experiments; Yang ZZ and Yang F reviewed variant interpretation; all authors contributed to the manuscript and approved the submitted version.

Informed consent statement: Written informed consent was obtained from the proband’s parents for the publication of any identifiable clinical data and images in this study.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Abstract

BACKGROUND
Ornithine transcarbamylase deficiency (OTCD) is a common ornithine cycle disorder, and OTC gene variation is the main pathogenic factor of this disease. This study explored and validated a variant in the OTC gene.

CASE SUMMARY
The neonate exhibited high blood ammonia, lactic acid, and homocysteine levels on the fifth day after birth. A novel deletion variant in the OTC gene [NM_000531.5, c.970_979delTTCCCAGAGG, p.Phe324GlnfsTer16] was uncovered by exome sequencing. The variant caused a protein-coding frameshift and resulted in early translation termination at the 16th amino acid after the variant site.

CONCLUSION
Our results provide a novel pathogenic variant in OTC and related clinical features for further OTCD screening and clinical consultation.

Key Words: OTC; Ornithine transcarbamylase deficiency; Deletion variant; Exome sequencing; Early translation termination; Case report

Core Tip: In this study, we introduce one boy with ornithine transcarbamylase deficiency caused by an unreported hemizygous variant of OTC gene. Our study delivered the importance of OTC gene testing in metabolism disease. We believe that our study will inspire more doctors to apply genetics testing when facing complex
INTRODUCTION

Ornithine transcarbamylase deficiency (OTCD; OMIM: 31250), also known as hyperammonemia type II, is an X-linked genetic disorder of the ornithine cycle (urea cycle)\[1\]. The incidence of OTCD is approximately 1/80000–1/56500. OTCD is the most common type of ornithine circulation disorder and accounts for 50%-66% of total ornithine circulation disorders. Both neonates and adults can be affected by complex clinical symptoms of this disorder, with varying degrees of severity. Due to this lack of specificity, OTCD is often misdiagnosed\[1-3\]. OTCD has a high mortality rate in neonates, and survivors often have varying degrees of neurological sequelae. Early diagnosis, individualized diet, medication, and liver transplantation are the main strategies for reducing the mortality and disability rates of patients with OTCD.

The OTC gene (OMIM: 300461) is located on chromosome Xp11.4, contains 10 exons and 9 introns, and encodes a 354 amino acid protein. The OTC gene is highly expressed in the liver\[4\]. Pathogenic variants in the OTC gene lead to a reduction or absence of OTC enzyme activity and the shutdown of citrulline synthesis and the ornithine cycle, resulting in an ammonia metabolism disorder and an increase in levels of ammonia in the blood\[5\]. Excessive accumulation of ammonia is highly toxic to the central nervous system, interferes with the energy metabolism of brain cells, and causes cytotoxic cerebral edema and acute or chronic traumatic encephalopathy as well as neuropsychiatric damage\[5\].

Based on the time of onset, patients with OTCD are divided into neonatal onset and late onset (age of onset > 28 d) groups\[6\]. Enzyme activity between the two groups is notably different. In the neonatal onset group, enzyme activity is completely reduced, and in the late onset group, enzyme activity is partially reduced. Most patients with neonatal-onset OTCD are males with hemizygous variants\[7\]. They demonstrate no symptoms at birth but gradually refuse to feed and begin to exhibit symptoms of vomiting, irritability, hyperventilation, and lethargy within a few hours to days after birth. Onset is sudden with rapid and complex clinical features, such as convulsions, coma, hypothermia, and respiratory failure\[8\]. Due to the lack of specificity in clinical features, patients are often misdiagnosed with neonatal sepsis, neonatal hypoxic-ischemic encephalopathy, birth injury, food poisoning, acute gastroenteritis, encephalitis, epilepsy, encephalopathy combined with visceral steatosis (Wright's syndrome), neurodegenerative disease, or schizophrenia. Elevated ammonia in the blood is a main abnormal indicator in patients with OTCD, and OTC gene variants are another crucial factor in the diagnosis of OTCD\[9\]. To date, over 530 variants in the OTC gene have been reported, but no hotspot mutations have been found. Therefore, the collection of as many pathogenic variants as possible is important for clinical diagnosis and screening.

This study involved a male neonate with a pathogenic variant in OTC. We comprehensively investigated the clinical features and enzymatic activity through genetic testing.

CASE PRESENTATION

Chief complaints

A five-day-old boy who did not feed and showed no movement or responsiveness was referred to our department for further treatment.
**History of present illness**
The proband was delivered via cesarean section due to "fetal distress" at 40 wk. There was no meconium-stained amniotic fluid, no abnormalities in the umbilical cord, and no premature rupture of membranes. His birth weight was 2350 g, and his Apgar score was normal. He was diagnosed as a "low birth weight infant with gastrointestinal bleeding" and showed improvement after unknown treatment. The amount of ordinary formula milk fed was increased gradually until he consumed 30 mL of milk at each feeding. Five days later, he stopped feeding, showed no movement, and exhibited poor responsiveness, which was accompanied by an abnormal increase in muscle tone, shortness of breath, moaning, foaming at the mouth, screaming, pumping, vomiting, abdominal distention, and blood in the stool.

**Physical examination**
Physical examination revealed a low body temperature (35 °C), low blood pressure (35/15 mmHg), bradycardia (97/min), and lack of spontaneous breathing.

**Laboratory examinations**
The final blood glucose level of the patient was 2.6 mmol/L. He had high blood ammonia [461.0 μmol/L (ref: 18–72)], high lactic acid [10.80 mmol/L (ref: 1.06–2.09)], and high homocysteine [29.21 μmol/L (ref: < 15)] levels (Table 1).

A hemizygous variant in the OTC [NM_000531.5, c.970_979delTTCCCAGAGG, p.Phe324GlnfsTer16] gene was identified by exome sequencing. The variant caused a 10-bp deletion and early translation termination in the OTC gene. Sanger sequencing confirmed that this variant was inherited from his mother (Figure 1). The variant was absent in public databases (gnomAD, Exome Aggregation Consortium, or 1000 Genomes). The variant was classified as likely pathogenic according to the ACMG guidelines (Table 2). Pathogenic variants in other genes associated with hyperammonemia have not yet been identified. We reported this variant in the ClinVar database (accession number: VCV001256051).

**FINAL DIAGNOSIS**
The male infant patient was diagnosed with OTCD caused by an OTC mutation.

**TREATMENT**
After admission, we ensured that the patient’s airway was unblocked, warmed the body, monitored vital signs, assisted breathing with the use of a ventilator, and corrected the blood pH with the administration of sodium bicarbonate. Meropenem and penicillin were utilized to combat infection, phenobarbital for spasms, dopamine for circulation, and 10% glucose to maintain the stability of the internal environment.

Arginine was used to reduce blood ammonia, and levocarnitine was used to promote metabolism. Lidocaine was used for nonparoxysmal ventricular arrhythmia, which was indicated by an electrocardiogram.

**OUTCOME AND FOLLOW-UP**
The patient remained in a coma since admission with weak heart sounds. After active rescue and treatment, the patient’s condition remained critical, with no remission or spontaneous breathing. His blood pressure, oxygen saturation, and heart rate were unstable; there was no response to stimulation. The patient was still in a coma when discharged and died soon after.

**DISCUSSION**
OTCD diagnosis is mainly based on clinical symptoms, blood ammonia levels, and other general biochemical tests, such as blood amino acids, urine organic acids, and genetic tests. For suspected cases, such as those in which patients present intermittent or progressive encephalopathy and high blood ammonia levels with unknown causes,
Table 1 Main clinical examination results of proband

<table>
<thead>
<tr>
<th>Item</th>
<th>Result</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature</td>
<td>35 ℃</td>
<td>36-37 ℃</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>35/15 mmHg</td>
<td>66-75/45 mmHg</td>
</tr>
<tr>
<td>Heart rate</td>
<td>97/min</td>
<td>120-140/min</td>
</tr>
<tr>
<td>Blood ammonia</td>
<td>461.0 μmol/L</td>
<td>18-72 μmol/L</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>10.80 mmol/L</td>
<td>1.06-2.09 mmol/L</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>29.21 μmol/L</td>
<td>&lt; 15 μmol/L</td>
</tr>
</tbody>
</table>

Table 2 Classification of the variants in OTC according to ACMG

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Inheritance</th>
<th>MAF</th>
<th>SIFT</th>
<th>Polyphen2</th>
<th>Mutation taster</th>
<th>Evidence</th>
<th>ACMG category</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTC</td>
<td>c.970_979del</td>
<td>Hemi</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>-</td>
<td>PS2 + PM2, supporting + PP3</td>
<td>Likely pathogenic</td>
</tr>
<tr>
<td></td>
<td>TTCCAGAGG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Transcript: NM_000531.5; MAF: Minor allele frequency; NE: Not existing.

Figure 1 The genogram of proband and parents. A: Mutation analysis of the OTC gene; B: The father was hemizygous for OTC, the mother and sister were heterozygous for OTC, and the proband was hemizygous for OTC. The red arrow represents the mutation site.

blood amino acid analysis and urine organic acid analysis should be performed as early as possible. If blood citrate is reduced or normal and urine whey acid or uracil is increased[9], OTCD diagnosis can be confirmed by combining these results with genetic testing. For neonates whose blood amino acid screening by tandem mass spectrometry indicates reduced citrulline levels, dynamic observation should be carried out, and urine organic acid and genetic tests should be performed.

