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REVIEW

Evaluation and management of acute pancreatitis

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Abstract

Acute pancreatitis (AP) is one of the most common gastrointestinal causes for hospi-talization in the United States. In 2015, AP accounted for approximately 390000 hospitalizations. The burden of AP is only expected to increase over time. Despite recent advances in medicine, pancreatitis continues to be associated with a substantial morbidity and mortality. The most common cause of AP is gallstones, followed closely by alcohol use. The diagnosis of pancreatitis is established with any two of three following criteria: (1) Abdominal pain consistent with that of AP; (2) Serum amylase and/or lipase greater than three times the upper limit of normal; and (3) Characteristics findings seen in cross-sectional abdominal imaging. Multiple criteria and scoring systems have been established for assessing severity of AP. The cornerstones of management include aggressive intravenous hydration, appropriate nutrition and pain management. Endoscopic retrograde cholangiopancreatography and surgery are important aspects in management of acute gallstone pancreatitis. We provide a comprehensive review of evaluation and management of AP.

Key words: Acute pancreatitis; Necrotizing pancreatitis; Resuscitation; Gallstone pancreatitis

Core tip: Acute pancreatitis (AP) is one of the most common gastrointestinal causes for hospitalization in the United States. In 2015, AP accounted for approximately 390000 hospitalizations. The most common cause of AP is gallstones, followed closely by alcohol use. Multiple criteria and scoring systems have been established for assessing severity of AP. The cornerstones of management include aggressive intravenous

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hydration, appropriate nutrition and pain management. Endoscopic retrograde cholangiopancreatography and surgery are important aspects in management of acute gallstone pancreatitis. We provide a comprehensive review of evaluation and management of AP.

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INTRODUCTION

Acute pancreatitis (AP) is one of the most common gastrointestinal causes for hospitalization in the United States. In 2015, AP accounted for 390940 hospitalizations making it one of the most frequent causes of gastrointestinal hospitalizations in the nation with the annual incidence only expected to increase over time[1-3]. Despite recent advances in gastroenterology, AP continues to be associated with substantial mortality, morbidity and healthcare resource utilization[2,3].

In this report, we provide a comprehensive review of the epidemiology, pathophysiology, evaluation, and management of AP.

EPIDEMIOLOGY

The annual incidence of AP ranges from 15.9 to 36.4 per 100000 persons. The burden of the disease on the healthcare resource utilization is expected to increase in the near future[2-5]. Despite the improvement we have seen in access to healthcare, imaging modalities and interventions, AP continues to have significant morbidity and mortality that has largely remained unchanged over time. The overall mortality rate being 5% to 17% in severe AP, and 1.5% in mild AP[2,4,6].

The three most common causes of AP are gallstone/biliary related, alcohol related, and idiopathic. These three causes account for the majority of cases of AP[2,7-10]. Biliary pathology was estimated to be 28%-38% of the cases while alcohol accounted for 19%-41% of the cases[8,9,11].

Prior reports have shown a significant relation of gender and race in regards to etiology of AP. Overall, a markedly higher frequency of AP was seen among blacks than whites, followed closely by Hispanics, Asians, and then American Indians. Patients with AP due to alcohol use were significantly younger and were more likely to be male and/or black, with blacks having the highest frequency of alcohol related pancreatic disease[5,9,12]. Females are more likely to have biliary related pancreatitis[5,12]. The increase in incidence of AP has been mostly seen in woman ages < 35 and men between the ages of 35 and 54[2].

ETIOLOGY

AP is the inflammation of the pancreas that is often associated with systemic inflammatory response syndrome (SIRS) that may impair the function of other organs. The etiology of AP can be readily identified in 75% to 85% of cases[8]. The American Gastroenterological Association (AGA) provides a comprehensive guide to determine the etiology of pancreatitis.

The evaluation should begin with a detailed history focusing on symptoms and presentation. The investigation should focus on evaluation of any previous documented gallstones, alcohol use, history of hypertriglyceridemia or hypercalcemia, family history of pancreatic diseases, prescription/non-prescription drug history, history of trauma, and presence of autoimmune disease. On presentation to the hospital, patients should have a serum amylase or lipase level checked along with liver chemistries (bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase), and abdominal ultrasound assessing for cholelithiasis or choledocholithiasis. Extensive or invasive evaluation should be avoided on presentation[10,13,14]. The most common etiologies of AP have been summarized in Table

1.

Biliary Tract disease

Gallstone pancreatitis is the most common cause of AP and is estimated to be 28%-38% of all cases of AP[8,9,11]. Gallstone induced pancreatitis is caused by duct obstruction by gallstone migration leading to temporary impaction of migrating stones at the duodenal ampulla, increased duct pressure, and unregulated stimulation of the digestive enzymes secreted by the pancreas[15,16]. This obstruction can be due to calculi lodged in the duodenal ampulla, spasms, and fibrosis of the sphincter of Oddi[15,17-19].

Alcohol

Alcoholic pancreatitis is the second most frequent cause of AP and is estimated to be 19%-41% of all AP cases[9-11]. The association between alcohol abuse and pancreatitis is poorly understood, but it is known that the majority of patients who abuse alcohol do not develop pancreatitis[10,19]. In addition, two thirds of patient's who present with acute alcoholic pancreatitis already have developed an underlying chronic pancreatitis[20]. In about 8% of cases of AP related to alcohol, mutations in the pancreatic secretory trypsin inhibitor gene (*SPINK1*) have been seen[21].

Hypertriglyceridemia

Hypertriglyceridemia induced pancreatitis is a rare cause of AP and is estimated to make up 1%-4% of cases[22,23]. Hypertriglyceridemia induced pancreatitis is thought to be due to the hydrolysis of excessive triglyceride rich lipoproteins releasing high concentration of free fatty acids which injure the vascular endothelium and acinar cells of the pancreas. This injury causes a self-perpetuating ischemic and acidic environment with resultant toxicity[23-26]. Specific genes associated with cystic fibrosis transmembrane conductance regular mutation and a tumor necrosis factor were found to be risk factors for AP secondary to hypertriglyceridemia[22,27]. We recommend checking a triglyceride level in all patients with AP in which history is not suggestive of alcohol use and imaging does not indicate a biliary pathology.

Genetic

Several genetic mutations have been associated with the development of AP. Specific cystic fibrosis gene (*CFTR*) genotypes have been shown to be significantly associated with AP, with the highest risk seen in mild phenotypic genotypes[28]. Hereditary pancreatitis is an autosomal dominant disease caused by cationic trypsinogen (*PRSS1*) gene mutation, but is usually associated with chronic pancreatitis[29,30]. In younger patients, with no identifiable cause of AP, genetic etiologies should be considered.

Drug

Drug induced AP is a rare entity. There should be a high level of suspicion after common causes of AP have been ruled out. An estimated 2%-4.8% of reported cases of AP have been related to some medications[31,32]. A wide variety of drugs have been reported as possible causes of AP including 6-mercaptopurine, sulfonamides, diuretics, didanosine, pentamidine, tetracycline, azathioprine, estrogen, and steroids[33]. The proposed mechanisms of drug induced AP include immunologic reactions, direct toxic effect, toxic metabolite, ischemia, and thrombosis[33].

Infectious

Various infections have been associated with AP including viral, bacterial, fungal, and parasitic. Infections which have been reported to cause AP include mumps, coxsackie virus, hepatitis B virus, cytomegalovirus, varicella-zoster virus, herpes simplex virus, Mycoplasma, Legionella, Leptospira, Salmonella, Aspergillus, Toxoplasma, and Cryptosporidium[34-36]. From infectious causes, viruses are the leading etiology of AP[35].

Trauma

Any blunt trauma to the pancreas can cause AP, but this diagnosis should be made when there is a high suspicion. The incidence of pancreatic injury comprises 0.2% to 12% of all abdominal traumas[37,38]. The majority of pancreatic trauma is related to direct trauma with only a minority associated with blunt trauma[39].

Post-endoscopic retrograde cholangiopancreatography (ERCP)

Serum amylase elevations up to three times the upper limit of normal have been reported after 24 h of an ERCP[40]. It has been reported in 1.3%-4.3% of ERCP procedures. The most common risk factors for post-ERCP related AP are younger age, female gender, history of sphincter of Oddi dysfunction, pancreatic duct opacification, cholangitis, and duodenal perforation[41-44].

Table 1 Etiologies of acute pancreatitis

Etiology	Incidence
Gallstones	28%-38%
Alcohol related	19%-41%
Hypertriglyceridemia	1%-4%
Idiopathic	10%-40%
Drug	2%-4.8%
Trauma	1%
Infectious	
Post-ERCP	
Hypercalcemia	
Vascular	
Genetic	

ERCP: Endoscopic retrograde cholangiopancreatography.

Hypercalcemia
Elevated calcium levels have also been linked to AP. The mechanism behind It stems from an exposure to high concentrations of calcium leading to toxicity, disruption of intracellular signaling, and cell damage[45]. In addition, AP has been reported in 1.5% of patients with hyperparathyroidism which is thought to be due to hypercalcemia[46].

Pancreatic anatomical abnormalities
Anatomical abnormalities of the pancreas including annular pancreas and pancreatic ductal stricture are accepted rare causes of AP as well as recurrent AP. However the role of pancreas divisum remains as an etiology of AP is controversial[9,47]. Pancreas divisum is a common variant seen in up to 14% of patients[48-50]. The clinical implications remain controversial and currently there is no consensus if pancreatic divisum alone can cause AP[9,47,51].

Vascular
Pancreatic ischemia secondary to rheumatological disease, ischemia secondary to shock, and atheromatous embolization have also been reported as rare causes of AP[52-54]. AP has been reported in numerous rheumatic diseases including systemic lupus erythematosus, Sögren's syndrome, scleroderma, and rheumatoid arthritis[52]. AP has also been reported as a rare but potential event within 48 h of transabdominal angiographic procedures secondary to atheromatous embolization[53].

Pregnancy
AP has been rarely reported in pregnancy. In these cases five of them were found to be due to gallstones while the other three were reported as idiopathic causes[55].

Malignancies
AP can present as a manifestation of underlying malignancy. Specifically in intraductal papillary mucinous neoplasms (IPMNs), AP has been reported to be a presenting symptom with AP occurring in up to 21% of patients diagnosed with IPMNs[56].

Autoimmune pancreatitis (AIP)
AIP is a rarely identified disorder that is presumed to be autoimmune in etiology associated with IgG4 cholangitis, salivary gland disorders, mediastinal fibrosis, and inflammatory bowel disease. AIP should be considered in patients presenting with AP, particularly those with previously diagnosed autoimmune disorders[57,58]. AIP is classified into two types - Type 1 and 2. Type 1 AIP is part of a systemic IgG4 positive disease meeting the HISORt criteria proposed by the Mayo Clinic[59]. The HISORt criteria includes the presence of one or more of the following: diagnostic histology, characteristic imagining on computed tomography (CT) scan, elevated serum IgG-4 levels, other organ involvement, and/or response of symptoms to glucocorticoid therapy[59]. Type 2 AIP or idiopathic duct-centric pancreatitis is defined by granulocytic lesions in the absence of IgG-4-positive cells and systemic involvement[58].

Idiopathic
Idiopathic or unidentifiable causes of pancreatitis have been reported in about 10%-

40% of all AP cases[9,60]. Idiopathic pancreatitis is often due to microlithiasis which is not picked up on routine abdominal imaging.

DIAGNOSIS

The revised Atlanta classification for AP helps to standardize the diagnosis of AP. The classification system defined pancreatitis as the presence of any two of the following three criteria being present in the patient: Abdominal pain consistent with that of AP, serum amylase and/or lipase levels greater than three times the upper limit of normal, and characteristics findings of AP seen in cross-sectional abdominal imaging[10,13,14,61-64].

Presentation

The diagnosis of AP begins early on in a patient's course and should be suspected in patients presenting with clinical symptoms and features consistent with AP - epigastric abdominal pain, nausea, vomiting, abdominal pain radiating to the back (seen in 40%-70% of patients)[10,13,14,61,64]. This pain can last several hours to several. Nausea has also been seen in about 90% of patients with AP which can last for several days as well[64].

Physical exam

Pancreatitis is an inflammatory condition of the pancreas extending to local and distant extra-pancreatic tissues[65]. Exam findings associated with AP vary greatly based on the severity of AP. Patients with mild disease may present with little tenderness to palpation throughout the abdomen, while patients with severe disease may present with severe abdominal pain to palpation and absence of bowel sounds[10,13,14].

Cullen's and Turner signs are seen in about 3% of patient's and are associated with a mortality of about 37%. These signs are many times associated with hemorrhagic pancreatitis, however neither sign is not specific to hemorrhage[66].

Laboratory tests

The evaluation of pancreatic enzymes (Lipase and Amylase) released from inflamed tissue is the cornerstone of biochemical diagnosis of AP[10,13,14,62,63,65,67]. The Atlanta criteria identified a serum amylase and/or serum lipase greater than three times the upper limit of normal as a contributory factor to the diagnosis of pancreatitis[10,13,14,62,63,67]. Although there is no optimal diagnostic test for pancreatitis, lipase is preferred over amylase in routine clinical practice[10].