The clinical symptoms and related examinations of OTCD patients lack specificity and should be differentiated from those of hyperammonemia caused by other factors, including different ornithine circulatory disorders; miscellaneous genetic metabolic diseases, including organic acid hematic disease, fatty acid oxidation disorder, beta oxygen defects, high insulin, and hepatic encephalopathy; severe liver damage; exogenous toxicity (e.g., carbamidine); and drugs (e.g., valproic acid). All these factors can elevate blood ammonia levels and should be identified according to the patient’s medical history and clinical symptoms[9]. Genetic testing of the OTC gene is another crucial factor in the diagnosis of this disease.
Liver transplantation is regarded as an effective treatment for OTCD. For patients with neonatal onset, liver transplantation should be performed at the earliest identification of disease. Surgery is recommended between three months (and/or body weight > 5 kg) and one year[9]. Once OTCD is suspected, clinical examinations for blood ammonia, blood amino acids, and urine organic acids should be performed rapidly in a specialized metabolic laboratory. Our case shows high blood ammonia [461.0 μmol/L (ref: 18-72)], high lactic acid [10.80 mmol/L (ref: 1.06-2.09)], and high homocysteine [29.21 μmol/L (ref: < 15)] levels. After interpreting the sequencing results, we confirmed the diagnosis of OTCD in this patient.

Genetic testing is a crucial method for the diagnosis of OTCD. As a routine practice of next-generation sequencing (NGS), high-throughput sequencing will rapidly uncover many pathogenic variants in neonates who are suspected to have OTCD with abnormal hyperammonemia. Array CGH or multiplex ligation-dependent probe amplification fails to detect OTC gene deficiency in SNVs or microinsertions and deletions in patients[10,11], whereas NGS has the advantage of detecting these variations. Our study uncovered an unreported variant in the OTC gene [NM_000531.5, c.970_979delTTCCCAGAGG, p.Phe324Glnfs*16], which caused the early termination of OTC. Our results provide a reference for the accurate diagnosis of patients with the same variant. A previous study reported that approximately 15% of female carriers become symptomatic[12]. Our findings also suggest heterozygote detection of at-risk female relatives as a promising direction for further investigation.

CONCLUSION

In our case study of one individual, a rare variant in the OTC gene was identified and confirmed by Sanger sequencing. This finding broadens the OTC variant spectrum and provides evidence for further OTCD screening and clinical consultation.

ACKNOWLEDGEMENTS

We thank the patient's family members for their participation in this study.

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Langerhans cell histiocytosis presenting as an isolated brain tumour: A case report

Han-Xiang Liang, Yue-Long Yang, Qing Zhang, Zhi Xie, En-Tao Liu, Shu-Xia Wang

Abstract

BACKGROUND
Langerhans cell histiocytosis (LCH) is a rare proliferative histiocyte disorder. It can affect any organ or system, especially the bone, skin, lung, and central nervous system (CNS). In the CNS, the hypothalamic-pituitary is predominantly affected, whereas the brain parenchyma is rarely affected. LCH occurring in the brain parenchyma can be easily confused with glioblastoma or brain metastases. Thus, multimodal imaging is useful for the differential diagnosis of these intracerebral lesions and detection of lesions in the other organs.

CASE SUMMARY
A 47-year-old man presented with a headache for one week and sudden syncope. Brain computed tomography (CT) and magnetic resonance imaging showed an irregularly shaped nodule with heterogeneous enhancement. On 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/CT, a nodule with 18F-FDG uptake and multiple cysts in the upper lobes of both lungs were noted, which was also confirmed by high-resolution CT. Thus, the patient underwent surgical resection of the brain lesion for further examination. Postoperative pathology confirmed LCH. The patient received chemotherapy after surgery. No recurrence was observed in the brain at the 12-mo follow-up.
CONCLUSION
Multimodal imaging is useful for evaluating the systemic condition of LCH, developing treatment plans, and designing post-treatment strategies.

Key Words: Langerhans cell histiocytosis; Brain neoplasms; Lung; Computed tomography; Magnetic resonance imaging; Positron emission tomography/computed tomography; Case report

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Core Tip: Langerhans cell histiocytosis (LCH) is a rare hematological disease characterized by a clonal proliferation of abnormal langerhans cells. It can affect any organ or system, especially the bone, skin, lung, and central nervous system (CNS). In the CNS, the hypothalamic-pituitary is predominantly affected, whereas the brain parenchyma is rarely affected. Cases of LCH involving the brain parenchyma and presenting as an isolated brain tumour have been reported, but all the reports lack complete multimodal imaging. In this manuscript, we have reported a case of LCH involving the brain parenchyma and bilateral lungs, which was assessed using computed tomography (CT), high-resolution CT, magnetic resonance imaging, and 18F-fluorodeoxyglucose positron emission tomography/CT. Furthermore, we have reviewed the relevant literature.

INTRODUCTION
Langerhans cell histiocytosis (LCH) is an uncommon disease characterized by clonal proliferation of myeloid precursors that differentiate into cluster of differentiation (CD)1a+/CD207+ (Langerin) cells in lesions[1,2]. It mainly affects children, with a reported incidence of 4-5 cases per million children aged < 15 years per year, while its incidence in adults is uncertain[3]. LCH may affect any organ or system, but it most frequently affects the bone, skin, pituitary, liver, spleen, hematopoietic system, lung, lymph nodes, and central nervous system (CNS)[4,5]. Cases of LCH involving the brain parenchyma and presenting as an isolated brain tumour have been reported, but all the reports lack complete multimodal imaging. Herein, we have reported a case of LCH involving the brain parenchyma and bilateral lungs, which was assessed using computed tomography (CT), high-resolution CT (HRCT), magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT. Furthermore, we have reviewed the relevant literature.

CASE PRESENTATION

Chief complaints
A 47-year-old man was referred to our hospital with a headache for one week and sudden syncope in the morning.

History of present illness
A 47-year-old man was referred to our hospital with a headache for one week and sudden syncope in the morning.

History of past illness
The patient had no history of polyuria or polydipsia. No other illnesses were observed.
**Personal and family history**
The patient had no known comorbidities or family history, but had a 15-year smoking history.

**Physical examination**
No rash or positive neurological signs were found on physical examination.

**Laboratory examinations**
Laboratory tests results showed increased in carcinoembryonic antigen (CEA) levels (7.03 ng/mL, reference: 0-5 ng/mL), with no other abnormal findings.

**Imaging examinations**
Non-contrast brain CT showed irregularly shaped nodular foci with isodensity at the left frontal corticomedullary junction. Large patches of hypodense edema were noted in the adjacent white matter (Figure 1A and B represent the lateral ventricular and basal ganglia levels, respectively). Contrast-enhanced brain CT showed significant heterogeneous enhancement in the left frontal foci (Figure 1C and D, the same level as the Figure 1A and B). Coronal and sagittal views of contrast-enhanced CT images showed irregular morphology of the lesion and poor demarcation with the adjacent skull (Figure 1E and F). Bone window CT showed no abnormalities in the adjacent skull (Figure 1G and H, the same level as the Figure 1E and F). Subsequently, the patient underwent a brain MRI. Axial T1-weighted images (T1WI) showed heterogeneous hypointense lesions in the left frontal lobe (Figure 2A). Axial T2-weighted images (T2WI) showed a heterogeneously mixed hyperintensity signals with hypointense areas in the left frontal lobe lesion (Figure 2B). After administration of gadolinium, the lesion showed heterogeneous enhancement on axial (Figure 2C), coronal (Figure 2D), and sagittal T1WI (Figure 2E). No abnormalities were found on sagittal T1WI of the sellar region (Figure 2F).

Considering the elevated CEA levels and CT and MRI manifestations, further investigation was required to rule out brain metastases. Therefore, 18F-FDG PET/CT was performed. Maximum-intensity-projection imaging showed a focal increase in 18F-FDG uptake in the right maxillary sinus and multiple foci of increased 18F-FDG uptake in the bilateral lung fields (Figure 3A). Axial (Figure 3B-D) and coronal (Figure 3E-G) views of the selected PET, non-enhanced CT (NE-CT), and fused PET/CT images showed moderately increased 18F-FDG uptake in the left frontal nodule [the maximum standardized uptake value (SUVmax) of the lesions and surrounding tissues are shown in Supplementary Figure 1]. No abnormal 18F-FDG uptake was observed in the sellar region (Supplementary Figure 2). Axial (Figure 3H-J) views of the selected PET, NE-CT, and fused PET/CT images showed multiple cysts with peripheral exudation in the upper lobes of bilateral lungs, with slightly increased 18F-FDG uptake. HRCT was performed to further evaluate the pulmonary lesions. Axial (Figure 4A), coronal (Figure 4B), and sagittal (Figure 4C and D, left and right lungs, respectively) views of HRCT images showed multiple scattered small thick-walled irregular cysts and small nodules. Sinusitis was diagnosed in the right maxillary sinus. Bilateral lung manifestations should be differentiated from pulmonary LCH, but brain nodules are more difficult to diagnose and should be differentiated from gliomas.

**Further diagnostic work-up**
The patient underwent brain tumour resection. Gross examination showed that the specimen was a grey-brown solid tumour (Figure 5A) and the cut surface was grey-brown and grey-white (Figure 5B). Histopathological examination revealed mononucleated and multinucleated histocytes with abundant cytoplasm and slight staining (haematoxylin and eosin, magnification, × 200; Figure 5C). On immunohistochemistry, the specimen stained positive for S100, CD207 (Langerin), CD4, and CD1a, and negative for CD3 and CD20. Ki67 (MIB-1) index was slightly > 30%.

**FINAL DIAGNOSIS**
The final histological diagnosis was LCH.
Figure 1 Brain computed tomography. A and B: Represent the lateral ventricular and basal ganglia levels on non-contrast computed tomography (CT), respectively. An irregularly shaped nodule is observed in the left frontal lobe with large perifocal low-density oedema; C and D: Represent the same level as the former on contrast-enhanced CT. The nodules are significantly enhanced heterogeneously; E and F: Represent the coronal and sagittal views of the contrast-enhanced CT; G and H: Represent the same level as the former, with no abnormalities in the adjacent skull. CT: Computed tomography.

Figure 2 Brain magnetic resonance imaging. A: Axial T1-weighted images (T1WI) show heterogeneous hypo-intensity of the left frontal lobe lesion; B: Axial T2-weighted images (T2WI) show heterogeneously mixed signal of hyperintensity with hypointense areas of the left frontal lobe lesion; C-E: Axial, coronal, and sagittal views of T1WI with contrast agent administration show heterogeneous enhancement of the lesion; F: Sagittal T1WI show no abnormality in the sellar region. T1WI: T1-weighted images; T2WI: T2-weighted images.
Liang HX et al. LCH in the frontal lobe

**TREATMENT**

The patient received chemotherapy (vinodesine and prednisone acetate) after surgery.

**OUTCOME AND FOLLOW-UP**

No recurrence was observed on brain MRI at the 12-mo follow-up (Supplementary Figure 3).

**DISCUSSION**

LCH involving the hypothalamic-pituitary or skull is not uncommon, but involvement of the brain parenchyma, such as the frontotemporal lobe, is rare. As of January 2019, fewer than 30 cases have been reported in the PubMed database (Table 1)[6-8]. We reviewed the relevant PubMed literature from 1990 to May 2021 and found 16 cases of brain parenchymal LCH with imaging data. The mean age was 31 years (95% confidence interval: 21.5-41.2). The male-to-female ratio was 14:2, which is consistent with that reported in previous literature reviews of intracerebral LCH, but higher than that in children with LCH[3,8,10]. The lesions were mostly located in the frontotemporal lobe (14 cases), particularly in the frontal lobe. The clinical presentation of LCH is non-characteristic and varies depending on the site. Most cases showed non-specific symptoms of mass effect such as headache, seizures, hemiparesis, and/or sensory disturbances. MRI findings without contrast were also largely non-specific.
## Table 1 Summary of 16 cases with brain parenchymal langerhans cell histiocytosis with imaging data

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Age/sex</th>
<th>Diameter (cm)</th>
<th>Location (Lobe)</th>
<th>MRI Finding</th>
<th>¹⁸F-FDG PET/CT finding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T1WI</td>
<td>T2WI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Careoso et al [24], 1991</td>
<td>29/Male</td>
<td>3.0</td>
<td>Right temporal lobe</td>
<td>Hypointense</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Itoh et al [21], 1992</td>
<td>7/Male</td>
<td>NA</td>
<td>Right frontal lobe</td>
<td>Hypo-/iso-intense</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Bogaert et al [22], 1994</td>
<td>40/Female</td>
<td>NA</td>
<td>Left parietal lobe</td>
<td>Hypointense</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Vital et al [23], 1996</td>
<td>32/Female</td>
<td>NA</td>
<td>Right insula lobe</td>
<td>NA</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Grant et al [24], 1999</td>
<td>20/Male</td>
<td>3.5</td>
<td>Right temporal lobe</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Katasi et al [25], 2002</td>
<td>36/Male</td>
<td>NA</td>
<td>Left temporal lobe</td>
<td>Hypointense</td>
<td>NA</td>
</tr>
<tr>
<td>Cagli et al [9], 2004</td>
<td>24/Male</td>
<td>1.5</td>
<td>Left temporal lobe</td>
<td>Hypointense</td>
<td>NA</td>
</tr>
<tr>
<td>Yamaguchi et al [26], 2004</td>
<td>2/Male</td>
<td>NA</td>
<td>Multiple lesions/bilateral frontal and temporal lobes</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rodriguez-Pereira et al [10], 2005</td>
<td>30/Male</td>
<td>5.0</td>
<td>Left frontal lobe</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rodriguez-Pereira et al [10], 2005</td>
<td>65/Male</td>
<td>2.5</td>
<td>Left parietal lobe</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dierer[27], 2017</td>
<td>4/Male</td>
<td>2.0¹</td>
<td>Multiple lesions, right frontal, and parietal lobe</td>
<td>Iso-/hyper-intense</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Cai et al [6], 2014</td>
<td>23/Male</td>
<td>4.1</td>
<td>Right frontal lobe</td>
<td>Hypo-/iso-intense</td>
<td>Iso-/hyper-intense</td>
</tr>
<tr>
<td>Dardis et al [28], 2015</td>
<td>64/Male</td>
<td>NA</td>
<td>Multiple lesions, left frontal and right temporal lobe, and brainstem</td>
<td>NA</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Kim et al [7], 2018</td>
<td>36/Male</td>
<td>3.0</td>
<td>Right frontal lobe</td>
<td>Isointense</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Bärtschi et al [8], 2019</td>
<td>42/Male</td>
<td>NA</td>
<td>Right insular lobe</td>
<td>NA</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Current case</td>
<td>47/Male</td>
<td>3.6</td>
<td>Left frontal lobe</td>
<td>Hypointense</td>
<td>Hyperintensity</td>
</tr>
</tbody>
</table>

¹The largest lesion.
NA: Not available; PET: Positron emission tomography; CT: Computed tomography; T1WI: T1-weighted images; T2WI: T2-weighted images; MRI: Magnetic resonance imaging.

Nonetheless, MRI showed hypointensity on T1WI and hyperintensity on T2WI in most cases. After administration of gadolinium, most cases showed intense homogeneous or heterogeneous enhancement. Another characteristic feature is sulcal enhancement around the lesion[6,7]. MRI images showed leptomeningeal involvement near the lesions in several cases, as reported by Kim et al [7]. This may be a characteristic sign of brain parenchymal LCH, but it needs to be confirmed in more cases.

There are no previous reports of ¹⁸F-FDG PET/CT for assessing the metabolic activity of brain parenchymal LCH. To our knowledge, our case report is the first with a PET/CT description. The SUVmax of the brain lesion was approximately 9.5, which was similar to the SUVmax of LCH lesions involving other regions reported in the literature[11]. Additional bilateral lung lesions were found, and pulmonary manifestations were decisive for diagnosis[12]. As 30% patients with LCH present with multi-organ system involvement, it is important to detect involvement of other tissues (such as the bone, soft tissue, the CNS, or the lungs)[3,13]. Single or isolated brain lesions
Figure 4 High-resolution computed tomography of the lung. Axial, coronal, and sagittal (the left and right lungs, respectively) views of high-resolution computed tomography images show multiple scattered small thick-walled irregular cysts as well as small nodules. A: Axial; B: Coronal; C: Left lungs; D: Right lungs.

Figure 5 Histopathological images. A: The specimen is a greyish brown and greyish dark solid tumour; B: The cut surface is greyish brown and greyish white; C: Histopathological examination reveals mononucleated and multinucleated histocytes with abundant cytoplasm and light staining (haematoxylin and eosin, magnification, $\times$ 400).

have previously been reported based on only brain CT or MRI, without whole-body scans[6,7]. Without whole-body evaluation, reports of isolated brain lesions may be non-rigorous or biased. More recent studies that performed whole-body evaluations have identified a higher rate of focal LCH lesions than that previously reported[14,15]. Therefore, PET/CT or PET/MRI seems to be more appropriate for evaluating this disease[16]. This is especially true for combined bone and lung lesions as some case without obvious symptoms are incidentally detected; they may be missed by relying solely on radiography or CT[8]. Several studies have confirmed the diagnostic value of systemic scans, such as PET/CT or PET/MRI for LCH[14,15,17,18]. The diagnostic evaluation of LCH plays a crucial role in treatment planning. PET/CT or PET/MRI can be used to assess multiple foci throughout the body, guide biopsy sites, and assist with post-treatment strategies.

Based on prospective trials, the combination of vinblastine plus prednisolone is the most commonly used induction chemotherapy regimen and is administered over six weeks[19].

CONCLUSION

As a systemic disease, LCH has the potential to involve the brain parenchyma, and its diagnosis is extremely challenging. The use of multimodal imaging or whole-body imaging, combined with the manifestation of lesions at other sites, can be helpful in the diagnosis of this disease. Moreover, multimodality imaging is useful for assessing the systemic status of LCH, developing treatment plans, and evaluating post-treatment strategies.

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Liang HX et al. LCH in the frontal lobe


Inflammatory myofibroblastic tumor after breast prosthesis: A case report and literature review

Peng Zhou, Yi-Hao Chen, Jiang-Hao Lu, Chun-Chun Jin, Xiao-Hong Xu, Xue-Hao Gong

BACKGROUND
Inflammatory myofibroblastic tumors (IMTs) are defined as tumors composed of differentiated myofibroblastic spindle cells, usually accompanied by numerous plasma cells and lymphocytes, and classified as intermediate (occasionally metastatic) by the World Health Organization. Its pathogenesis and biological behavior have not yet been elucidated. Breast IMT is extremely rare, and prosthesis implantation combined with IMT has not been reported. This study reports a case of IMT following resection of a malignant phyllodes tumor of the left breast and implantation of a prosthesis.

CASE SUMMARY
A 41-year-old female presented to our hospital with a mass in the left breast for 3 mo. The patient had undergone resection of a large mass in her left breast pathologically diagnosed as a malignant phyllodes tumor and implantation of a prosthesis five years prior. Ultrasonic examination revealed an oval mass in the left breast, and the patient underwent left breast mass resection and prosthesis removal. Light microscopy revealed the spindle cells to be diffusely proliferated, with a large number of neutrophil, lymphocytes, and plasma cell infiltration. Immunohistochemical staining revealed that the spindle cells were positive for smooth muscle actin, which is positive for BCL-2 and cluster of differentiation (CD) 99 but were negative for anaplastic lymphoma kinase, cytokeratin, S-100 protein, desmin, and CD34. The final diagnosis was IMT. No recurrence or metastasis was observed during the 5-year postoperative follow-up.
CONCLUSION
Prosthesis implantation may be one of the causes of IMT, but further investigation is necessary to prove it.