Tyrpsinogen activation peptide is cleaved from trypsinogen to produce active trypsin and can also be seen in AP[68]. This can be measured in both the urine and serum. These tests are not readily available and hence not routinely used in clinical practice.

All patients with AP should get a complete blood cell count, basic metabolic panel, liver function tests (LFTs), coagulation profile, C-reactive protein (CRP), and total albumin as part of their initial laboratory work-up. An arterial blood gas should be performed in patients with hypoxia[10,13,14].

Imaging

Contrast enhanced CT scan of the abdomen and magnetic resonance imaging (MRI) of the abdomen is the best imaging modalities for visualization of pancreatic pathology. Although these tests are not routinely indicated in patients with mild AP. The classic feature seen in AP is the presence of focal or diffuse enhancement of the pancreas[10,13,14,69].

CT scan of the abdomen is used to both diagnose pancreatitis and many times helps establish scales of severity[69]. A non-contrast CT scan helps to establish the extent of pancreatic and extra-pancreatic inflammation[10,13,14]. A contrast enhanced CT scan of the abdomen is the gold standard for the establishment of severity of pancreatitis[10,13,14]. The CT severity index is based on a combination of peri-pancreatic inflammation, phlegmon, and degree of pancreatic necrosis seen on initial CT scan study and was developed to grade the severity of pancreatitis and establish the correlated mortality[10,13,14,70]. A high CT severity index correlated with a 92% morbidity and 17% mortality rate, while a low CT severity index correlated with a 2% morbidity and 0% mortality rate[70]. An early CT scan of the abdomen on admission has not been shown to affect the disease course as the CT scoring system for severity of AP is similar to that of clinical scoring system. Thus, a CT scan of the abdomen on admission solely to assess severity is not recommended[10,13,14,71]. It is recommended that an ultrasound of the abdomen be obtained on all patients with AP to assess the

presence of biliary tract obstruction from gallstones[10,13,14].

An MRI of the abdomen is indicated in patients who have elevated LFTs with suspected common bile duct disease which cannot be visualized on ultrasound. Otherwise, an MRI is not indicated for the diagnosis of pancreatitis[10,13,14,71].

ASSESSMENT OF SEVERITY

About 15%-20% of patient with AP will develop severe disease and will have an elongated hospital stay with likely complications including possible death[10,13,14]. Thus, the determination of the severity of AP is one of the most important first steps in the management of AP. It helps in selecting appropriate treatments, ensuring proper patient triage, initiation of applicable therapies, and stratifying patient risk for complications. This is important because of the possibly of death related to severe AP. Mortality rates with AP in tertiary care centers alone is reported to be between 4.8%-9%, and when considering severe forms of the disease the mortality rates increased to 13.5%[72-74]. Several tools and scoring systems have been developed to assess the severity of AP. These scoring systems have been summarized in Table 2. We have reviewed the most commonly used scoring systems below:

Acute Physiology and Chronic Health Examination (APACHE) II Score

The APACHE II score was originally developed for patients in the intensive care unit (ICU) and utilizes 12 variables in order to help calculate a score that can be used upon admission, 24 h, and 48 h. This allows the advantage of the score being recalculated throughout the patient's stay allowing for appropriate adjustments and interventions. Each of the 12 variables are translated into weights using the original APACHE score and help to stratify a patient's risks[75].

In comparative studies the APACHE II score was the most accurate score in predicating the severity of the disease and the outcome of the disease. After 48 h, the APACHE II score predicted the outcome in 88% of cases and outperformed both the Ranson's and Imrie scores[10,76]. The APACHE II score has many limitations that make its use cumbrous. The complexity and difficulty to use, inability to distinguish between interstitial and necrotizing pancreatitis, and poor predictive value at 24 h are just a few of the limitations of the APACHE II score[64].

Bedside Index of Severity in Acute Pancreatitis (BISAP) Score

This score was developed in 2008 to be a mortality based prognostic tool for physicians to use within the first 24 h of admission[77]. The scoring system takes into account 5 variables: Blood urea nitrogen (BUN) > 25 mg/dL, impaired mental status, SIRS, age greater than 60, or the presence of a pleural effusion. Mortality was shown to be greater than 20% in the highest risk group or a score of 5 and less than 1% in the lowest group or score of 0[77]. The prognostic value of the BISAP score was found to be similar to those of other scoring systems such as the Ranson's, APACHE II, and computed tomography severity index (CTSI) in determining pancreatic necrosis and mortality[78]. The BISAP score is easy to use and authors recommend that all patients with AP should have BISAP score calculated to assess the severity of the disease.

Glasgow criteria

This scale is also known as the Imrie score and includes 8 of the variables used in the Ranson's Criteria. This scale has been used in gallstone induced AP. This scale must be determined after 48 h and uses SI units making its use difficult in the United States[10,13,14,79].

Ranson's criteria

The Ranson's criteria were one of the earliest criteria developed for assessing the severity of AP. The score takes into account 11 variables: 5 of which are measured at admission while 6 of these are measured 48 h after admission[10,79]. The limitation to this scoring system is that the criteria must be taken promptly at the correct time, and results cannot be determined until 48 h after admission. Many times the criteria are not completely measured during the hospital stay[10]. The mortality rises with increasing scores. Mortality was reported to be 0%-3% in patients with a score less than 3, 11%-15% in a score greater than or equal to 3, and 40% when the score was greater than or equal to 6[64]. The Ranson's criteria can be cumbersome to use in routine clinical practice at times.

Computed Tomography Severity Index

The CT severity index is based on a combination of peri-pancreatic inflammation, phlegmon, and degree of pancreatic necrosis seen on initial CT scan of the abdomen

Table 2 Scoring systems for assessing severity of acute pancreatitis

Atlanta Revision (2013)	Ranson's Criteria	BISAP
Mild acute	After 24 h of admission	Within 24 h of admission
(1) Absence of organ failure; (2) Absence of local complications	Age greater than 55; WBC > 16000; Blood Glucose > 200 mg/dL; Serum LD > 350 IU/L; Serum AST > 250/L	(1) BUN > 25 mg/dL; (2) Impaired mental status; (3) Systemic inflammatory response syndrome (SIRS); (4) Age > 60; (5) Presence of a pleural effusion
Moderately severe	After 48 h of admission	
(1) Local complications[a] and/or (2) transient organ failure[b] for less than 48 h	Fall in Hematocrit > 10%; Fluid Sequestration > 6L; Hypocalcemia < 8 mg/dL; Hypoxemia; Increase in BUN of > 5 mg/dL after IV fluid; Base deficit of > 4 mmol/L	
Severe	Mortality based on score	Mortality based on score
Persistent organ failure for greater than 48 h	Score of 0 to 2: 0%-3%; Score of 3 to 5: 11%-15%; Score of 6 to 11: 40%	Score of 0: 0.1%-0.2%; Score of 1: 0.5%-0.7%; Score of 2: 1.9%-2.1%; Score of 3: 5.3%-8.3%; Score of 4: 12.7%-19.3%; Score of 5: 22.5%-26.7%

[a]Local Complications: Interstitial edematous pancreatitis, necrotizing pancreatitis, pancreatic pseudocyst, acute necrotic collection, walled off necrosis, and pleural effusion. [b]Organ Failure: Failure of main organ systems - respiratory, cardiac, renal, hepatic, hematological, neurological. WBC: White blood cells; LD: Lactate dehydrogenase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; BISAP: Bedside Index of Severity in Acute Pancreatitis.

within one week of AP. This study was developed to grade the severity of pancreatitis (Balthazar score) and establish a correlated mortality rate[10,13,14,70]. The presence of necrosis on CT scan of the abdomen was a predictor of worse outcome[77,79]. In prior studies, a high CT severity index correlated with a 92% morbidity and 17% mortality while a low CT severity index correlated with a 2% morbidity and 0% mortality[70].

Atlanta Criteria for Severity and Revised Atlanta Classification

The Atlanta criteria was developed in 1992 and helped identify severity of AP based on organ failure, local complications, and unfavorable prognostic signs[10,63]. The criteria helped define specific definitions of organ failure such as shock, pulmonary insufficiency, renal failure, and gastrointestinal bleeding. The Atlanta criteria also helped define pancreatic complications which were the development of pseudocyst, abscess, or parenchymal necrosis[10,63]. The Atlanta Criteria was then revised in 2012 in an attempt to further classify the severity of AP. The revised Atlanta Classification divides AP into interstitial edematous or necrotizing pancreatitis, distinguish early and late phase pancreatitis, and emphasizes the importance of SIRS and multiorgan failure[62]. Furthermore, severe AP is defined by persistent organ failure lasting greater than 48 h[62].

Laboratory findings

There are a wide range laboratory markers that have been identified as being elevated in AP including interleukin-B, interleukin-6, CRP, procalcitonin, antithrombin III, substance P. However, only two of these markers have been used regularly including C-reactive protein and hematocrit[10]. Seventh day CRP concentration was shown to have similar accuracy to both Ranson's and Glasgow criteria. This is a quick and simple test that can be performed to help aid in assessing severity[80]. AP results in third spacing increasing the hematocrit, which has been shown as an early marker for organ failure and necrotizing pancreatitis[81].

In conclusion, no one system or criteria exists to precisely predict prognosis of AP on admission. However, the use of clinical judgment, appropriate laboratory values, BISAP and the APACHE II scoring systems serve as an important guide for the triage, management and prognostication in patients with AP. CT scan of the abdomen after 72 h can help provide additional information about the severity of disease[10,13,14,71]. Both the American College of Gastroenterology and International Association of Pancreatology/American Pancreatic Associations suggest the following as predictors of disease severity: advanced age, any comorbid disease, body mass Index greater than 30, presence of pleural effusion, rising hematocrit, hematocrit > 44, BUN > 20, elevated creatinine, SIRS score > 1, and persistent organ failure[13,82].

MANAGEMENT

The cornerstones in the management of AP include aggressive early intravenous hydration, appropriate nutrition, necessary interventions, and pain management. Below we review the current and most up to date treatment options in AP.

Initial assessment and triage

A crucial early step in the management of patients with AP is the initial assessment and triage to the appropriate hospital setting. This should be addressed early within the hospitalization to allow for appropriate management. Recent guidelines from the AGA recommend that patients with organ failure and/or severe inflammatory response syndrome (SIRS) should be admitted directly to the ICU[13]. The BISAP scoring system in particular is very useful with initial assessment of AP patients with a score of greater than or equal to three being an appropriate score to identify a patient with a high risk of mortality and hence should undergo evaluation for ICU admission[83]. However, we recommend that patients should be assessed on a case by case basis.

Fluid resuscitation

The current guidelines regarding fluid resuscitation in the management of AP are evolving. Despite these changes, there continues to be consensus in the importance and need for aggressive early fluid resuscitation[10,13,14,84]. Early goal directed fluid resuscitation has been shown to reduce mortality in patients with severe sepsis[85]. However, the administration of excessive fluid has been shown to have worse outcomes after 24 h[86]. We suggest that the need of aggressive fluid resuscitation should be evaluated after 6 and 24 h of admission and rate of fluids should be adjusted based on changes in mean arterial pressure, urine output, changes in BUN and respiratory status. Two recent articles showed the importance of aggressive intravenous fluids in hastening clinical improvement in patients with AP, as well large volume fluid resuscitation in severe AP within the first 24 h is associated with decreased mortality[87,88].

The choice of fluids for patients with AP has been a topic of great debate in recent years. Prior guidelines suggested that Ringer's Lactate was superior to Normal Saline and should be used as the initial fluid therapy in patients with AP, with one randomized trial showing Ringer's Lactate reduced the incidence of systemic inflammation in comparison to Normal Saline[10,89]. However, the more recent guidelines from the AGA suggest that Normal Saline and Ringer's Lactate are equally efficacious in the management of AP. This is based on poor quality of evidence behind prior studies and not focusing on important clinical outcome such as organ failure, pancreatic necrosis or mortality[84,90]. The guidelines do state against the use of hydroxyethyl starch (HES) fluids, since the literature has showed no differences in mortality when comparing fluids with and without HES[84,91,92].

Nutrition

The paradigm of nutrition in AP has shifted to early initiation of nutritional supplementation as compared to the conventional nil per oral strategies used in the past. The AGA now recommends initiating early oral feedings (within 24 h) in patients with mild AP. There was no type of diet that was specified in these recommendations, but it is thought that beginning early feedings helps to protect the gut-mucosal barrier and reduce bacterial translocation, which in return will reduce the risk of worse outcomes associated with AP. These findings were based on the results of 11 randomized control trials which examined early *vs* delayed feeding. Although enteral tube feeding was started within 24 h in some of these studies, no study reported the initiation of oral feeding within 24 h. Thus, whether the 24-h time-frame is appropriate for the oral intake of food is still unclear and will need to be studied further[10,13,14,84,93,94].

In patients who are unable to eat, enteral feeding should be considered early through nasogastric/nasojejunal routes as opposed to total parenteral nutrition[10,13,64,82,84]. There has been no difference in outcomes when compared with nasogastric *vs* nasojejunual feeds.

Pain management

Pain management remains essential in the management of AP. Uncontrolled pain can lead to hemodynamic instability leading to worse outcomes. Opioids remain the first line choice of pain medication in AP. Recent studies showed no differences in the risk of complications related to pancreatitis or adverse events when comparing different opioids and routes of administration[95].