Key Words: Inflammatory myofibroblastic tumor; Breast; Prosthesis; Ultrasonography; Surgery; Case report

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Core Tip: We believe that our study makes a significant contribution to the literature because inflammatory myofibroblastic tumors (IMTs) of the breast are rare and unique; however, whether they are reactive or neoplastic in nature remains unelucidated. This case presented the opportunity to review studies regarding cases of inflammatory myofibroblastic breast tumors and determine whether they are reactive lesions due to an exaggerated response to tissue injury or indicate a true neoplastic process. This report prompts that prosthesis implantation may cause IMT.

INTRODUCTION
Inflammatory myofibroblastic tumors (IMTs) are rare lesions of mesenchymal origin, with a global incidence of approximately 0.04%–0.7%[1]. They primarily occur in the lungs, abdomen, pelvis, and retroperitoneum of adolescents. Unlike IMTs in other organs, most breast IMTs occur in middle-aged women > 40 years old[2]. Although reported in various organs, the occurrence of IMT in the breast is rare, and to the best of our knowledge, only 35 cases have been reported. Herein, we report a case of IMT following resection of a malignant phyllodes tumor of the left breast and implantation of a prosthesis. In addition, we review current studies on breast IMT.

CASE PRESENTATION

Chief complaints
A 41-year-old female had a mass in the left breast for 3 mo.

History of present illness
During the 3 mo, the breast mass had slowly enlarged, but the patient did not have clinical symptoms, such as fever and pain.

History of past illness
The patient had undergone implantation of a prosthesis five years prior and resection of a large mass in her left breast, pathologically diagnosed as a malignant phyllodes tumor.

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

Physical examination
Physical examination revealed an abnormal shape of the left breast and prosthesis, which was palpable. Additionally, an approximately 4 cm × 3 cm non-tender mass, with a clear boundary and poor activity, was identified at the 9 o’clock position.
Laboratory examinations
No abnormalities were found in the patient’s laboratory examinations.

Imaging examinations
Ultrasonic examination (Esaote M7, Genova, Italy) revealed an oval, hypoechoic mass (approximately 4.2 cm × 1.8 cm in size) with clear borders and smooth edges at the 9 o’clock position in the left breast that is 3.5 cm from the nipple. Internal echo was heterogeneous, with scattered small fleck echo and slightly enhanced rear echo. A disc-shaped anechoic area was observed behind the left breast, with good internal sound transmission. Color Doppler flow imaging (CDFI) indicated a limited blood flow signal within the hypoechoic mass (Figure 1).

FINAL DIAGNOSIS
The diagnosis was IMT.

TREATMENT
The patient underwent left breast mass resection and prosthesis removal in our hospital due to the abnormal shape of the left breast and the large mass. Specimens mainly included the breast glandular tissue, tumor tissue, prosthesis, spindle-shaped flap, and nipple (Figure 2). A complete prosthesis was identified behind the breast tissue, with a knot observed under the skin 3.5 cm from the nipple section (2.5 cm × 2.5 cm × 1.5 cm), which was gray-red and soft, with missing central tissue. Light microscopy revealed that the spindle cells to be diffusely proliferated, irregularly arranged, and scattered in the nucleus. Additionally, mildly atypical cells, mitosis, interstitial vascular proliferation, and dilation and congestion with hemorrhage were evident, as well as a large number of neutrophils and lymphocytes and plasma cell infiltration (Figure 3). Immunohistochemical staining revealed that the spindle cells were partially positive for smooth muscle actin (SMA), positive for BCL-2 and cluster of differentiation (CD) 99 but were negative for anaplastic lymphoma kinase (ALK), cytokeratin (CK), S-100 protein, desmin, and CD34. The Ki-67 score was approximately 5%, which is atypical for an IMT (Figure 4).

OUTCOME AND FOLLOW-UP
The patient was followed up every year. Each follow-up examination included a physical examination, a chest X-ray, a breast ultrasound (US), an abdominal US, and a routine blood examination. During the 5-year postoperative follow-up, the patient had no symptoms or imaging evidence of recurrence or metastasis.

DISCUSSION
IMTs of the breast are rare and unique; however, whether they are reactive or neoplastic in nature remains unelucidated. IMTs were widely considered inflammatory lesions and have been referred to as inflammatory pseudotumors, plasma cell granulomas, fibrous xanthomas, and inflammatory myofibrohistiocytic proliferation. Conversely, cases of local recurrence and metastasis have challenged the theory of reactive post-inflammatory lesions. As proven through cytogenetic analysis, approximately 50% of IMTs are positive for rearrangements involving the ALK gene, while cytogenetic abnormalities support the neoplastic nature of IMTs[3]. Nevertheless, the pathogenesis of ALK-negative IMT remains controversial. These lesions might not undergo gene rearrangements and might be caused by trauma, surgery, infection, or other factors that cause excessive inflammation in human tissues, which activate the abnormal proliferation of myofibroblasts[4].

Among the 35 cases of breast IMT reported in the literature, all but one occurred in females[5]. The patients’ ages ranged from 13 to 86 years, with a mean age of 47.1 years (Table 1). In our case, the patient was a 41-year-old middle-aged woman who sought medical attention due to a palpable mass. Retrospective analysis of the
Table 1 Literature reports on breast inflammatory myofibroblastic tumor

<table>
<thead>
<tr>
<th>No.</th>
<th>Ref.</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>ALK</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pettinato et al[18]</td>
<td>1988</td>
<td>29</td>
<td>F</td>
<td>Right</td>
<td>NED</td>
<td>30 mo</td>
</tr>
<tr>
<td>2</td>
<td>Coffin et al[19]</td>
<td>1995</td>
<td>13</td>
<td>F</td>
<td>Right</td>
<td>NED</td>
<td>12 mo</td>
</tr>
<tr>
<td>3</td>
<td>Chetty et al[20]</td>
<td>1997</td>
<td>16</td>
<td>F</td>
<td>Right</td>
<td>NED</td>
<td>12 mo</td>
</tr>
<tr>
<td>4</td>
<td>Chetty et al[20]</td>
<td>1997</td>
<td>46</td>
<td>F</td>
<td>Right</td>
<td>NED</td>
<td>12 mo</td>
</tr>
<tr>
<td>5</td>
<td>Chetty et al[20]</td>
<td>1997</td>
<td>18</td>
<td>F</td>
<td>Right</td>
<td>NED</td>
<td>6 mo</td>
</tr>
<tr>
<td>6</td>
<td>Yip et al[12]</td>
<td>1997</td>
<td>66</td>
<td>F</td>
<td>Bilateral</td>
<td>Bilateral recurrence at 5th month; after second excision NED 9 mo</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Gobbi et al[21]</td>
<td>1999</td>
<td>86</td>
<td>F</td>
<td>Left</td>
<td>NA</td>
<td>NED</td>
</tr>
<tr>
<td>8</td>
<td>Sastre et al[22]</td>
<td>2002</td>
<td>64</td>
<td>F</td>
<td>Right</td>
<td>Neg</td>
<td>NED, 33 mo</td>
</tr>
<tr>
<td>9</td>
<td>Haj et al[23]</td>
<td>2003</td>
<td>31</td>
<td>F</td>
<td>Right</td>
<td>NA</td>
<td>NED</td>
</tr>
<tr>
<td>11</td>
<td>Ilvan et al[24]</td>
<td>2005</td>
<td>60</td>
<td>F</td>
<td>Right</td>
<td>NED</td>
<td>85 mo</td>
</tr>
<tr>
<td>12</td>
<td>Khanafsa et al[13]</td>
<td>2005</td>
<td>33</td>
<td>F</td>
<td>Left</td>
<td>Neg</td>
<td>Recurrence at 3 mo; after second excision, 12 mo</td>
</tr>
<tr>
<td>13</td>
<td>Khanafsa et al[13]</td>
<td>2005</td>
<td>75</td>
<td>F</td>
<td>Left</td>
<td>Neg</td>
<td>NED, 14 mo</td>
</tr>
<tr>
<td>15</td>
<td>Zen et al[25]</td>
<td>2005</td>
<td>46</td>
<td>F</td>
<td>Left</td>
<td>Neg</td>
<td>NED, 12 mo</td>
</tr>
<tr>
<td>16</td>
<td>Akbulut et al[6]</td>
<td>2007</td>
<td>38</td>
<td>F</td>
<td>Left</td>
<td>Neg</td>
<td>NED, 12 mo</td>
</tr>
<tr>
<td>17</td>
<td>Kim et al[26]</td>
<td>2009</td>
<td>60</td>
<td>F</td>
<td>Left</td>
<td>Neg</td>
<td>NED, 24 mo</td>
</tr>
<tr>
<td>18</td>
<td>Park et al[27]</td>
<td>2010</td>
<td>47</td>
<td>F</td>
<td>Right</td>
<td>NED</td>
<td>36 mo</td>
</tr>
<tr>
<td>19</td>
<td>Hill et al[28]</td>
<td>2010</td>
<td>53</td>
<td>F</td>
<td>Right</td>
<td>Neg</td>
<td>NA</td>
</tr>
<tr>
<td>20</td>
<td>Vecchio et al[5]</td>
<td>2011</td>
<td>22</td>
<td>M</td>
<td>Left</td>
<td>Neg</td>
<td>NA</td>
</tr>
<tr>
<td>21</td>
<td>Zhou et al[17]</td>
<td>2013</td>
<td>46</td>
<td>F</td>
<td>Right</td>
<td>Pos</td>
<td>NED</td>
</tr>
<tr>
<td>22</td>
<td>Li et al[29]</td>
<td>2013</td>
<td>39</td>
<td>F</td>
<td>Left</td>
<td>Pos</td>
<td>NED, 5 years</td>
</tr>
<tr>
<td>23</td>
<td>Zhao et al[14]</td>
<td>2013</td>
<td>56</td>
<td>F</td>
<td>Right</td>
<td>Pos</td>
<td>Local recurrence and metastasis to left groin area</td>
</tr>
<tr>
<td>27</td>
<td>Choi et al[31]</td>
<td>2015</td>
<td>27</td>
<td>F</td>
<td>Right</td>
<td>Neg</td>
<td>NED, 12 mo</td>
</tr>
<tr>
<td>28</td>
<td>Greenleaf et al[32]</td>
<td>2016</td>
<td>69</td>
<td>F</td>
<td>Right</td>
<td>NA</td>
<td>NED, 8 mo</td>
</tr>
<tr>
<td>29</td>
<td>Goto et al[33]</td>
<td>2016</td>
<td>52</td>
<td>F</td>
<td>Left</td>
<td>Neg</td>
<td>NED, 9 mo</td>
</tr>
<tr>
<td>30</td>
<td>Talu et al[34]</td>
<td>2016</td>
<td>38</td>
<td>F</td>
<td>Left</td>
<td>Neg</td>
<td>NED, 16 mo</td>
</tr>
<tr>
<td>31</td>
<td>Mao et al[2]</td>
<td>2018</td>
<td>43</td>
<td>F</td>
<td>Left</td>
<td>Neg</td>
<td>NED, 12 mo</td>
</tr>
<tr>
<td>32</td>
<td>Inoue et al[35]</td>
<td>2018</td>
<td>16</td>
<td>F</td>
<td>Right</td>
<td>Pos</td>
<td>NED, 9 mo</td>
</tr>
<tr>
<td>33</td>
<td>Dani et al[36]</td>
<td>2018</td>
<td>73</td>
<td>F</td>
<td>Bilateral</td>
<td>Neg</td>
<td>NED, 7 years</td>
</tr>
<tr>
<td>34</td>
<td>Fernández et al[9]</td>
<td>2018</td>
<td>52</td>
<td>F</td>
<td>Right</td>
<td>Neg</td>
<td>NED, 8 mo</td>
</tr>
<tr>
<td>35</td>
<td>Lv et al[1]</td>
<td>2020</td>
<td>44</td>
<td>F</td>
<td>Right</td>
<td>Neg</td>
<td>NED, 4 mo</td>
</tr>
<tr>
<td>36</td>
<td>Present case</td>
<td>2021</td>
<td>41</td>
<td>F</td>
<td>Left</td>
<td>Neg</td>
<td>NED, 5 years</td>
</tr>
</tbody>
</table>