Role of antibiotics

There is no role for prophylactic antibiotics in patients with AP. Recent studies have shown no association between the initiation antibiotic therapy in AP and severe outcomes such as organ failure, necrosis or mortality[13,84,96].

Antibiotics do however play a large role in patients with infected pancreatitis. Infected necrosis should considered in patient's failing to improve after one week.

This should be assessed promptly with acquisition of a CT scan guidance fine-needle aspiration for gram stain or presence of gas on CT scan[13,82,97]. In these patients, empiric treatment should be effective against common pathogens including: Escherichia coli, Bacteroides species, Enterobacter species, Klebsiella species, Streptococcus faecalis, Staphylococcus epidermidis and Staphylococcus aureus[14,97]. Appropriate antibiotic choices include carbapenems, quinolones, and metronidazole which are all known to penetrate pancreatic necrosis and target these bacteria. The routine use of antifungals is not recommended in these patients[13]. Antibiotics should be initiated early in patients who have infected pancreatitis and may help prevent the need for surgical necrosectomy. Delaying intervention may result in poor outcomes for these patients[98-100].

Endoscopy

Endoscopic intervention is indicated in patients with AP who have concurrent cholangitis or biliary obstruction. In a small subgroup of patients, persistent choledocholithiasis can become obstructive and can lead to pancreatic/biliary tree obstruction. This will eventually lead to severe AP that can be complicated with cholangitis[13]. Guidelines recommend patients who have cholangitis should undergo ERCP within twenty four hours of admission[10,13,14]. Prior reports have shown that patients undergoing ERCP within 24 h *vs* patients with conservative management had fewer complications[101]. In addition, patients with AP complicated with cholangitis or biliary sepsis who receive early ERCP have been shown to have lower morbidity and mortality rates[102].

However, timing of ERCP in patients with biliary pancreatitis continued to be controversial. Recent studies have shown that urgent ERCP in patient's having acute biliary pancreatitis without cholangitis had no impact on clinical outcomes such as mortality, pancreatitic infections, and organ failure[84,96].

Surgery

Indications for surgical intervention include the presence of gallstones in the gallbladder or biliary tree, infected necrosis preferably for more than 4 wk after antibiotics if stable, and necrosectomy in symptomatic patients [13,84].

All patients with mild AP related to gallstones should undergo cholecystectomy during the same admission prior to discharge. Early surgical intervention in biliary pancreatitis drastically reduces mortality and gallstones related complications[103]. In addition, patients with moderately severe and severe AP should undergo an interval cholecystectomy after discharge[104]. Overall, cholecystectomy in patients with gallstone related pancreatitis have been shown to drastically reduce the incidence of recurrent AP[9].

Patients who are asymptomatic with findings of pseudocysts and/or necrosis of the pancreas or extrapancreatic tissue do not require surgical intervention[105]. While historically the treatment for pancreatic necrosis was surgical intervention, most recent guidelines point away from immediate surgical intervention[10,13,14]. Current guidelines recommend postponing necrosectomy for four weeks in patients who are stable[10,13,14]. This delay in surgery was shown to be associated with a decreased mortality from 39% to 12% in patients with severe AP[106]. However, in symptomatic patients with infected necrosis, necrosectomy is still recommended with minimally invasive methods such as endoscopic necrosectomy as compared to surgery[10,13,14].

Alcohol cessation

All patients admitted with AP should undergo counselling for alcohol cessation[84]. A single randomized controlled trial showed that alcohol cessation counseling at the time of AP leads to decreased incidence of recurrent AP over a 2-year period[107]. We suggest that all patients admitted with AP should be provided with resources to assist with cessation of alcohol use on discharge from the hospital.

COMPLICATIONS

Local complications

The most common complications following AP include acute peri-pancreatic fluid collection, pancreatic pseudocyst, acute necrotic collections, and walled off necrosis[10,13,14,62]. The complications of AP have been outlined in Table 3.

Interstitial edematous pancreatitis: Interstitial edematous pancreatitis is an acute inflammation of the pancreatic parenchyma and peri-pancreatic tissues. However, this does not have any signs of recognizable tissue necrosis. On contrast enhanced CT scan, enhancement of the pancreatic parenchyma with no signs of necrosis is

Table 3 Complications of acute pancreatitis

Region	Complications	Manifestation
Local	Interstitial Edematous Pancreatitis	Description: Acute inflammation of parenchyma or peripancreatic tissues; Radiology: Enhancement of the pancreatic parenchyma with no signs of necrosis
	Necrotizing Pancreatitis	Description: Necrosis encompassing pancreatic parenchyma or pancreatic tissues; Radiology: Acute necrotic collection lacking definable wall containing variable amounts of fluid OR Walled off necrosis containing a well-defined encapsulated collection
	Acute peripancreatic Fluid Collection	Description: Homogenous collection of fluids with no distinct inflammatory walls outside pancreas containing minimal or no necrosis; Timing: Within the first four weeks after onset of interstitial edema; Radiology: Homogenous collection with fluid confined by normal fascial planes
	Pancreatic Pseudocyst	Description: Collections of fluids that contain distinct inflammatory walls outside the pancreas containing minimal to no necrosis; Timing: After four weeks of initial onset of interstitial edematous pancrea-titis; Radiology: Clear homogenous fluid density with well-defined borders that is encapsulated
	Acute Necrotic Collection	Description: Collection of both fluid and necrosis associated with necrotizing pancreatitis; Radiology: intrapancreatic or extrapancreatic heterogenous non-liquid density of varying degrees with no definite wall
	Walled Off Necrosis	Description: Encapsulated collection of pancreatic or peripancreatic necrosis that has formed a distinct inflammatory wall; Radiology: Heterogenous liquid/non-liquid density with varying loculations. The structure has a well demarcated wall that is en-tirely encapsulated
Peripancreatic	Thrombosis	Description: Thrombosis of splanchnic venous circulation including splenic vein, portal and/or superior mesenteric veins
	Pseudoaneurysm	Description: Collection of blood forming between the two most outer layer of the artery – muscularis propria and adventitia
	Abdominal Compartment Syndrome	Description: Tissue edema that is secondary to aggressive fluid resuscitation, peripancreatic inflammation and ascites

seen[10,13,14,62].

Necrotizing pancreatitis: Necrotizing pancreatitis commonly manifests as necrosis encompassing pancreatic parenchymal and/or peripancreatic tissues. On imaging, these findings manifest either as an acute necrotic collection lacking a definable wall containing variable amounts of fluid, or walled off necrosis containing a well-defined encapsulated collection of pancreatic parenchymal and/or peripancreatic tissues. These findings are initially sterile and may eventually become infected[10,13,14,62].

Acute peripancreatic fluid collection (APFC): APFC are homogenous collections of fluids with no distinct inflammatory walls outside the pancreas containing minimal to no necrosis. APFC often occurs within the first four weeks after the initial onset of interstitial edematous pancrea-titis. On contrast enhanced CT scan, APFC is visualized as a homogenous collection with fluid that is confined by normal fascial planes adjacent to the pancreas[10,13,14,62].

Pancreatic pseudocyst: Pancreatic pseudocysts are collections of fluids that contain distinct inflammatory walls outside the pancreas containing minimal to no necrosis. This often occurs four weeks after the initial onset of interstitial edematous pancreatitis. Contrast enhanced CT scan criteria include a clear homogenous fluid density with well-defined borders that is encapsulated[10,13,14,62].

Acute necrotic collection: An acute necrotic collection is a collection of both fluid and

necrosis associated with necrotizing pancreatitis. This involves either the pancreatic and/or peripancreatic tissue. Contrast enhanced CT scan shows an intra-pancreatic or extra-pancreatic heterogenous non-liquid density of varying degrees with no definite wall[10,13,14,62].

Walled-off necrosis: Walled off necrosis is defined as an encapsulated collection of pancreatic or peri-pancreatic necrosis that has formed a distinct inflammatory wall. This occurs greater than four weeks after the initial onset of necrotizing pancreatitis. Contrast enhanced CT scan of the abdomen shows a heterogenous liquid/non-liquid density with varying loculations. The structure has a well demarcated wall that is entirely encapsulated[10,13,14,62].

Hemorrhagic pancreatitis: Although rare, hemorrhagic complications can be seen and are considered late sequelae of AP. Hemorrhage may develop secondary to ruptured or leaking pseudoaneurysms, bleeding associated in pancreatic necrosis, and hemorrhagic pseudocysts. Early detection of this complication is important and surgical embolization or intervention has been shown to decrease mortality[108].

Peripancreatic complications

Peripancreatic complications encompass a number of complications. An uncommon complication of AP includes thrombosis of the splanchnic venous circulation. This predominantly occurs in the splenic vein but can occur in the portal and/or superior mesenteric veins. This manifestation is seen in up to 24% of patients with AP[109]. This can also lead to development of gastric varices leading to gastrointestinal bleeding.

Another rare but serious complication that may occur in AP includes a pseudoaneurysm. This should be suspected when patients develop sudden gastrointestinal bleeding, drop in hemoglobin and worsening abdominal pain[62,82]. CT scan can often show signs of hemorrhagic pancreatitis. These patients benefit from angioembolization which is often performed by interventional radiology and surgical intervention is reserved as the last resort.

Patients with AP are also at increased risk for abdominal compartment syndrome secondary to tissue edema from aggressive fluid resuscitation, peripancreatic inflammation, and ascites[110].

Systemic complications

Any patient with AP is at an increased risk for exacerbation of underlying conditions including cardiac, lung, hepatic, and nephrogenic disease. These complications should be treated as they arise[10,14,62,82]. We suggest that patients with AP who develop serious systemic complications should be managed in the ICU with the assistance of other colleagues including pulmonologists, cardiologists and nephrologist.

CONCLUSION

AP continues to be a common reason for hospitalization. The most common etiologies include gallstones, followed by alcohol. It has significant impact on healthcare resource utilization, morbidity and mortality. Disease can vary from mild disease to severe disease with systemic complications. The cornerstones to management include aggressive early fluid resuscitation, appropriate nutritional supplementation and management of complications. Patients with mild acute gallstone related pancreatitis should undergo cholecystectomy prior to discharge to prevent recurrent episodes. Severe AP and pancreatitis with local and systemic complications should be managed in a multidisciplinary approach with involvement of internists, gastroenterologists, hepatobiliary surgeons and interventional radiologists.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Rituximab-induced IgG hypogammaglobulinemia in children with nephrotic syndrome and normal pre-treatment IgG values

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Abstract

BACKGROUND

In paediatric patients with complicated nephrotic syndrome (NS), rituximab (RTX) administration can induce persistent IgG hypogammaglobulinemia among subjects showing low basal immunoglobulin G (IgG) levels.

AIM

To evaluate the effect of RTX on IgG levels and infections in patients with complicated NS and normal basal IgG levels.

METHODS

We consecutively enrolled all patients with complicated NS and normal basal IgG levels undergoing the first RTX infusion from January 2008 to January 2016. Basal IgG levels were dosed after 6 wk of absent proteinuria and with a maximal interval of 3 mo before RTX infusion. The primary outcome was the onset of IgG hypogammaglobulinemia during the follow-up according to the IgG normal values for age [mean ± standard deviation (SD)].

RESULTS

We enrolled 20 patients with mean age at NS diagnosis of 4.2 ± 3.3 years. The mean age at the first RTX infusion was 10.9 ± 3.5 years. Eleven out of twenty patients (55%) developed IgG hypogammaglobulinemia. None of these patients showed severe or recurrent infections. Only one patient suffered from recurrent acute otitis media and underwent substitutive IgG infusion. Three patients undergoing only the two "starting doses" experienced normalization of IgG levels. Using Kaplan-Meier analysis, the cumulative proportion of patients free of IgG hypogammaglobulinemia was 57.8% after the first RTX dose, 51.5% after the third dose, 44.1% after the fourth dose, and 35.5% after the fifth dose.

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CONCLUSION
RTX can induce IgG hypogammaglobulinemia in patients with pre-RTX IgG normal values. None of the treated patients showed severe infections.

Key words: Nephrotic syndrome; Rituximab; IgG hypogammaglobulinemia; Immunoglobulin

Core tip: In paediatric patients with complicated nephrotic syndrome (NS), rituximab (RTX) administration can induce persistent immunoglobulin G (IgG) hypogammaglobulinemia among subjects showing low basal IgG levels. Our case series shows that RTX can induce IgG hypogammaglobulinemia also in patients with pre-RTX IgG normal values and that persisting IgG hypogammaglobulinemia could be dose-dependent. When evaluating a patient with complicated NS and post-RTX IgG hypogammaglobulinemia, IgG supplementation may not be needed because, to date, no severe infections have been detected and the possibility of adverse events related to IgG supplementation exists.

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INTRODUCTION

Rituximab (RTX) is an effective and safe treatment for childhood-onset, complicated, frequently relapsing, and steroid-dependent nephrotic syndrome (NS)[1]. Data about long-term safety are limited. Recent reports have highlighted the impact of RTX treatment on immunoglobulin (Ig) levels. In studies involving adults with multisystem autoimmune diseases, it had been found that following RTX treatment 34%-56% of patients showed reduced IgG levels, with 13%-26% of them presenting already IgG level reduction before RTX initiation[2-4]. On the other hand, it has been shown in paediatric patients with NS that RTX administration can induce persistent IgG hypogammaglobulinemia among subjects showing low basal IgG levels and in a few cases with normal baseline IgG levels[5-7]. The aim of our study was to evaluate the effect of RTX on IgG levels and infections in patients with complicated, frequently relapsing, and steroid- and cyclosporine-dependent NS who have normal baseline IgG levels.

MATERIALS AND METHODS

We consecutively enrolled patients with complicated NS and normal basal IgG levels undergoing the first RTX infusion from January 2008 to January 2016. The study was approved by our Research Ethical Committee. Informed consent was obtained before any procedure.

Basal IgG levels were dosed after 6 wk of absent proteinuria and with a maximal interval of 3 mo before RTX infusion. Patients with IgG levels under the range of normality for age before the first RTX infusion [mean ± standard deviation (SD)] and with missing data were excluded[8].

Initial RTX course was performed as two infusions of 375 mg/m^2 with an interval of 7-14 d between the two infusions ("starting doses"). Additional RTX injections were made after every NS relapse just after obtaining remission independently from the levels of CD19-positive cells. IgG levels, white cell blood count, and CD19-positive cells were evaluated at 3 mo and 6 mo after the first RTX infusion and then every 6 mo. After RTX initiation, we slowly tapered cyclosporine dose before stopping completely and then slowly tapered corticosteroid doses stopping their administration.

Primary outcome

The primary outcome was the onset of IgG hypogammaglobulinemia during the follow-up according to normal IgG values for age (mean ± SD) (Figure 1A)[8]. We also documented possible recovery from IgG hypogammaglobulinemia and recorded infections and neutropenia.

Statistical analysis

P values ≤ 0.05 were considered statistically significant. Differences for continuous variables were analysed with the independent-sample *t* test for normally distributed variables and with the Mann-Whitney test in case of non-normality. Qualitative variables were compared using the chi-squared test. The development of primary outcome was determined by survival analysis according to the Kaplan-Meier method. The day of first RTX infusion was considered the starting point, while the end point was the date of the primary outcome onset. Patients arriving at their last available follow-up without showing primary outcome were right censored. The Stat-Graph XVII software for Windows was used for all statistical analyses with the exception of Kaplan-Meir analysis, which was done using Graphpad Prims 7 software for Windows (La Jolla, CA, United States).

RESULTS

A total of 20 patients were enrolled. The mean age of the study population at the time of NS diagnosis was 4.2 ± 3.3 years (range 1.6-11.5 years). All patients developed complicated, frequently relapsing, and steroid- and cyclosporine-dependent NS and were treated with the "starting doses" of RTX at mean age of 10.9 ± 3.5 years. RTX doses were repeated in 11 patients because of NS relapses. Therefore, a total of 79 doses of RTX were administered in the study period: Only the two "starting doses" in eight patients, three doses in 2 patients, four doses in five patients, five doses in 1 patient, seven doses in 1 patient, eight doses in 2 patients, nine doses in 1 patient. The mean follow-up available after the last RTX infusion was 29.8 ± 17.5 mo.

IgG hypogammaglobulinemia after RTX therapy was recorded in 11/20 (55%) patients. In 8 out of 11 patients, IgG hypogammaglobulinemia occurred after the RTX "starting doses" and in the remaining three patients after the subsequent doses (Figure 1A). Only 3 out of the 11 patients experienced subsequent normalization of IgG levels. These 3 patients underwent only the two "starting doses" of RTX and did not receive further RTX infusions. None of the patients who developed IgG hypogammaglobulinemia showed severe infections. Only one patient (Figure 1A) suffered from recurrent acute otitis media and underwent substitutive IgG infusion after immunological consultation. The first episode of NS in this patient was at the age of 1.6 years. Before the RTX infusion, he showed 16 NS relapses despite corticosteroids, cyclophosphamide, tacrolimus, and mycophenolate treatments. This patient underwent his first RTX doses at 6.8 years of age and showed persisting IgG hypogammaglobulinemia after the fifth dose of RTX. After the eighth RTX dose, he had six episodes of acute otitis media in 8 mo. Therefore, substitutive IgG infusion was started. He has undergone substitutive IgG infusions for 18 mo, and he has not shown other acute otitis media episodes.

CD19-positive cell depletion was found in all the patients with a mean recovery time of 6.3 ± 17.5 mo from every RTX infusion. None of the patients showed neutropenia. When comparing patients showing and not showing IgG hypogammaglobulinemia, no differences were found in the utilization of corticosteroids, cyclosporine, cyclophosphamide, other immunosuppressive agents, and more than one immunosuppressive agent (Table 1). The months of follow-up after the last RTX infusion, the number of RTX infusions, and the months of CD-19 cells depletion were similar between patients showing and not showing IgG hypogammaglobulinemia. Moreover, a non-significant trend showing a lower number of relapses after RTX infusion and younger age at first RTX infusion for the patients presenting IgG hypogammaglobulinemia compared with the patients not presenting IgG hypogammaglobulinemia was present (Table 1).

Using Kaplan-Meier analysis, the cumulative proportion of patients free of IgG hypogammaglobulinemia was 57.8% after the first dose of RTX, 51.5% after the third dose, 44.1% after the fourth dose, and 35.5% after the fifth dose (Figure 1B).

DISCUSSION

Evidence on the impact of RTX treatment on IgG levels in children with complicated

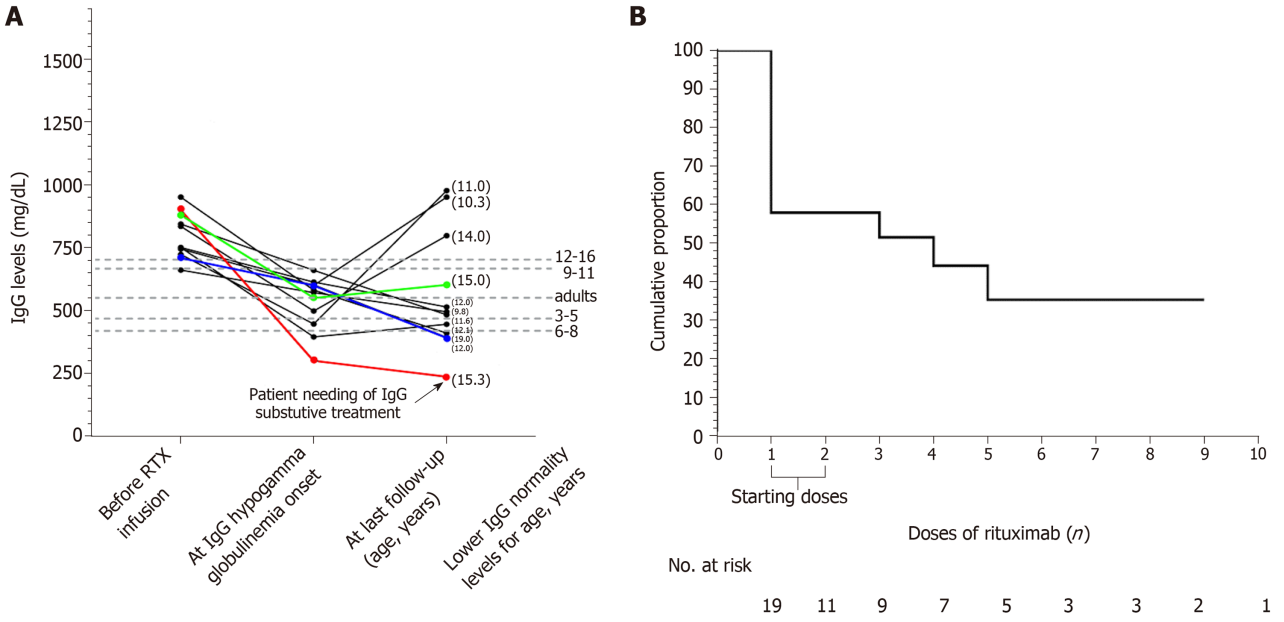

Figure 1 Trend of the IgG values among patients presenting IgG hypogammaglobulinemia and survival from IgG hypogammaglobulinemia. A: Trend of the IgG values among patients presenting with IgG hypogammaglobulinemia. Eight patients (dark coloured) developed IgG hypogammaglobulinemia after the "starting doses" (7 out of 8 patients showed IgG hypogammaglobulinemia at the scheduled follow-up 3 mo after the RTX "starting doses", and one patients developed IgG hypogammaglobulinemia 24 mo after the RTX infusion), one (green coloured) patient after the third dose (this patient showed IgG hypogammaglobulinemia 3 mo after the third dose), one (blue coloured) after the fourth (this patient showed IgG hypogammaglobulinemia 3 mo after the fourth dose), and one (red coloured) after the fifth dose (this patient showed IgG hypogammaglobulinemia 13 mo after the fifth dose); B: Survival from IgG hypogammaglobulinemia. The cumulative proportion of patients free of IgG hypogammaglobulinemia was 57.8% after the first dose of RTX, 51.5% after the third dose, 44.1% after the fourth dose, and 35.5% after the fifth dose. The time between the RTX infusion and IgG hypogammaglobulinemia onset is specified in the legend of **Figure 1A**. RTX: Rituximab; IgG: Immunoglobulin G.

NS having normal baseline IgG levels are limited to few cases for each available study[5-7]. Delbe-Bertin *et al*[5] reported that persisting post-RTX IgG hypogammaglobulinemia was observed in 7 patients with IgG hypogammaglobulinemia before RTX infusion, while none of the 4 patients with normal pre-RTX IgG levels presented IgG hypogammaglobulinemia after RTX initiation. In addition, Fujinaga *et al*[6] found that nine out of 60 patients with complicated steroid-dependent NS showed hypogammaglobulinemia (defined as IgG levels < 500 mg/dL) after RTX infusion. Among these 9 patients, only 3 patients had normal IgG levels before the RTX infusion. In another multi-centre case series, Guigonis *et al*[7] found that 4 out of 22 patients with severe steroid- and cyclosporine-dependent NS developed RTX-related hypogammaglobulinemia. In that case series, no further follow-up of IgG levels was reported.

The present single-centre study was specifically designed to enrol only patients with complicated, frequently relapsing, and steroid- and cyclosporine-dependent NS with normal basal IgG levels. We found that 11 out of 20 patients (55%) developed IgG hypogammaglobulinemia after RTX therapy, with eight of them having developed IgG hypogammaglobulinemia after the "starting doses" and three after the following RTX doses. Noteworthy, we found recovery from IgG hypogammaglobulinemia only in the 3 who underwent "starting doses" of RTX without receiving further RTX infusions. None of the patients who developed IgG hypogammaglobulinemia showed severe infections. Only one patient (Figure 1A) suffered from recurrent acute otitis media, and he underwent substitutive IgG infusion

We failed to demonstrate potential risk factors of developing IgG hypogammaglobulinemia after RTX treatment in patients with NS probably because of the limited population number. However, we did identify a trend showing that the patients developing IgG hypogammaglobulinemia were younger both at NS onset and first RTX infusion than patients who did not develop IgG hypogammaglobulinemia. In the literature, data about risk factors of developing post-RTX hypogammaglobulinemia in children with NS are not yet available. However, more than one course of RTX, previous exposure to purine analogues, more than eight doses of RTX, RTX maintenance regimens, age at the administration of RTX, and post-RTX mycophenolate administration have been identified as risk factors in adults undergoing RTX administration because of non-Hodgkin lymphoma, rheumatoid arthritis, and systemic Lupus Erythematous[9].

Table 1 Characteristics of the patients presenting and not presenting post-rituximab IgG hypogammaglobulinemia

	Presenting IgG hypogammaglobulinemia, *n* = 11	Not presenting IgG hypogammaglobulinemia, *n* = 9	*P*-value
Age at NS onset, yr	2.8 (1.1)	5.2 (4.7)	0.07
Female sex *n* (%)	0 (0)	3 (33.3)	0.1
Corticosteroids *n* (%)	11 (100)	9 (100)	> 0.99
Corticosteroids (mean ± SD, mo)	76.5 ± 54.2	73.2 ± 30.9	0.87
Cyclosporine *n* (%)	11 (100)	9 (100)	> 0.99
Cyclosporine (mean ± SD, mo)	56.1 ± 23.1	66.4 ± 40.0	0.48
Cyclophosphamide *n* (%)	8 (72.3)	6 (66.7)	0.9
Cyclophosphamide (mean ± SD, mo)	3 ± 0.27	3 ± 0.33	0.9
Other immunosuppressive agents *n* (%)	2 (0.2)	3 (0.33)	0.43
> 1 immunosuppressive agents *n* (%)	8 (72.3)	7 (77.8)	0.43
Relapses (mean ± SD)	11.5 ± 4.6	16.5 ± 9.7	0.15
Relapses after first RTX infusion (mean ± SD)	1.6 ± 1.5	3.9 ± 4.6	0.15
RTX infusions (mean ± SD)	3.3 ± 1.8	5.0 ± 2.7	0.11
Age at first RTX infusion, (mean ± SD, yr)	9.2 ± 1.8	11.8 ± 4.5	0.09
Months of CD19-positive cells depletion (mean ± SD)	6.4 ± 3	6.2 ± 2.6	0.9
Months of follow-up after the last RTX infusion (mean ± SD)	31.1 ± 14.9	27.4 ± 20.7	0.59

RTX: Rituximab; IgG: Immunoglobulin G; NS: Nephrotic syndrome; SD: Standard deviation.