IMT: Inflammatory myofibroblastic tumor; F: Female; M: Male; Neg: Negative; Pos: Positive; NED: No evidence of disease; NA: Not available.

ultrasonograms revealed that the uneven, low echo in the mass was primarily related to the diffuse proliferation and irregular array of spindle cells in the tumor. Conversely, the scattered and small high echo could have been caused by considerable mixed acute and chronic inflammatory cell infiltration, while the spotty blood flow
Figure 1 Ultrasound manifestations of inflammatory myofibroblastic tumor. A: An oval, hypoechoic mass with clear borders of approximately 4.2 cm × 1.8 cm in size was identified at the 9 o’clock position in the left breast. The internal echo was heterogeneous, with scattered small fleck echo and slightly enhanced rear echo; B: Color Doppler flow imaging indicated limited blood flow signal within the hypoechoic mass.

Figure 2 Tumor and prosthesis in the left breast, with fusiform skin flap and nipple. A: A prosthesis was observed in the breast tissue, with a subcutaneous nodule identified 3.5 cm away from the nipple (arrow); B: The left breast mass was grayish red and soft, with partial tissue deletion.

Figure 3 Histopathological findings of inflammatory myofibroblastic tumor. A: Hematoxylin-eosin (HE) staining (magnification, × 100) revealed that the spindle cells were diffusely proliferated, irregularly arranged, and scattered in the nucleus, with mildly atypical cells, mitosis, interstitial vascular proliferation, and dilation and congestion with hemorrhage; B: HE staining (magnification, × 200) revealed that a large number of neutrophils and lymphocytes and plasma cell infiltration were observed.

Signal detected in the mass may be related to interstitial vascular hyperplasia with hemorrhage determined via light microscopy. The above-mentioned ultrasound manifestations lacked specificity; thus, it was difficult to distinguish them from those of phyllodes tumors or giant fibroadenomas. IMTs may also manifest with the imaging features of malignant tumors and show the diversity and lack of specificity in ultrasound imaging (Table 2). Furthermore, some scholars believe that the definitive diagnosis of IMT is difficult based on cytology alone. A reliable diagnosis may require histological samples because IMT cytology may mimic other benign or malignant
Table 2 Literature reports presenting ultrasonograms of Inflammatory myofibroblastic tumor of the breast

<table>
<thead>
<tr>
<th>No.</th>
<th>Ref.</th>
<th>Year</th>
<th>Ultrasonographic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Haj et al[23]</td>
<td>2003</td>
<td>Well-defined, homogeneous hypoechoic mass with an irregular border. No change in the rear echo.</td>
</tr>
<tr>
<td>2</td>
<td>Kim et al[26]</td>
<td>2009</td>
<td>Irregularly shaped, ill-defined, homogeneous hypoechoic mass, with anechogenic halo. CDFI: Moderate vascularity in the peripheral halo.</td>
</tr>
<tr>
<td>3</td>
<td>Park et al[27]</td>
<td>2010</td>
<td>Irregular, mostly hypoechoic, complex mass, with ill-defined margins and acoustic enhancement. CDFI: Increased vascular flow within the mass.</td>
</tr>
<tr>
<td>6</td>
<td>Choi et al[31]</td>
<td>2015</td>
<td>Irregularly shaped, microlobulated, and hypoechoic, with combined posterior features. CDFI: Increased vascular flow to the peripheral portion.</td>
</tr>
<tr>
<td>7</td>
<td>Inoue et al[35]</td>
<td>2018</td>
<td>Well-circumscribed, oval, and hypoechoic, with a central hyperechoic area.</td>
</tr>
<tr>
<td>8</td>
<td>Mao et al[2]</td>
<td>2018</td>
<td>Irregularly shaped with unclear boundaries; the internal echo was heterogeneous with a strong fleck echo evident. CDFI: Limited blood flow signal.</td>
</tr>
<tr>
<td>9</td>
<td>Present case</td>
<td>2021</td>
<td>Clear borders and smooth edges; the internal echo was heterogeneous, with scattered small fleck echo, and slightly enhanced rear echo. CDFI: Limited blood flow signal.</td>
</tr>
</tbody>
</table>

IMT: Inflammatory myofibroblastic tumor; CDFI: Color Doppler flow imaging.

Figure 4 Immunohistochemical staining. A: The cells were partially positive for smooth muscle actin (magnification, ×200); B: Negative for anaplastic lymphoma kinase (magnification, ×200).

breast lesions without specific features[6]. Therefore, the final diagnosis still requires postoperative histopathological examination.

This case is a patient we diagnosed and treated five years ago. Due to insufficient experience and inefficient equipment at the time, we only performed gray-scale ultrasound and CDFI on the patient, which was insufficient. In current practice, we will recommend contrast-enhanced ultrasound (CEUS) to patients with similar cases before surgery. CEUS as a pure blood pool phenomenon technology, especially the rapid development of high-frame-rate CEUS in recent years, can show the richness of the blood supply and the blood supply pattern of the tumor, which help differentiate benign and malignant tumors. In addition, CEUS can further clarify the boundary of the tumor and show whether the surrounding normal tissues have been invaded. If there is an invasion, it can show the range of invasion, which helps determine the scope of surgical resection and ensure that the resection margin is negative.

The patient had undergone prosthesis implantation in our hospital 5 years prior and resection of a large mass (approximately 10 cm × 10 cm × 5 cm in size) pathologically diagnosed as a malignant phyllodes tumor following a surgery in the left breast. Due to this history of phyllodes tumor, we first considered the possibility of lobular tumor recurrence. Histological analysis of phyllodes tumors indicates that they are typically arranged in a slit-like epithelial bilayer component rich in cells surrounding the mesenchymal overgrowth and interstitial inflammatory cell-free components. In the present embodiment, the optical microscope did not meet the performance; thus, phyllodes tumor recurrence may be excluded. Since metaplastic breast carcinoma...
appears similar to IMT under the light microscope, there is a marked difference in management and prognosis. Therefore, immunohistochemistry should be performed to rule out this possibility. Following an immunohistochemical assay, we found that the spindle cells were reactive for SMA, while the tumor cells were negative for CK, which ruled out the possibility of metaplastic carcinoma. Based on a comprehensive assessment of the patient history and histopathological and immunohistochemical results, IMT was considered the final diagnosis.

This case presented the opportunity to critically review the literature regarding the cases of breast IMTs (Table 1) to determine whether they are reactive lesions due to an exaggerated response to tissue injury or indicate a true neoplastic process. Although approximately half of all IMTs across anatomical sites undergo clonal rearrangements of the ALK gene on chromosome 2p23 activating ALK protein expression (Table 1), ALK overexpression in breast IMTs is rare. In this article, we discuss ALK-negative breast IMT especially its possible etiology of trauma and surgery, which could challenge the theory that the tumorigenic nature of chromosomal abnormalities supports IMTs. The patient had undergone left breast mass resection and prosthesis implantation due to a large malignant lobular tumor of the left breast. Moreover, newly developed IMT presented 5 years following surgery. Notably, most cases of breast IMT are spontaneous, and only a few cases that had a history of trauma and tumor resection before IMTs have been reported[3,5]. Vecchio et al[5] reported a male patient with breast IMT that had developed 4 mo following mechanical trauma; its location was consistent with the site of the trauma. Mao et al[2] reported a 43-year-old female who developed IMT 18 mo following resection of a left breast fibroadenoma. Both studies of Vecchio et al[5] and Mao et al[2] speculated that trauma and surgery could be important factors that promote the development of IMT. Moreover, Vecchio et al[5] reported that IMT was essentially reactive due to an absence of ALK expression and benign clinical behavior without any evidence of metastasis. IMT and inflammatory pseudotumors are thus different variants of the same disease[5]. Based on the view that chronic inflammation is considered the cause, we humbly propose a new viewpoint that prosthesis implantation also causes IMT.

Considering the origin cells of IMTs, myofibroblasts are mainly involved in the growth, repair, and scarring of normal tissue. An abnormal inflammatory response induces the over proliferation of myofibroblasts, thereby forming IMTs. In this case, a large number of acute and chronic inflammatory cells, such as neutrophils, lymphocytes, and plasma cells, were observed under the light microscope. We hypothesized that this abnormal inflammatory response could have been attributed to the surgical trauma caused by the resection of the large malignant tumor and the prolonged stimulation of the prosthesis as a foreign body. Previous studies reported that prosthesis implantation was closely related to the incidence of breast fibromatosis [7]. Notably, breast fibromatosis and IMT originate from myofibroblasts. In addition, this case and those reported by Vecchio et al[5] and Mao et al[2] were negative for ALK, indirectly indicating that ALK gene fusion may not have occurred. This supports the speculation that these mammary lesions are reactive in nature; however, through genetic testing, some studies have observed that ALK gene fusion can occur in very few ALK-negative IMTs from the lung[8]. Whether a similar phenomenon can occur in ALK-negative breast IMT has not been reported. Unfortunately, genetic testing was not performed in this case as ALK was not expressed, with no evidence to prove that ALK gene changes had occurred. While it can be inferred from Table 1 that ALK-negative IMT has almost no recurrence, whether ALK-negative expression is a good prognostic factor for IMT remains unelucidated[9].

The malignant potential of IMT is incompletely characterized. Radical resection is the preferred method of treatment for breast IMTs. Kovach et al[10] confirmed that the recurrence rate of the primary surgical approach was 8%. Moreover, if there are no contraindications related to patient anatomy or morbidity, surgical resection of all lesions is recommended. In our review of 35 cases of breast IMTs, all tumors were initially treated with surgery, and the outcome of most breast IMTs is favorable. Recurrences occurred in four cases[11-14], including two cases of bilateral metastasis [11,12]. In one case, local recurrence occurred, and metastasis to the groin area was confirmed[14]. In addition to surgery, some scholars believe that ALK-targeted inhibitors, such as crizotinib, are used to treat patients with metastatic or unresectable ALK-positive IMT and provide surgical opportunities[15]. Sporadic cases show that treatment with corticosteroids improves the outcome[16]; however, these results are still under discussion, whereas adjunctive therapy after surgery needs further clinical investigation. Although most patients achieved satisfactory results, follow-up remains essential. Notably, no clear molecular cytogenetics or clinical characteristics following resection could predict the risk of recurrence or metastasis[17]. Therefore, ultrasono-
graphy has great value in the timely detection of breast IMTs, preoperative lesion range determination, postoperative monitoring, and follow-up due to its convenience and radiation-free nature.

CONCLUSION
Breast IMT is extremely rare; prosthesis implantation may cause IMT, although further investigation is necessary to prove it. Its clinical manifestations lack specificity, and imaging manifestations are diverse. Therefore, Sonographers should perform a comprehensive analysis of the medical history for the diagnosis, especially in patients with pathogenic factors, such as trauma or prosthesis implantation surgery, the possibility of IMT should be considered. Radical resection and postoperative close follow-up are recommended, although the pathogenesis and biological behavior of IMT remain unelucidated.

REFERENCES

Zhou P et al. IMT after breast prosthesis


Eustachian tube involvement in a patient with relapsing polychondritis detected by magnetic resonance imaging: A case report

Daisuke Yunaiyama, Akiko Aoki, Hiroshi Kobayashi, Miwako Someya, Mitsuru Okubo, Kazuhiro Saito

Abstract

BACKGROUND
Relapsing polychondritis (RP) is a rare inflammatory disease involving the systemic cartilage, such as the auricle, trachea, and bronchiule, among others. A patient with RP shows variable symptoms based on the affected cartilage.

CASE SUMMARY
A 72-year-old Japanese woman with a history of redness of the bilateral auricles for 3 d was referred to a clinician. The clinician prescribed antibiotics to the patient; however, the symptoms worsened; thus, she was referred to our hospital. Head and neck magnetic resonance imaging (MRI) showed edematous auricle with remarkable contrast, fluid collection in the bilateral mastoid cells, suggesting otitis media. The eustachian tube (ET) on the right side was also edematous with contrast enhancement. The patient was suspected of RP according to the diagnostic criteria. A biopsy of the auricular cartilage was performed by an otorhinolaryngologist, confirming pathological proof of RP. Treatments with steroids were immediately administered thereafter.

CONCLUSION
We highlight a rare case of RP with radiologically confirmed involvement of ET in the MRI.
INTRODUCTION

Relapsing polychondritis (RP) is a rare autoimmune inflammatory disease of the systemic cartilages and proteoglycan-rich structures[1]. The real incidence and prevalence of RP are still unknown. The major inflammatory sites of this disease are the ears, nose, eyes, respiratory tract, and joints[2-5]. The clinical manifestations in the otological area are auricular chondritis, otitis externa, chronic myringitis, eustachian tube (ET) dysfunction, conductive or sensorineural hearing loss, dizziness, and tinnitus[6,7]. The cause of fluid collection in a middle ear of a patient with RP should be derived from ET dysfunction due to ET cartilage inflammation; however, no report has proven the inflammation of an ET itself radiographically. We hereby present a case of a patient with RP confirmed by biopsy of the auricular cartilage, manifesting the involvement of ET detected by magnetic resonance imaging (MRI).

CASE PRESENTATION

Chief complaints
A 72-year-old Japanese woman with a history of redness of the bilateral auricles for 3 d was referred to a clinician.

History of present illness
The clinician prescribed antibiotics to the patient (2 g in a day of cefminox sodium hydrate for 3 d); however, the symptoms worsened, and thus, the patient was referred to our hospital.

History of past illness
The patient’s medical history included hypertension, type 2 diabetes mellitus, lumbar disc hernia, postmenopausal osteoporosis, and reflux esophagitis.

Personal and family history
The patient had no family history of similar illnesses.

Physical examination
Her body temperature was 37°C. No abnormal chest sound was not heard; however, the patient was suffered from dry cough. Tender, erythematous and edematous bilateral auricles were observed (Figure 1A). Left conjunctival hyperemia was also
observed (Figure 1B). Additionally, trismus was observed, which resulted in mastication difficulty. A pure tone audiogram showed sensorineural hearing loss at the high sound area, and the patient complained of tinnitus. Nasal cartilage inflammation or dyspnea was not observed. The patient met four indices of McAdam’s criteria[8]. A tympanic membrane proliferation was not observed.

**Laboratory examinations**
White blood cell count of 14200/μL (segmented 77.8%), red blood cell count of 383 × 10^4 /μL, a hemoglobin level of 12.1 g/dL, platelet count of 29.8 × 10^4 /μL, the total protein level of 7.6 g/dL, albumin level of 3.6 g/dL, total bilirubin level of 0.7 mg/dL, creatinine level of 0.88 mg/dL, eGFR of 48.3 mL/min, C-reactive protein level of 11.03 mg/dL, hemoglobin A1c of 7.0%, and antinucleus antibody level of < 40 U were observed.

**Imaging examinations**
Chest computed tomography showed no subglottal, tracheal, or bronchial swelling. ETs are located in the parapharyngeal space on noncontrast-enhanced 3D T1-weighted image (flip angle, 120; repetition time, 600; echo time, 12; number of excitations, 1; slice thickness, 0.8 mm; and field of view, 25 cm × 28.4 cm). The Merkmal of the ET is the levator veli palatine muscle on the upper side and the tensor veli palatine muscle on the lower side (Figure 2A). Noncontrast-enhanced fat-saturated T2-weighted images (flip angle, 111; repetition time, 6060; echo time, 64; number of excitations, 1; slice thickness, 4 mm; slice space, 4.8 mm; and field of view, 25 cm × 28.4 cm) of the patient demonstrated edematous bilateral ETs (Figure 2B). The contrast-enhanced 3D-volumetric interpolated breath-hold examination T1-weighted image (flip angle, 11; repetition time, 5.5; echo time, 2.46; number of excitations, 2; slice thickness, 1 mm; and field of view, 30 cm × 34.1 cm) demonstrated enhanced bilateral ETs (Figure 2C).

**Pathology**
A biopsy from the auricular cartilage, a tissue composed of hyaline cartilage and connective tissue, was performed by an otorhinolaryngologist, and moderate chronic inflammatory cell infiltration including the lymphocytes and plasma cells is observed in the fibrous connective tissue and is partially vitrified. Inflammatory cells have infiltrated part of the hyaline cartilage.

**FINAL DIAGNOSIS**
The final diagnosis was RP.
TREATMENT

The patient started undergoing steroid therapy using 30 mg/d of prednisolone with preventive antifungal medications as there was no life-threatening symptom. The patient also started taking sulfamethoxazole trimethoprim to prevent Pneumocystis jirovecii pneumonia.

OUTCOME AND FOLLOW-UP

The clinical course of the patient was summarized in Table 1. The patient’s symptoms decreased after drug treatment within 2 wk. Laboratory inflammation markers also decreased. We are following up to see if there is any improvement in sensorineural hearing loss. The edema and contrast enhancement of ETs disappeared in the follow-up MRI at 8 wk.