Regarding the risk of severe infections following RTX infusion in paediatric patients affected by NS, among the 27 patients showing post-RTX IgG hypogammaglobulinemia (including our patients and other in the literature with available follow-up)[5,6], no life-threatening infections were detected. Among non-life-threatening infections, one patient presented bronchitis[6], one enteritis[6], and one recurrent episodes of acute otitis media. Moreover, evaluating the need of substitutive IgG infusion, 4 out of the 27 patients underwent IgG supplementation. Among these 4 patients, 3 received IgG supplementation only for low IgG levels[5,6], and one for recurrent acute otitis media. It is important to emphasize that one of these patients in IgG supplementation presented aseptic meningitis as an adverse effect of IgG supplementation[5].

Finally, evaluating the percentage of recovery of serum levels of IgG in patients developing IgG hypogammaglobulinemia, Fujinaga *et al*[6] showed IgG levels recovery in 6 out of 9 patients, Delbe-Bertin *et al*[5] showed IgG recovery in 1 out of 8 patients, and in the present case series we found IgG recovery in 3 out of 11 patients.

In conclusion, our case series shows that RTX can induce IgG hypogammaglobulinemia in patients with pre-RTX IgG normal values and that persisting IgG hypogammaglobulinemia could be dose-dependent.

When evaluating a patient with complicated NS and post-RTX IgG hypogammaglobulinemia, IgG supplementation may not be needed because, to date, no severe infections have been detected and the possibility of adverse events related to IgG supplementation exists.

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ARTICLE HIGHLIGHTS

Research background

It has been shown in paediatric patients with complicated nephrotic syndrome (NS) that

rituximab (RTX) administration can induce persistent IgG hypogammaglobulinemia among subjects showing low basal IgG levels.

Research motivation
RTX is an effective and safe treatment for childhood-onset, complicated, frequently relapsing, and steroid-dependent NS. Data about long-term safety are limited. Evidence on the impact of RTX treatment on IgG levels in children with complicated NS having normal baseline IgG levels are limited to a few cases for each available study. Here, we aimed to provide further evidence about RTX safety in childhood and provide a way for possible future perspective multi-centre studies about this topic.

Research objectives
The aim of our study was to evaluate the effect of RTX on IgG levels and infections in patients with complicated, frequently relapsing, and steroid- and cyclosporine-dependent NS with normal baseline IgG levels.

Research methods
We consecutively enrolled all patients with complicated NS and normal basal IgG levels undergoing the first RTX infusion from January 2008 to January 2016. Basal IgG levels were dosed after 6 wk of absent proteinuria and with a maximal interval of 3 mo before RTX infusion. The primary outcome was the onset of IgG hypogammaglobulinemia during the follow-up according to IgG normal values for age (mean ± SD).

Research results
We enrolled 20 patients with a mean age at NS diagnosis of 4.2 ± 3.3 years. The mean age at the first RTX infusion was 10.9 ± 3.5 years. Eleven out of twenty patients (55%) developed IgG hypogammaglobulinemia. None of these patients showed severe or recurrent infections. Only one patient suffered from recurrent acute otitis media and underwent substitutive IgG infusion. Three patients undergoing only the two "starting doses" experienced normalization of IgG levels. When comparing patients showing and not showing IgG hypogammaglobulinemia, no differences were found in the utilization of corticosteroids, cyclosporine, cyclophosphamide, other immunosuppressive agents, and more than one immunosuppressive agent. A non-significant trend showing a lower number of relapses after RTX infusion and younger age at first RTX infusion for the patients presenting IgG hypogammaglobulinemia compared with the patients not presenting IgG hypogammaglobulinemia was present. Using Kaplan-Meier analysis, the cumulative proportion of patients free of IgG hypogammaglobulinemia was 57.8% after the first RTX dose, 51.5% after the third, 44.1% after the fourth, and 35.5% after the fifth dose.

Research conclusions
Our study is the first study specifically designed to enrol only children with complicated, frequently relapsing, and steroid- and cyclosporine-dependent NS with normal basal IgG levels. Our case series shows that RTX can induce IgG hypogammaglobulinemia in patients with pre-RTX IgG normal values and that persisting post-RTX IgG hypogammaglobulinemia could be dose-dependent. None of the patients developing IgG hypogammaglobulinemia showed severe infections. Only one patient suffered from recurrent acute otitis media and underwent substitutive IgG infusion.

Research perspectives
This article adds to our knowledge about the safety of RTX in children with complicated NS. Future studies should prospectively collect multicentre data on the effects of RTX on IgG levels and risk of severe infections. This will improve management of post-RTX IgG hypogammaglobulinemia and help define patients who could benefit from substitutive IgG infusion.

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ORIGINAL ARTICLE

Retrospective Study

Causes associated with recurrent choledocholithiasis following therapeutic endoscopic retrograde cholangiopancreatography: A large sample sized retrospective study

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Abstract

BACKGROUND

Recurrence of primary choledocholithiasis commonly occurs after complete removal of stones by therapeutic endoscopic retrograde cholangiopancreatography (ERCP). The potential causes of the recurrence of choledocholithiasis after ERCP are unclear.

AIM

To analyze the potential causes of the recurrence of choledocholithiasis after ERCP.

METHODS

The ERCP database of our medical center for the period between January 2007 and January 2016 was retrospectively reviewed, and information regarding eligible patients who had choledocholithiasis recurrence was collected. A 1:1 case-control study was performed for this investigation. Data including general characteristics of the patients, past medical history, ERCP-related factors, common bile duct (CBD)-related factors, laboratory indicators, and treatment was analyzed by univariate and multivariate logistic regression analysis and Kaplan-Meier analysisly.

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RESULTS

First recurrence of choledocholithiasis occurred in 477 patients; among these patients, the second and several instance (≥ 3 times) recurrence rates were 19.5% and 44.07%, respectively. The average time to first choledocholithiasis recurrence was 21.65 mo. A total of 477 patients who did not have recurrence were selected as a control group. Multivariate logistic regression analysis showed that age > 65 years (odds ratio [OR] = 1.556; $P = 0.018$), combined history of choledocholithotomy (OR = 2.458; $P < 0.01$), endoscopic papillary balloon dilation (OR = 5.679; $P = 0.000$), endoscopic sphincterotomy (OR = 3.463; $P = 0.000$), CBD stent implantation (OR = 5.780; $P = 0.000$), multiple ERCP procedures (≥2; OR = 2.75; $P = 0.000$), stones in the intrahepatic bile duct (OR = 2.308; $P = 0.000$), periampullary diverticula (OR = 1.627; $P < 0.01$), choledocholithiasis diameter ≥ 10 mm (OR = 1.599; $P < 0.01$), bile duct-duodenal fistula (OR = 2.69; $P < 0.05$), combined biliary tract infections (OR = 1.057; $P < 0.01$), and no preoperative antibiotic use (OR = 0.528; $P < 0.01$) were independent risk factors for the recurrence of choledocholithiasis after ERCP.

CONCLUSION

Patient age greater than 65 years is an independent risk factor for the development of recurrent choledocholithiasis following ERCP, as is history of biliary surgeries, measures during ERCP, and prevention of postoperative complications.

Key words: Choledocholithiasis; Endoscopic retrograde cholangiopancreatography; Recurrence; Common bile duct

Core tip: The potential causes of the recurrence of choledocholithiasis after endoscopic retrograde cholangiopancreatography (ERCP) are unclear. By a large sample sized retrospective study of 954 patients, we concluded that patient age greater than 65 years is an independent risk factor for the development of recurrent choledocholithiasis following ERCP, as is history of biliary surgeries, measures during ERCP, and prevention of postoperative complications.

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INTRODUCTION

Due to its minimal trauma and high safety, endoscopic retrograde cholangiopancreatography (ERCP) has become one of the most important methods for the clinical diagnosis and treatment of choledocholithiasis. Currently, ERCP technology is very advanced, but the recurrence of choledocholithiasis after ERCP is still a challenging problem. Follow-up studies have shown that the incidence of choledocholithiasis recurrence after endoscopic treatment is 2%-22%[1-5]. Many studies have reported that choledocholithiasis is associated with bacterial infection, an abnormal biliary structure, inflammation, endoscopic and surgical treatment, and other factors[1-3,6-8]. However, risk factors for the recurrence of choledocholithiasis have not been thoroughly defined, and the risk factors identified are different across studies. This study aimed to explore the independent risk factors for stone recurrence by comprehensively analyzing the relevant factors for stone recurrence in a large-sized sample.

MATERIALS AND METHODS

Patients

From January 2007 to January 2016, we retrospectively reviewed cases from a well-designed ERCP database at the First Affiliated Hospital of Nanchang University. The follow-up period was from the date of the initial removal of choledocholithiasis to the date of the visit to the hospital for choledocholithiasis recurrence or more than one year for the control group. The patients with the symptoms of fever, abdominal pain, jaundice, or other typical symptoms who revisited our hospital underwent abdominal computed tomography (CT) and ERCP to confirm choledocholithiasis. The patients who underwent choledocholithiasis removal by ERCP and were confirmed to have had their stones completely removed were enrolled. The exclusion criteria were as follows: (1) History of previous ERCP; (2) Patients with tumors of the liver, gallbladder, common bile duct (CBD), or duodenal papilla; (3) Patients were confirmed not to have had their stones completely removed after first choledocholithiasis removal by ERCP; and (4) Patients with incomplete clinical data. The study was approved by the institutional review board of the First Affiliated Hospital of Nanchang University (No. 2017-040).

Outcome measurements

The primary outcomes were risk factors for recurrence of choledocholithiasis. Choledocholithiasis recurrence was defined as recurrence of symptoms of fever, abdominal pain, jaundice, or other typical symptoms, and choledocholithiasis was confirmed by abdominal B-scan ultrasonography, CT, or magnetic resonance cholangiopancreatography 6 mo after the stones were completely removed. The patients were classified into two groups: Recurrence and control groups. The following clinical data were recorded: (1) General characteristics, including sex, age, time from disease onset to stone removal, and history of drinking and smoking; (2) Past medical history, including history of hypertension, diabetes, hepatitis B, fatty liver, cirrhosis, cholecystectomy, biliary-enteric anastomosis, choledocholithotomy, or Billroth II gastrectomy; (3) ERCP-related factors, including endoscopic mechanical lithotripsy (EML), endoscopic papillary balloon dilation (EPBD), endoscopic sphincterotomy (EST), CBD stent implantation, endoscopic nasobiliary drainage, and the number of ERCP procedures; (4) CBD-related factors, including the presence of a combined biliary tract infection, gallstones, stones in the intrahepatic bile duct, a bile duct-duodenal fistula, CBD stenosis, duodenal ulcers, periampullary diverticula (PAD) or ectopic duodenal papilla, duodenal papilla shape, bile duct angle referring to the angle between the horizontal part of the CBD and a horizontal line[9], common bile diameter, CBD diameter, and the number of stones; and (5) Laboratory indicators and treatment, including total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, gallbladder parameters, triglycerides, and the use of preoperative antibiotics.

Statistical analysis

Continuous variables are reported as the mean and standard deviation (SD), and categorical variables are reported as absolute numbers and percentages. Variables found to be statistically significant in the univariate logistic regression analysis were introduced into a multivariate logistic analytic model (stepwise regression) to identify independent risk factors with odds ratios (ORs) and 95% confidence intervals (CIs). A P-value < 0.05 was considered statistically significant. Data were analyzed using SPSS software (v17.0; SPSS Inc., Chicago, IL, United States).

RESULTS

General characteristics

From January 2007 to January 2016, 477 patients revisited the hospital for their choledocholithiasis recurrence. Among these patients, the second and several instance (≥ 3 times) recurrence rates were 19.5% (93/477) and 44.07% (41/477), respectively. The average number of instances of stone recurrence was 1.45, and the average time to first stone recurrence was 21.65 mo. A 1:1 case-control study was used for this investigation, and the controls were 477 patients without choledocholithiasis recurrence after ERCP in more than one year of follow-up. The average age of all patients was 57.43 ± 14.92 years, and the study included 445 males (46.65%) and 509 females (53.35%). There were more patients > 65 years old in the recurrence group than in the control group (OR = 2.437, 95%CI: 1.818-3.266; P = 0.000). No statistically significant differences between the two groups were observed in terms of sex, weight, time from the onset of stone removal to recurrence, or history of drinking or smoking (Table 1).