DISCUSSION

To the best of our knowledge, this is the first report of a patient with RP manifesting as enhanced and edematous ET on MRI by reviewing previous mass reports and imaging review[3-5,9,10]. The only head and neck lesion other than auricles and nasal cartilage...
was orbital involvement reported by Moore et al[11]. Otitis media has been known as a common manifestation of a patient with RP; however, the reason behind its occurrence has not been discussed to date. Theoretically, an ET might be involved in a patient with RP as it comprises cartilages, the inflammatory target of RP. Otitis media in adults can be divided into four types of manifestations: microorganism infections in the ET from the nasopharynx to middle ear that manifesting acute otitis media; obstruction of the ET orifice to the nasopharynx due to nasopharyngeal carcinoma, nasopharyngeal inflammation, or ET dysfunction, resulting in a fluid collection in the middle ear manifesting otitis media with effusion (OME); a proliferation of tympanic membrane results in chronic inflammation of the middle ear manifesting chronic otitis media; and cholesteatoma, a keratinized, desquamated epithelial collection in the middle ear. In this patient, infectious symptoms, tympanic membrane proliferation, or cholesteatoma was not observed so that OME was suspected. Fluid collection in the middle ear of patients with RP could be due to ET dysfunction caused by inflammation of the involved cartilages as in this case; however, this has not been proven as a pathological examination at this site.

**CONCLUSION**

We experienced a case of patients with RP representing edematous and enhancing ET on MRI accompanying otitis media. Otitis media in patients with RP was suggested to be caused by ET dysfunction through inflammatory changes.

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CASE REPORT

Endoscopic clipping for the secondary prophylaxis of bleeding gastric varices in a patient with cirrhosis: A case report

Guang-Chao Yang, Ya-Xian Mo, Wei-Hua Zhang, Li-Bin Zhou, Xu-Ming Huang, Li-Ming Cao

BACKGROUND
Bleeding from gastroesophageal varices (GOV) is a serious complication in patients with liver cirrhosis, carrying a very high mortality rate. For secondary prophylaxis against initial and recurrent bleeding, endoscopic therapy is a critical intervention. Endoscopic variceal clipping for secondary prophylaxis in adult GOV has not been reported.

CASE SUMMARY
A 66-year-old man with cirrhosis was admitted to our hospital complaining of asthenia and hematochezia for 1 wk. His hemoglobin level and red blood cell counts were significantly decreased, and his fecal occult blood test was positive. An enhanced computed tomography of the abdomen showed GOV. The patient was diagnosed with hepatitis B cirrhosis-related GOV bleeding. A series of palliative treatments were administered, resulting in significant clinical improvement. Subsequently, an endoscopic examination revealed severe gastric fundal varices, prompting endoscopic variceal clipping. There were no further episodes of gastrointestinal bleeding. The GOV improved significantly on follow-up imaging and was confirmed as improved on endoscopy at the 5th post-operative month.

CONCLUSION
Our results suggest that endoscopic clipping is an inexpensive, safe, easy, effective, and tolerable method for the secondary prophylaxis of bleeding from gastric type 2 GOV. However, additional research is indicated to confirm its long-term safety and efficacy.
Key Words: Endoscopy; Metal clips; Gastric varices; Endoscopic variceal clipping; Secondary prophylaxis; Case report

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Core Tip: Gastrointestinal bleeding as a sequela of portal hypertension can be catastrophic and fatal. For patients without secondary prevention, the rebleeding and mortality rate is high; therefore, secondary prophylaxis is vital, and endoscopic techniques are primary methods used to perform this. Our novel endoscopic technique could play a critical role in the prevention of variceal re-bleeding, and we propose that it is a safe and efficacious method for the secondary prophylaxis of Type 2 GOV rebleeding. Our work provides an idea for the further study in this field.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i4.1447

INTRODUCTION

One of the most life-threatening complications of liver cirrhosis is acute variceal bleeding, which is associated with an increased mortality rate of approximately 20% at 6 wk[1]. For patients without secondary prevention, the rebleeding rate was as high as 60%, and the mortality rate reached 33% within 1-2 years[2]. Therefore, secondary prophylaxis is vital, and endoscopy is the primary method used to perform secondary prophylaxis techniques. A variety of techniques, including endoscopic variceal ligation (EVL), endoscopic injection sclerotherapy (EIS), and tissue adhesive injection, are available to manage gastroesophageal varices (GOV). GOV can be divided into Type 1 GOV and Type 2 GOV (GOV 2). GOV1 manifests as relatively straight varices extending along the lesser curvature of stomach to 2-5 cm below the gastroesophageal junction, while GOV 2 extends beyond the gastroesophageal junction into the fundus of the stomach [3]. However, these treatments are not without potentially serious complications. EVL, which can cause cerebral air embolism[4] and infective endocarditis[5], has not been widely used in gastric varices. EIS has a high complication rate for gastric ulceration, perforation, and rebleeding (37%-53%)[3,6], and its sclerosing agent can leak into the inferior vena cava[7]. The tissue adhesive injection procedure can result in embolization, leading to potentially fatal complications such as pulmonary[8] and spinal cord embolisms[9]. Endoscopic hemostatic metal clips were first designed by Hayashi et al[10] in 1975 and were initially used to achieve hemostasis in focal gastrointestinal bleeding[11] with the added benefit of a low rebleeding rate[12]. To our knowledge, endoscopic variceal clipping (EVC) for secondary prophylaxis in adult GOV has not been reported. Therefore, we present a retrospective case in which metal clips were utilized for the treatment of severe GOV 2 in a cirrhotic patient and evaluate the efficacy of EVC.

CASE PRESENTATION

Chief complaints
A 66-year-old man with cirrhosis was admitted to our hospital with a complaint of asthenia and hematochezia for 1 wk.

History of present illness
The patient had black stool for 1 wk and frequent bouts of asthenia.

History of past illness
He had a significant medical history of diabetes, hypersplenism, hypoalbuminemia,
cholecystitis, mild anemia and bradycardia, and hepatitis B/decompensated cirrhosis, for which he received entecavir.

**Personal and family history**
He had no history of alcohol abuse, toxic exposure, or hereditary disease.

**Physical examination**
His vitals at admission and pertinent physical examination findings were notable for a pulse of 84 and blood pressure 134/76 mmHg; he was lucid with a hepatic face, pale lips and conjunctiva, palmar erythema, chest spider angiomas, and mild bilateral pitting edema; the rest of his examination findings were unremarkable.

**Laboratory examinations**
Initial laboratory test results were shown in Table 1. The 14C-urea breath test was negative.

**Imaging examinations**
Chest computed tomography (CT) showed inflammation in the middle lobe of the right lung, and an enhanced upper abdominal CT showed gastric varices (Figure 1A-D).

**FINAL DIAGNOSIS**
The patient was diagnosed with hepatitis B cirrhosis-related GOV bleeding.

**TREATMENT**
The patient and their family members refused emergency endoscopy as they were worried about endoscopy related complications. At the same time, blood transfusion therapy with 1000 mL of packed red blood cells, acid suppressive agents (lansoprazole), hemostatic agents, antibiotic therapy (levofloxacin), somatostatin injection, glycemic control agents, enteral fasting, parenteral nutrition, and a laxative (lactulose) were all administered for 11 d. He responded well to treatment as his hemoglobin level stabilized (> 70 g/dL) and no rebleeding occurred. On day 4, he was administered meperidine and diazepam before an upper gastrointestinal endoscopy [Olympus CV290 (Olympus Corporation, Tokyo, Japan)] was performed; several large gastric fundal varices without a spurting bleeding point were found (Figure 1E-H). The patient refused EIS and tissue adhesive injection as he was worried about procedural complications and treatment costs. We therefore used EVC to treat the severe gastric varices. Subsequently, the varicose veins were successfully managed with 20 metal clips (Nanwei Medical Pharmaceutical Co., Ltd, Nanjing, China; Figure 1I-L). Specifically, we adopted the rotatable metal clips ROCC-F-26-195-C (opening size 14 mm, working length 1950 mm) and ROCC-D-26-195 (opening size 10 mm, working length 1950 mm), respectively. In the reversal location for endoscope, we adjusted the front end of endoscope to be perpendicular to the vessel cross-section, and subsequently, pushed the clip from biopsy channel, then slowly closed the clip after the varicose vein was completely caught in the clip; with the cardia as the center, we first clamped the small diameter and relatively isolated varicose veins, then clamped the larger varices. First, we clamped the inflow segment of the varices, and then clamped the outflow segment of the varices. The clip should be as close as possible to muscularis propria when clamping the varices, and the distance between the clip and dentate margin of cardia must be more than 10 mm.

**OUTCOME AND FOLLOW-UP**
The patient had no black stools on the 2nd postoperative day and was discharged a week after operation. He had no further episodes of gastrointestinal bleeding with a normal hemoglobin level and liver function tests noted at the 5th month of follow-up. Follow-up imaging showed significantly improved gastric varices (Figure 2A-D), and the follow-up endoscopy showed well-healed gastric varices at the 5th postoperative month (Figure 2E-H).
Table 1 Laboratory findings on admission