Table 1 General characteristics compared between the recurrence group and control group

Variable	Recurrence group (*n* = 477)	Control group (*n* = 477)	OR (95%CI)	*P*-value
Sex (male/female)	216/261	229/248	1.116 (0.865-1.439)	0.399
Age > 65 yr (Y/N)	181/296	134/343	2.437 (1.818-3.266)	0.000
Weight (kg), mean ± SD	57.94 ± 16.80	58.24 ± 11.31	0.992 (0.980-1.004)	0.196
[1]Recurrence time (d), mean ± SD	17.77 ± 19.30	17.85 ± 17.25	1.000 (0.993-1.007)	0.950
History of drinking (Y/N)	42/423	61/416	0.677 (0.447-1.026)	0.066
History of smoking (Y/N)	69/395	86/391	0.794 (0.562-1.123)	0.192

[1]Recurrence time was defined as time from the onset of stone removal to recurrence. OR: Odds ratio; 95%CI: 95% confidence interval; Y: Yes; N: No.

Univariate analysis

On univariate analysis, significant differences were noted between the two groups in terms of medical history: A medical history of cholecystectomy (OR = 1.4, 95%CI: 1.085-1.806; *P* = 0.01) and choledocholithotomy (OR = 3.255, 95%CI: 2.114-5.01; *P* = 0.000) (Table 2). Moreover, significant differences in ERCP-related factors were observed: ERCP with EML (OR = 2.068, 95%CI: 1.375-3.11; *P* = 0.000), EPBD (OR = 5.669, 95%CI: 3.594-8.941; *P* = 0.000), EST (OR = 1.701, 95%CI: 1.197-2.417; *P* = 0.003), CBD stent implantation (OR = 3.737, 95%CI: 2.587-5.398; *P* = 0.000), and multiple ERCP procedures (OR = 3.043, 95%CI: 2.242-4.13; *P* = 0.000) (Table 3). CBD-related factors, such as complications including biliary tract infections (OR = 1.034, 95%CI: 1.007-1.061; *P* = 0.014), stones in the intrahepatic bile duct (OR = 2.687, 95%CI: 1.919-3.762; *P* = 0.000), PAD (OR = 1.607, 95%CI: 1.227-2.105; *P* = 0.001), bile-duct duodenal fistula (OR = 2.324, 95%CI: 1.088-4.964; *P* < 0.05), CBD stenosis (OR = 1.661, 95%CI: 1.051-2.626; *P* < 0.05), CBD diameter (OR = 1.988, 95%CI: 1.589-2.486; *P* = 0.000), and choledocholithiasis diameter ≥ 10 mm (OR = 1.580, 95%CI: 1.202-2.067; *P* = 0.001) also showed significant differences between the two groups (Table 4). Additionally, compared with patients in the control group, patients in the recurrence group used fewer antibiotics before ERCP (OR = 0.523, 95%CI: 0.385-0.711; *P* = 0.000) (Table 5).

Multivariate analysis

Multivariate stepwise logistic regression analysis showed that age > 65 years (OR = 1.556, 95%CI: 1.079-2.244; *P* = 0.018), history of choledocholithotomy (OR = 2.474, 95%CI: 1.417-4.320; *P* = 0.001), EPBD (OR = 5.545, 95%CI: 3.026-10.162; *P* = 0.000), EST (OR = 3.378, 95%CI: 1.968-5.797; *P* = 0.000), CBD stent implantation (OR = 5.562, 95%CI: 3.326-9.301; *P* = 0.000), multiple ERCP procedures (OR = 3.601, 95%CI: 1.778-3.805; *P* = 0.000), stones in the intrahepatic bile duct (OR = 2.359, 95%CI: 1.516-3.668; *P* = 0.000), PAD (OR = 1.579, 95%CI: 1.090-2.289; *P* = 0.016), choledocholithiasis diameter ≥ 10 mm (OR = 1.599, 95%CI: 1.117-2.290; *P* = 0.010), biliary-duodenal fistula (OR = 2.720, 95%CI: 1.094-6.765; *P* = 0.031), no use of preoperative antibiotics (OR = 0.527, 95%CI: 0.346-0.801; *P* = 0.003), and biliary tract infections (OR = 1.059, 95%CI: 1.021-1.099; *P* = 0.003) were independent risk factors for the recurrence of choledocholithiasis after ERCP (Table 6). A Kaplan-Meier analysis showed that as age increased, the rate of choledocholithiasis recurrence increased proportionally (Figure 1).

DISCUSSION

The recurrence rate of choledocholithiasis after ERCP is reported to be 2%-22%[1-5]. In our studies, once choledocholithiasis recurred, the next recurrence rate increased in proportion to the number of instances of recurrence, as reported previously[1,10]. Several risk factors have been reported in various studies[1-3,6-8]. This study showed that age > 65 years, history of choledocholithotomy, EPBD, EST, CBD stent implantation, multiple ERCP procedures (≥ 2), stones in the intrahepatic bile duct, PAD, choledocholithiasis diameter ≥ 10 mm, bile duct-duodenal fistula, biliary tract infection, and no preoperative antibiotic use were independent risk factors for the recurrence of choledocholithiasis after ERCP.

It has been reported that the recurrence rate of choledocholithiasis in elderly patients (age > 65 years) can be as high as 30%[11]. The specific mechanism is unclear, but Keizman *et al*[4] believe that elderly patients have more risk factors for the recurrence of stones, such as CBD dilatation, CBD angulation, and PAD, which are related to the recurrence of stones. PAD is rare in patients younger than 40 years of

Table 2 Past medical history compared between the recurrence group and control group

Variable	Recurrence group (*n* = 477)	Control group (*n* = 477)	OR (95%CI)	*P*-value
Hypertension (Y/N)	84/393	63/414	1.405 (0.985-2.002)	0.060
Diabetes (Y/N)	34/441	26/452	1.334 (0.788-2.261)	0.284
Hepatitis B (Y/N)	37/440	34/438	1.083 (0.668-1.758)	0.746
Fatty liver (Y/N)	15/462	23/454	0.641 (0.330-1.244)	0.189
Liver cirrhosis (Y/N)	17/460	10/461	1.704 (0.772-3.760)	0.187
Cholecystectomy (Y/N)	252/225	212/265	1.400 (1.085-1.806)	0.010
Biliary-enteric anastomosis (Y/N)	5/471	2/475	2.521 (0.487-13.06)	0.270
Choledocholithotomy (Y/N)	88/389	31/446	3.255 (2.114-5.010)	0.000

Y: Yes; N: No.

age. It is found more often in older patients, and the occurrence of PAD increases with increasing age.

The surgical removal of choledocholithiasis, whether open or laparoscopic, is seldom performed and is usually reserved for patients in whom ERCP has failed[12]. Laparoscopic CBD exploration is considered in patients with larger stones in whom ERCP has failed. Stone recurrence caused by a history of choledocholithotomy may be due to long-term compression of the biliary tract by the T-tube placed during the choledocholithotomy leading to necrosis and scarring of the epithelial cells of the biliary tract, which easily cause biliary tract stenosis and disorders of biliary excretion[13].

Under physiological conditions, the sphincter of Oddi functions as a "switch" that controls the excretion of pancreatic juice and bile and prevents the reflux of intestinal fluid. Intraoperative ERCP surgeries, such as EPBD, EST, and multiple ERCP procedures, can cause dysfunction of the sphincter of Oddi, which cannot be restored within a short period of time. Then, the barrier against intestinal fluid reflux weakens or disappears, and intestinal fluid can reflux into the bile duct. Because intestinal fluid contains a large amount of bacteria, digestive juices, and food residues, when it refluxes into the bile duct, it changes the bile duct loop and leads to bile duct infection[14]; the colonized bacteria produce β-glucuronic acid, which is associated with the formation of bilirubin calcium stones[5,6,15,16], thus promoting the recurrence of stones. Because bacterial contamination of the bile duct is a common finding in patients with choledocholithiasis, incomplete duct clearance may put patients at risk of cholangitis. Therefore, it is important for endoscopists to ensure that adequate biliary drainage is achieved in patients with choledocholithiasis that cannot be retrieved[17]. However, stents have been placed for long periods of time, leading to bile salt deposition and adherence to the stents. The stents can be a nidus for CBD stones. Bile duct stent placement affects biliary tract dynamics, predisposing the patient to cholestasis. On the one hand, siltation of bile is conducive to bacterial reproduction. On the other hand, concentration of bile stimulates inflammatory changes in the bile duct mucosa, resulting in the precipitation of bile bacteria, shedding cells, and inflammatory cells, which promote the recurrence of stones[18].

PAD form adjacent to the biliary and pancreatic duct confluence. When a diverticulum is large, it can directly compress the CBD, resulting in poor bile excretion. When a diverticulum is complicated by duodenal dysfunction, the food and refluxed intestinal fluid can remain in the diverticulum, stimulating long-term inflammation of the sphincter of Oddi, leading to dysfunction, duodenal papillary stenosis, and cholestasis[19]. PAD promotes the multiplication of beta-glucuronidase-producing bacteria, leading to earlier binding of dissociated glucuronide to bilirubin salts and promoting the pigmentation and formation of stones[20,21]. Larger stones often require lithotripsy, which may increase the risk of postoperative recurrence of stones. Larger stones cause greater forced expansion of the bile ducts and induce impaired function of normal bile ducts, leading to difficulties in bile excretion, which can easily cause cholestasis and bacterial infections[22,23]. Biliary tract infections mainly result from preoperative infections and retrograde reflux of intestinal fluid caused by reduced biliary pressure after cholecystectomy. Studies have shown that more than 94.6% of patients with pigmentary stones have positive bacterial cultures in their bile samples[24]. A variety of causes, such as abnormal biliary anatomy, PAD, abnormal biliary secretion, and biochemistry, can contribute to biliary tract infections. Bile duct bacteria is present, and the resulting beta-glucuronidase causes bilirubin hydrolysis to nonconjugated bilirubin, which can easily combine with calcium to form bilirubin

Table 3 Endoscopic retrograde cholangiopancreatography-related factors compared between the recurrence group and control group

Variable	Recurrence group (*n* = 477)	Control group (*n* = 477)	OR (95%CI)	*P*-value
EML (Y/N)	74/391	40/437	2.068 (1.375-3.110)	0.000
EPBD (Y/N)	111/345	25/461	5.669 (3.594-8.941)	0.000
EST (Y/N)	404/60	382/96	1.701 (1.197-2.417)	0.003
CBD stent implantation (Y/N)	130/334	45/432	3.737 (2.587-5.398)	0.000
ENBD (Y/N)	271/192	282/195	0.976 (0.753-1.266)	0.855
ERCP procedures, mean ± SD	1.38 ± 0.55	1.14 ± 0.39	3.043 (2.242-4.130)	0.000

ERCP: Endoscopic retrograde cholangiopancreatography; EML: Endoscopic mechanical lithotripsy; EPBD: Endoscopic papillary balloon dilation; EST: Endoscopic sphincterotomy; CBD: Common bile duct; ENBD: Endoscopic nasobiliary drainage; Y: Yes; N: No.

calcium and promote gallstone formation[6,25-29]. The lack of preoperative use of antibiotics may increase the risk of biliary tract infections and promote the recurrence of stones. The presence of a biliary-duodenal fistula is a risk factor for the recurrence of choledocholithiasis. No relevant literature has been reported. Bile duct-duodenal fistulas often exist for a long time, and the refluxed intestinal fluid irritates the biliary mucosa, eventually leading to chronic inflammation.

This study was a single-center retrospective study. Although the clinical data of the patients were comprehensively analyzed and the risk factors for recurrence of choledocholithiasis after ERCP were studied in all aspects, there were still limitations to this retrospective study. This study did not further analyze the accuracy of individual risk factors for predicting the recurrence of choledocholithiasis. In conclusion, patient age greater than 65 years is an independent risk factor for the development of recurrent choledocholithiasis following ERCP, as is history of biliary surgeries, measures during ERCP, and prevention of postoperative complications.

Table 4 Common bile duct-related factors compared between the recurrence group and control group

Variable	Recurrence group (*n* = 477)	Control group (*n* = 477)	OR (95%CI)	*P*-value
Gallstones (Y/N)	274/203	272/205	1.017 (0.787-1.315)	0.896
Intrahepatic bile duct stones (Y/N)	133/344	60/417	2.687 (1.919-3.762)	0.000
Ectopic duodenal papilla (Y/N)	3/462	1/476	3.091 (0.32-29.822)	0.329
Duodenal ulcers (Y/N)	21/443	26/451	0.822 (0.456-1.483)	0.516
PAD (Y/N)	188/276	142/335	1.607 (1.227-2.105)	0.001
Bile duct angle (Y/N)	36/429	25/452	1.517 (0.896-2.570)	0.121
CBD diameter (cm), mean ± SD	1.27±0.73	1.01±0.55	1.988 (1.589-2.486)	0.000
Choledocholithiasis diameter ≥ 10 mm (Y/N)	229/134	126/236	1.580 (1.202-2.067)	0.001
Number of stones (*n*), (mean ± SD)	1.90 ± 1.19	1.82 ± 1.02	1.12 (0.992-1.265)	0.067
Biliary tract infections (Y/N)	46/418	20/457	2.515 (1.463-4.321)	0.001
Bile-duct duodenal fistula (Y/N)	22/442	10/467	2.324 (1.088-4.964)	0.029
CBD stenosis (Y/N)	51/413	33/444	1.661 (1.051-2.626)	0.030

PAD: Periampullary diverticula; CBD: Common bile duct; Y: Yes; N: No.