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference range</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell count, × 10^12/L</td>
<td>1.89</td>
<td>3.8-5.8</td>
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<tr>
<td>Hemoglobin level, g/dL</td>
<td>59</td>
<td>115-175</td>
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</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>43</td>
<td>45-125</td>
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<tr>
<td>Albumin, g/L</td>
<td>29.4</td>
<td>40-55</td>
<td>Decreased</td>
</tr>
<tr>
<td>Total protein, g/L</td>
<td>56.1</td>
<td>65-85</td>
<td>Decreased</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>16</td>
<td>9-50</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>75</td>
<td>57-111</td>
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</tr>
<tr>
<td>Direct bilirubin, μmol/L</td>
<td>7.9</td>
<td>0-6.89</td>
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</tr>
<tr>
<td>Plasma fibrinogen level, g/L</td>
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</tr>
<tr>
<td>Random blood glucose, mmol/L</td>
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<td>3.89-6.11</td>
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</tr>
<tr>
<td>Plasma D-dimer, mg/L</td>
<td>0.61</td>
<td>0.5</td>
<td>Increased</td>
</tr>
<tr>
<td>Urea nitrogen, mmol/L</td>
<td>9.76</td>
<td>3.6-9.5</td>
<td>Increased</td>
</tr>
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<td>Serum lipase, U/L</td>
<td>133.9</td>
<td>13-60</td>
<td>Increased</td>
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<td>Creatine kinase, U/L</td>
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<td>50-310</td>
<td>Increased</td>
</tr>
<tr>
<td>Alpha-fetoprotein, ng/mL</td>
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<td>0-13.6</td>
<td>Increased</td>
</tr>
<tr>
<td>Glycosylated hemoglobin, %</td>
<td>7.6</td>
<td>4.0-6.5</td>
<td>Increased</td>
</tr>
<tr>
<td>Hepatitis B virus DNA, iu/ml</td>
<td>9020</td>
<td>&lt; 100</td>
<td>Increased</td>
</tr>
<tr>
<td>Hepatitis B virus surface antigen</td>
<td>Positive</td>
<td>Negative</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Hepatitis B E antibody</td>
<td>Positive</td>
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<td>Abnormal</td>
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<tr>
<td>Hepatitis B core antibody</td>
<td>Positive</td>
<td>Negative</td>
<td>Abnormal</td>
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<tr>
<td>Fecal occult blood test</td>
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<tr>
<td>Hepatitis C virus antibody</td>
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<td>Helicobacter pylori antibody</td>
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<tr>
<td>Human immunodeficiency virus antibody</td>
<td>Negative</td>
<td>Negative</td>
<td>Normal</td>
</tr>
<tr>
<td>Syphilis antibody</td>
<td>Negative</td>
<td>Negative</td>
<td>Normal</td>
</tr>
</tbody>
</table>

This retrospective case report was approved by the ethics review board of Shenzhen Shiyan People’s Hospital (Approval no. 2021SZSY-01). The patient provided written informed consent for the participation and publication of this report. He was satisfied with the treatment received.

**DISCUSSION**

A new method of endoscopic therapy using metal clips for the secondary prevention of bleeding from gastric varices in patients with cirrhosis was devised. Our study expands the clinical application of endoscopic clipping and offers a new solution for secondary prophylaxis of bleeding from gastric varices. The results suggested that our endoscopic clip method is safe, inexpensive, easy, and effective and was well tolerated by a patient with GOV 2.

EVC appears to be an effective technique for the secondary prophylaxis of bleeding from GOV 2. During the procedure, the endoscope did not have to be withdrawn, simplifying the operation by shortening the surgical time while minimizing medical risks. In addition, metal clips are more cost-efficient than tissue adhesives and sclerosing agents and have good histocompatibility; furthermore, their safety and efficacy profile in endoscopic hemostasis has garnered more approval in the literature. Employing EVC not only simplifies the endoscopy but precludes the need for surgery and long-term conventional treatment. Mitsunaga *et al*[13] reported 82 prophylactic
Figure 1 Preoperative abdominal computed tomography, preoperative and intraoperative endoscopy images. A-D: Preoperative abdominal computed tomography showing esophagogastric venous plexus presenting multiple dilated, tortuous blood vessels (arrows, gastric varices); E-H: Preoperative endoscopic examination revealing several large, nodular gastric fundal varices (largest diameter 15 mm), with no bleeding points or red-color signs revealed during endoscopy; I-L: Immediately after deployment of the clips, the outlet and inlet of the gastric varices were closed by clips, resulting in variceal atelectasis.

(secondary prevention) EVCs without variceal progression in 89.9% with good security. Miyoshi et al[14] first reported EVC applied prophylactically to 9 patients with esophageal (rather than gastric) varices without major complications such as massive bleeding, achieving the desired effect. In this case, we utilized EVC for the secondary prophylaxis of gastric varices with encouraging results.

We believe that EVC is suitable for LDRI Type D 1.0-2.0 gastric varices and GOV 2, which are long, nodular, and tortuous veins that are continuous with esophageal varices[3]. Following the flow direction of varicose veins, metal clips were used by clipping both ends of the vein; this effectively blocks part of the blood flow, resulting in vessel collapse. The clips should be applied gently and released slowly to avoid pulling the veins. The time of shedding of the clips was longer, and more clips were required for simple EVC. Somatostatin was then employed, which reduces splanchnic blood flow, decreases portal venous pressure, and improves the safety and efficacy of the endoscopic procedure[2]. EVC relieves gastric varices and decreases portal vein pressures, so we had expected liver function to improve. The patient had normal liver function at postoperative five-month follow-up, indicating that our theory was correct.

However, there were some EVC complications, such as uncorrected hemorrhagic shock, uncontrolled hepatic encephalopathy, and uncooperative patients, that must also be considered. Therefore, future large-scale randomized controlled trials would be prudent to provide qualitative evidence and confirm the efficacy of EVC for secondary prophylaxis in bleeding from gastric varices.

CONCLUSION

In conclusion, gastrointestinal bleeding can be a fatal complication of portal
hypertension. Endoscopic techniques play a critical role in the prevention of variceal rebleeding. We propose that EVC is a safe and effective method for the secondary prophylaxis of GOV 2. Our report supports endoscopic clipping as an important treatment modality in the secondary prophylaxis of GOV. However, additional research is needed to confirm its long-term safety and efficacy.

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Rituximab as a treatment for human immunodeficiency virus-associated nemaline myopathy: What does the literature have to tell us?

Jucier Gonçalves Júnior, Samuel Katsuyuki Shinjo

Abstract

We presented a letter about a case of a 37-year-old Black female with a history of human immunodeficiency virus and an undetectable viral load. She was evaluated with weakness in the scapular (grade III) and pelvic girdles (grade II), elevation of creatine phosphokinase levels and muscle biopsy compatible with nemaline myopathy. She was treated with rituximab showing improvement of the condition.

Key Words: Case report; Human immunodeficiency virus; Nemaline myopathy; Rituximab; Rheumatology; Therapy

Core Tip: Rituximab may be a therapeutic possibility for the treatment of nemaline myopathies (e.g., human immunodeficiency virus-associated and monoclonal gammopathy of undetermined significance-associated) because it is less aggressive and has fewer side effects compared to current therapies. It may be especially helpful in cases of severe visceral involvement. However, the cost and unavailability of therapy can be a limiting factor.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i4.1454
TO THE EDITOR

Dear Journal Editor,

We read the paper of Profs. Wang and Hu[1] who presented a case report about nemaline myopathy (NM) with dilated cardiomyopathy. The authors aimed to describe a rare myopathy with severe cardiovascular impairment and whose outcome was positive.

We would like to present a case of human immunodeficiency virus (HIV)-associated NM (HIV-NM), and it responded to rituximab treatment.

The case involves a 37-year-old Black female with a history of HIV and an undetectable viral load with regular use of dolutegravir, darunavir and ritonavir. Six years ago, the patient started to present objective muscle weakness in all four limbs, in addition to increased muscle enzymes and electroneuromyography with evidence of a myopathic pattern. With the initial hypothesis of polymyositis, the patient received prednisone (1 mg/kg/d) with partial improvement of clinical and laboratory status. The patient was admitted to our service for a clinical reassessment and follow-up 5 years ago. The patient had an undetectable viral load, normal protein electrophoresis and serum levels of creatine phosphokinase at 2550 U/L using methotrexate 25 mg/wk and prednisone 5 mg/d.

She had weakness in the scapular (grade III) and pelvic girdles (grade II), required a wheelchair for locomotion and showed muscle magnetic resonance with evidence of symmetrical and bilateral muscle edema in the muscular bellies of the pelvic girdle and thighs. A muscle biopsy showed a myopathic and dystrophic patterns with the presence of marginal vacuoles with nemaline rods. Regarding the possibility of HIV-NM, methylprednisolone pulse therapy 3 g was started in one dose, and immunosuppressive drugs (azathioprine 300 mg/d, methotrexate 20 mg/wk and prednisone 20 mg/d) of previous use were maintained without significant improvement. Due to refractory disease and despite off-label, the patient consented to introduce rituximab 2 g/week as a possible option to promote disease induction.

The patient had progressive improvement. After two rituximab cycles, there was an important improvement in muscle weakness (lower limbs grade III and upper limbs grade IV) and independence for basic activities of daily living and a drop in creatine phosphokinase (275 U/L).

According to the literature, HIV-NM usually has a good response to immunosuppressive therapy[2-4]. A case report of a 65-year-old woman with severe cardiomyopathy and NM was recently described, in which the treatment was clinical compensation for cardiomyopathy associated with autologous stem cell transplantation[4]. A German cohort demonstrated that the most effective treatment strategy in NM was autologous bone marrow transplantation, but the one performed was immunosuppression with glucocorticoids (62%)[3]. Thus, in severe cases such as the one presented by the authors[1], we ask ourselves if the use of rituximab could not be an option as a way to delay the evolution of the NM.

Among the postulated theories, two stand out: (1) HIV should result in the formation of rods and/or serve as a trigger for the immune system to destroy muscle fibers; and (2) Genetic disorders caused by HIV cause rod formation[3]. In this context, therapy with rituximab may be an interesting treatment option in NM because: (1) Recent studies have shown improvement in the weakness of rituximab with no side effects obtained; (2) Lymphocytic infiltrates in muscles of NM patients are commonly confused with polymyositis; and (3) Limited effects with treatment[5].

Another interesting point to remember is that NM is often associated with monoclonal gamopathy of undetermined significance in case series[6], retrospective studies[7] and cohorts[3], denoting exacerbated lymphocyte activity. The cause for this association, as well as for the association of NM with HIV, is still unknown. However, the good response of this pathology to immunosuppressive therapies[2-4] and bone marrow transplantation[4] denote that options, such as rituximab, with fewer side effects, better dosage comorbidity and lower risks may be a real therapeutic possibility. Even more aggressive treatment regimens such as associations with dexamethasone, thalidomide and cyclophosphamide have already been proposed[8].

Finally, we emphasize that these treatment modalities might be used as an optional treatment to the autologous stem cell transplantation or before that. However, despite the rarity of the disease, further studies with a higher number of patients and adequate follow-up are required.
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