Table 5 Laboratory indicators and treatment compared between the recurrence group and control group

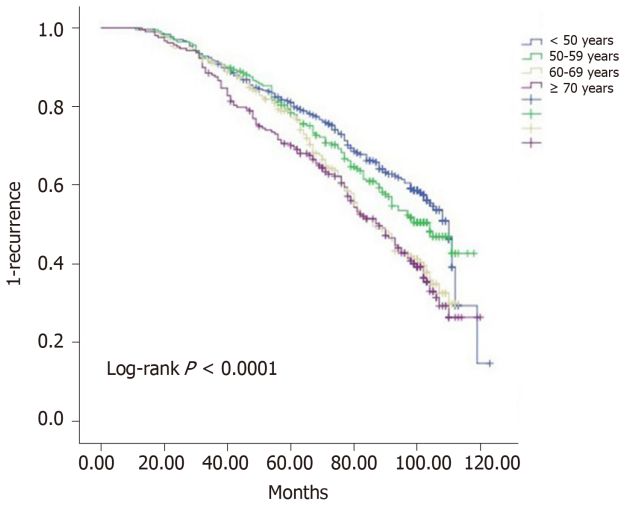
Variable	Recurrence group (*n* = 477)	Control group (*n* = 477)	OR (95%CI)	*P*-value
TBi (umol/L), mean ± SD	53.02 ± 69.91	102.47 ± 126.1	1.000 (0.999-1.001)	0.795
DBi (umol /L), mean ± SD	31.41 ± 44.64	71.21 ± 126.1	1.000 (0.998-1.002)	0.961
ALT (U/L), mean ± SD	129.3 ± 142.91	98.39 ± 127.62	0.999 (0.998-1.000)	0.201
AST (U/L), mean ± SD	96.99 ± 132.68	64.86 ± 103.69	0.999 (0.998-1.000)	0.123
GGT (U/L), mean ± SD	288.3 ± 262.92	306.3 ± 267.96	1.000 (1.000-1.001)	0.441
Cholesterol (mmol /L), mean ± SD	4.77 ± 14.09	4.33 ± 1.53	0.990 (0.886-1.105)	0.852
Triglyceride (mmol /L), mean ± SD	1.30 ± 0.82	1.43 ± 0.85	0.888 (0.742-1.063)	0.197
Used antibiotics before ERCP (Y/N)	336/141	387/85	0.523 (0.385-0.711)	0.000

TBi: Total bilirubin; DBi: Direct bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyltransferase; ERCP: Endoscopic retrograde cholangiopancreatography; Y: Yes; N: No.

Table 6 Multivariate stepwise logistic regression analysis for the recurrence of choledocholithiasis

Variable	OR (95%CI)	*P*-value
Age > 65 yr	1.556 (1.079-2.244)	0.018
Choledocholithotomy	2.474 (1.417-4.320)	0.001
EPBD	5.545 (3.026-10.162)	0.000
EST	3.378 (1.968-5.797)	0.000
CBD stent implantation	5.562 (3.326-9.301)	0.000
ERCP procedures	2.601 (1.778-3.805)	0.000
Stones in the intrahepatic bile duct	2.359 (1.516-3.668)	0.000
PAD	1.579 (1.090-2.289)	0.016
Choledocholithiasis diameter ≥ 10 mm	1.435 (1.094-1.883)	0.009
Biliary-duodenal fistula	2.720 (1.094-6.765)	0.031
Used antibiotics before ERCP	0.527 (0.346-0.801)	0.003
Biliary tract infections	1.059 (1.021-1.099)	0.003

ERCP: Endoscopic retrograde cholangiopancreatography; EPBD: Endoscopic papillary balloon dilation; EST: Endoscopic sphincterotomy; CBD: Common bile duct; PAD: Periampullary diverticula.



The cumulative rate of choledocholithiasis recurrence (%)

Age (yr)	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr
< 50	0.3	3	8.5	15.2	19	24.4	34.8
50-59	0.4	3.5	8.8	13.3	21.6	39.7	39
60-69	0.5	5.1	9.4	15.6	21.8	35.7	48.6
≥ 70	0.5	4.8	12.4	23.1	29.9	37.2	49

Figure 1 Kaplan–Meier curves showing the recurrence rate of CBD stones according to age (< 50 years, blue line; 50-59 years, green line; 60-69 years, yellow line; ≥ 70 years, red line) (log-rank *P* < 0.0001).

ARTICLE HIGHLIGHTS

Research background

Currently, endoscopic retrograde cholangiopancreatography (ERCP) technology is very advanced, but the recurrence of choledocholithiasis after ERCP is still a challenging problem. The potential causes of the recurrence of choledocholithiasis after ERCP are unclear.

Research motivation

To explore the independent risk factors for stone recurrence by comprehensively analyzing the relevant factors for stone recurrence in a large-sized sample.

Research objectives

The study aimed to analyze the potential causes of the recurrence of choledocholithiasis after ERCP.

Research methods

The ERCP database of our medical center was retrospectively reviewed, and information regarding eligible patients was collected. A 1:1 case-control study was used for this investigation. Data were analyzed by univariate and multivariate logistic regression and Kaplan-Meier analyses.

Research results

Multivariate logistic regression analysis showed that age > 65 years, combined history of choledocholithotomy, endoscopic papillary balloon dilation, endoscopic sphincterotomy, common bile duct stent implantation, multiple ERCP procedures (≥2), stones in the intrahepatic bile duct, periampullary diverticula, choledocholithiasis diameter ≥ 10 mm, bile duct-duodenal fistula, combined biliary tract infections, and no preoperative antibiotic use were independent risk factors for the recurrence of choledocholithiasis after ERCP.

Research conclusions

In this large sample sized retrospective study, we concluded that patient age greater than 65 years is an independent risk factor for the development of recurrent choledocholithiasis following ERCP, as is history of biliary surgeries, measures during ERCP, and prevention of postoperative complications.

Research perspectives

The pathogenesis of recurrence of choledocholithiasis should be studied in future, as well as the prevention and treatment.

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CASE REPORT

Laparoscopic appendectomy for elemental mercury sequestration in the appendix: A case report

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Abstract

BACKGROUND

Despite negligible absorption of elemental mercury after acute ingestion, retention in the appendix with subsequent local and systemic complications is possible. We present a case of elemental mercury sequestration in the appendix, managed by laparoscopic appendectomy.

CASE SUMMARY

A 57-year-old Caucasian female was found unconscious following application of long-lasting insulin detemir and ingestion of elemental mercury in a suicidal attempt. Diagnostic investigations revealed several radiopaque collections in the gastrointestinal (GI) tract and elevated mercury levels in the blood. Much of the ingested elemental mercury was eliminated from the GI tract with stools stimulated by several enemas. However, a significant amount of mercury remained sequestrated in the appendix despite all conservative measures. Consequently, following deliberations by an interdisciplinary team of specialists, laparoscopic appendectomy was performed 29 d after the mercury ingestion. The surgery itself and postoperative course were uneventful.

CONCLUSION

Since conservative measures are often unsuccessful in the management of mercury retention in the appendix, surgery remains a compelling option to prevent possible associated complications.

Key words: Mercury poisoning; Appendix; Mercury ingestion; Mercury retention; Appendectomy; Case report

Core tip: Despite negligible absorption of elemental mercury after acute ingestion,

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retention in the appendix with subsequent local and systemic complications is possible. The question of whether or not to perform appendectomy in an asymptomatic patient remains open. We present a case of elemental mercury sequestration in the appendix, managed by laparoscopic appendectomy in order to prevent possible complications. Given the limited evidence regarding the optimal management approach for patients with retained mercury, the choice of treatment strategy should be determined on a case-by-case basis by a multidisciplinary team.

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INTRODUCTION

Mercury is a heavy metal which compounds occur in different chemical dispositions including elemental, inorganic and organic forms[1,2]. Its human toxicity is well-established and varies with the form of mercury, the dose and the type of exposure[1]. Acute ingestion of elemental mercury is considered non-toxic due to the negligible absorption by intact gastrointestinal (GI) mucosa (oral bioavailability of 0.04%)[3]. However, after ingestion of even small amounts of elemental mercury, sequestration in the appendix is possible and subsequent local complications can occur[3,4]. Due to limited data in the literature the optimal management of patients is still not clear.

In the present report, we describe the clinical presentation, management, and outcome of mercury sequestration in appendix following elemental mercury ingestion in a suicidal attempt. The management approach is discussed in the context of available literature.

CASE PRESENTATION

Chief complaints

A 57-year-old Caucasian female was found unconscious near her house by her brother several hours after application of approximately 4 pens of long-lasting insulin detemir and ingestion of elemental mercury in a suicidal attempt.

History of present illness

Besides being treated for depression she had already threatened to commit suicide before.

History of past illness

Background medical history was remarkable for depression, type 2 diabetes, arterial hypertension and dyslipidemia. She had also undergone two previous abdominal surgical procedures – bariatric gastric by-pass operation and GI cyst removal.

Physical examination upon admission

The patient was noted to be unconscious (GCS 6) by the paramedics, with respiratory rate of 12/min, heart rate of 89/min, blood pressure of 162/72 mmHg and unmeasurable pO_2 saturation in peripheral blood. She was brought to hospital in severe hypothermia with body core temperature of only 28.4 °C.

Laboratory examinations

The laboratory blood tests were performed showing elevation of mercury levels in the blood (elemental blood mercury being 136.10 μg/L; normal value is up to 5 μg/L).

Imaging examinations

X-ray of abdomen was performed and showed several radiopaque foreign bodies, mostly in GI tract (Figure 1).

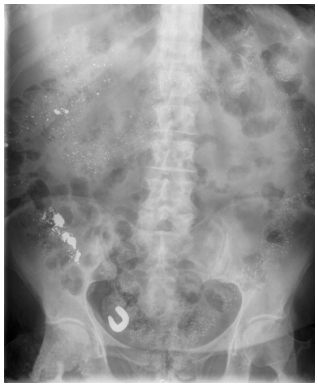

Figure 1 Abdominal X-ray 16 d after the elemental mercury ingestion showing a lot of radiopaque particles along gastrointestinal tract, mostly in colon with obvious sequestration in the appendix.

FINAL DIAGNOSIS

Intentional self-poisoning, elemental mercury ingestion, foreign bodies in GI tract with retention in appendix, insulin poisoning, hypoglycemia, depression, suicidal attempt.

TREATMENT

After admission to ICU in general hospital, a gastric lavage was performed and osmotic laxatives (Moviprep®) were administered. Due to discovered elemental mercury ingestion and subsequent elevation of blood mercury levels the patient was transferred to the National Center for Clinical Toxicology and Pharmacology for potential treatment with chelating agents. Treatment with metal-chelating agent dimercaprol (200 mg every 4 h) was commenced and administered for 8 d. The expected rise of mercury in urine and fall of mercury in blood occurred (elemental mercury in urine was 52.12 μg/L and in blood 81.53 μg/L).

In the meantime, the majority of the ingested elemental mercury had been already eliminated from the GI tract with stools stimulated by several enemas (Figure 2). However, a certain amount of elemental mercury was still sequestrated in the appendix despite all conservative measures.

Due to the risk of developing appendicitis and possible continuous absorption of sequestrated elemental mercury with its potential toxic effects, the decision to perform appendectomy was made by an interdisciplinary team of specialists. Laparoscopic appendectomy was subsequently performed 29 d after elemental mercury ingestion, with special care taken to avoid intraperitoneal spillage of mercury during the procedure. At the end of the surgical procedure, an intraoperative x-ray of the abdomen was performed to exclude any elemental mercury retained at the stapler line. Following removal of the appendix, dissection of the specimen was performed, revealing a copious collection of elemental mercury inside its lumen (Figure 3). Histopathology report described a 6 cm long appendix with mild chronic and focally purulent appendicitis with elemental mercury in its lumen. The surgery itself and postoperative course were uneventful. The patient was dis-charged home three days after the operation.

OUTCOME AND FOLLOW-UP

The surgery itself and postoperative course were uneventful. The patient was discharged home three days after the operation.

DISCUSSION

We report a case of elemental mercury ingestion in a suicidal attempt with subsequent retention of mercury in the appendix. In order to prevent complications from the retained mercury, laparoscopic appendectomy was performed. Histopathology report of the removed appendix described a mild chronic and focally purulent appendicitis

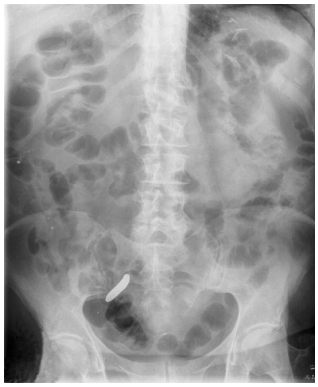

Figure 2 X-ray of the abdomen after several enemas showing almost no remnant of elemental mercury in gastrointestinal tract except sequestration of mercury in the appendix.

approximately 1 mo after the mercury ingestion.

In a recently published paper by Michielan *et al*[3], a review of similar case reports was performed. Including their own case, they found only 10 described cases of elemental mercury sequestration in the appendix after oral ingestion. The clinical consequences of oral ingestion of mercury are largely unknown since the vast majority of systemic toxicity is associated with the inhalation route[4]. Acute ingestion of elemental mercury is even considered non-toxic due to negligible absorption by intact GI mucosa (oral bioavailability of 0.04%)[3] Furthermore, most foreign bodies that enter the GI tract are eliminated in four to six days[5]. However, due to the vertical anatomy at the coecal region, foreign bodies heavier than other bowel contents are capable of entering the lumen of the appendix (elemental mercury for instance) where the peristalsis is insufficient to push it back into the GI tract[4-6].

Despite oral bioavailability of elemental mercury being close to nil, there are still several reasons to justify the measures for removal of mercury sequestrated in the appendix. The first is the possible interaction of mercury with gut bacteria which might lead to the conversion of elemental mercury into organic mercury compounds[7]. Unlike elemental mercury, the bioavailability of organic mercury compounds is high via the GI route as they can be absorbed almost completely[8,9] with subsequent systemic toxicity. The second reason to consider is possible local complications such as development of acute appendicitis with consequent perforation and spillage of mercury into the abdominal cavity. To date, there are only two case reports describing acute inflammation of the appendix due to elemental mercury retention, with both papers published over 50 years ago[10,11]. To the best of our knowledge, the index case report is the third describing appendicitis consequent on retained elemental mercury.

Different conservative and surgical approaches of management of elemental mercury sequestrated in appendix have been reported in the literature. In general, conservatives measures such as whole bowel irrigation and endoscopic irrigation are recommended as first line of treatment[3]. Besides irrigation methods, the Trendelenburg position (30°) combined with left lateral decubitus position has also been reported to be successful in one patient[12]; although this approach failed to remove the mercury from the appendix in other patients[3]. Moreover, one report also described a complete spontaneous elimination of appendiceal mercury within 7 mo without any associated complication[13]. We believe that the effectiveness of the conservative methods may be significantly influenced by the variations in the anatomy and location of the appendix. Meanwhile, since conservative measures are often unsuccessful, surgery remains a compelling option to prevent possible associated complications of retained mercury in the appendix.

Nevertheless, the question of whether or not to perform appendectomy in an asymptomatic patient remains open[3], since surgery itself bears risks of potential complications. Remarkable in this regard is the potential perforation of the appendix during the procedure and spillage of elemental mercury into the peritoneal cavity causing life-threatening peritonitis. However, in the hands of the experienced surgeon, the rate of complications of laparoscopic appendectomy is very low.

Given the paucity of evidence regarding the optimal treatment of patients with retained ingested mercury, it is prudent to recommend that the choice of treatment strategy should be determined on a case-by-case basis by a multidisciplinary team (MDT) including toxicologists, gastroenterologists and abdominal surgeons[3]. Based on the presumed amount of retained mercury and the patient's overall clinical circumstances, the MDT should carefully weigh the potential complications of reta-

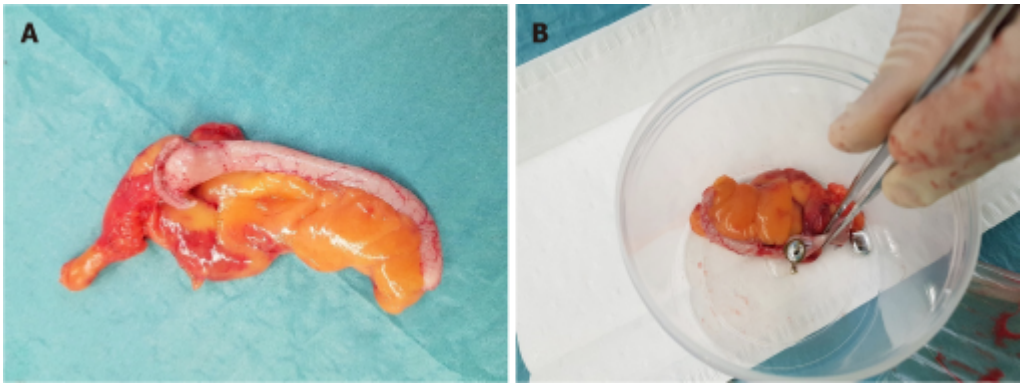

Figure 3 Specimen of the appendix after laparoscopic appendectomy. A: Intact specimen; B: After the incision elemental mercury showed and spilled out of the lumen of the appendix.

ined mercury against the potential risks and benefits of surgical intervention for each patient.

CONCLUSION

Since conservative measures are often unsuccessful for elemental mercury sequestration in appendix, surgery seems feasible and safe option. Given the limited evidence the choice of treatment should be determined on a case-by-case basis by a MDT. More case reports are needed to determine optimal treatment strategy.

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CASE REPORT

Sofosbuvir/Ribavirin therapy for patients experiencing failure of ombitasvir/paritaprevir/ritonavir + ribavirin therapy: Two cases report and review of literature

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Author contributions: Sato K designed the study and drafted the article and analyzed and interpreted the data; Yamazaki Y, Kobayashi T, Takakusagi S, Horiguchi N, Kakizaki S, and Uraoka T analyze the data. Andou M, Matsuda Y assisted the diagnosis and interpreted the data. Ohnishi H analyzed the virological data. Okamoto H approved the final version to be published. All authors read and approved the final manuscript.

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Abstract

BACKGROUND

The effectiveness of sofosbuvir/ribavirin (SOF/RBV) combination therapy, which is one of the 1st-choice therapeutic options for patients with hepatitis C virus (HCV) genotype 2 (HCV-G2) in Japan according to the most recent version of the Japan Society of Hepatology guideline, for patients who experienced failure of the ombitasvir/paritaprevir/ritonavir plus ribavirin (OBV/PTV/r+RBV) combination therapy, which was another option for patients with HCV-G2, is unknown.

CASE SUMMARY

We evaluated the effects of SOF/RBV combination therapy in two patients with genotype 2a who could not achieve a sustained virological response (SVR) by OBV/PTV/r+RBV combination therapy. One patient was complicated with Vogt-Koyanagi-Harada (VKH) disease. Resistance-associated variations before SOF/RBV combination therapy were not detected in two patients. Both patients had an SVR at 12 wk after the treatment (SVR12). Regarding adverse events (AEs), itching, chill, a dull feeling in the throat and cough as well as increase of alanine transaminase level were shown in one patient, while a headache and

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deterioration of light aversion probably due to the recurrence of VKH disease were shown in the other patients. In addition, the latter patient developed arthralgia and morning stiffness approximately 7 wk after the therapy and turned out to be diagnosed with rheumatoid arthralgia.

CONCLUSION
SOF/RBV therapy might be effective for patients experiencing failure of OBV/PTV/r+RBV therapy, but caution should be taken regarding the AEs.

Key words: Direct-acting antiviral agent failure; Hepatitis C; Genotype 2; Ribavirin; Sofosbuvir; Case report

Core tip: The effectiveness of sofosbuvir/ribavirin (SOF/RBV) therapy was unknown for patients who experienced failure of ombitasvir/paritaprevir/ritonavir plus ribavirin therapy and had hepatitis C virus genotype 2. Although there were only 2 patients, SOF/RBV therapy was effective. However, both patients experienced adverse events including unanticipated development or deterioration of autoimmune diseases. Because SOF/RBV therapy is generally well-tolerated, one of the patients was considered a specific case. However, the cases suggest SOF/RBV therapy should be carefully applied in case of the existence of baseline autoimmune disease. Our case reports warrant future studies, but careful observation during and after treatment is required.

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INTRODUCTION

The combination therapies with sofosbuvir/ribavirin (SOF/RBV) and glecaprevir/pibrentasvir (GLE/PIB) are the 1st-choice therapeutic options for hepatitis C virus (HCV)-infected patients with genotype 2 in Japan according to the most recent version (ver. 6.2) of the Japan Society of Hepatology (JSH) guideline for the management of HCV infection. Ombitasvir/paritaprevir/ritonavir plus ribavirin (OBV/PTV/r+RBV) was the 1st-choice therapeutic option for HCV-infected patients with genotype 2 in Japan according to the previous version (ver. 5.4) of the JSH guideline, and this regimen was completely replaced by the combination therapy of GLE/PIB in the most recent version (ver. 6.2) of the JSH guideline.

The sustained virological responses at 12 wk after treatment (SVR12) for HCV-infected patients with genotype 2 are 97% and 91.5% for the 12-wk SOF/RBV regimen[1] and 16-wk OBV/PTV/r+RBV regimen[2], respectively. The combination therapy of GLE/PIB for HCV-infected patients with genotype 2 shows SVR12 rates of 97.8% and 100% for patients with chronic hepatitis and those with liver cirrhosis, respectively[3]. These direct-acting antiviral agent (DAA)-based therapies have a relatively favorable safety profile.

Although the efficacy of DAA-based therapy is quite high, we have recently experienced a certain percentage of patients with on-treatment virologic failure during treatment and virologic relapse during post-treatment for DAA-based therapy. Currently, three interferon (IFN)-free DAA-based therapies as mentioned above are available, and SOF/ledipasvir (LDV) combination therapy has just become available for HCV-infected patients with genotype 2 in Japan.

An SVR to the combination therapies of OBV/PTV/r+RBV and GLE/PIB in HCV-infected patients with genotype 2 who showed virologic failure with the SOF/RBV regimen was achieved[3,4]. However, it is unknown whether an SOF-based regimen can rescue patients with treatment failure by the combination therapy with OBV/PTV/r+RBV or GLE/PIB to date. We therefore examined the efficacy and safety of the combination therapy with SOF/RBV in two patients infected with HCV

genotype 2a who could not achieve an SVR by the combination therapy with OBV/PTV/r+RBV.

CASES PRESENTATION

Baseline patient demographics and characteristics

The two patients were Japanese and comprised of a man and a woman. Both patients did not undergo liver biopsy. The severity of liver disease was judged as being chronic hepatitis in both patients by practical discriminant function to perform the distinction between chronic hepatitis and liver cirrhosis in patients with HCV infection[5] before the registration for the phase 3, randomized, open-label study with OBV/PTV/r+RBV[2]. Actually, the disease severity in both cases, however, was considered chronic hepatitis with advanced fibrosis that is close to liver cirrhosis based on the laboratory and imaging data. For example, although portosystemic shunt was not observed, FIB4 index and AST-to-platelet ratio index were relatively high in both cases (Table 1). HBsAg, HBcAb, and HBsAb were all negative in both patients. After starting the combination therapy with SOF/RBV, we principally checked the laboratory data and adverse events (AEs) at least once a fortnight. We obtained informed consent from both patients.

Diagnostic procedure

HCV genotypes were evaluated in commercial laboratories (BML, Inc., Tokyo, Japan). A TaqMan HCV test, version 2.0, real-time polymerase chain reaction (PCR) assay (F. Hoffmann, La Roche Ltd., Basel, Switzerland) was used to quantify HCV RNA.

Regarding resistance-associated variations (RAVs), we evaluated Y56 and D168 in the HCV/2a-NS3 for PTV[6], T24, F28, M31, and C92 in the HCV/2a-NS5A for OBV[6], and S282 in the HCV/2a-NS5B for SOF[7]. The genome sequences were analyzed using the serum samples before the combination therapy with OBV/PTV/r+RBV. PCR amplification and subsequent direct sequencing were performed to determine the RAVs. Table 2 shows the primers used for cDNA synthesis and amplifications.

The IL28B rs12979860 gene polymorphism of both patients was evaluated by the central laboratory of AbbVie Inc.

The HLA-DRB1 and DQB1 genotyping was determined by sequence based typing and HLA-DQA1 genotyping was determined by sequence-specific primers in commercial laboratories (SRL, Inc., Tokyo, Japan).

Study subjects

Patient 1: A 61-year-old female was diagnosed with chronic hepatitis C in 1995. Although the exact transmission source of the HCV could not be identified, the hemostatic agent used for a caesarotomy in 1989 might have been contaminated with HCV. She had received pegylated interferon/RBV therapy in 2013 after receiving partial splenic embolization. However, the treatment was discontinued due to erythema and itching at approximately 1 mo of the therapy. Resultantly, the viral response was a relapse. Then, she enrolled in a phase 3, randomized, open-label study with OBV/PTV/r+RBV. She received 25 mg OBV/150 mg PTV/100 mg r, which was administered orally once daily, and 600 mg RBV, which was administered orally twice daily. She was assigned to the 12w-treatment arm in the open-label study. Although the serum HCV RNA was disappeared at week 1 of the therapy and she achieved a rapid virological response (RVR), the HCV RNA reappeared at post-treatment week (PTW) 8 of the therapy.

Patient 2: A 50-year-old male was diagnosed with chronic hepatitis C in 2010. He has suffered from Vogt-Koyanagi-Harada (VKH) disease since 2011. He has a history of drug abuse and thus, the transmission source of the HCV may be from sharing needles. It has been reported that there is an association between VKH disease and IFN with RBV therapy, so he has not received IFN-based therapy. Although we had been concerned about the effect of RBV on VKH disease, we decided to apply DAA-based therapy including RBV due to the predicted advanced fibrosis based on laboratory data, including a relatively high level of alpha-fetoprotein and fluctuating serum alanine aminotransferase (ALT) level, although liver cirrhosis was denied due to practical discriminant function to perform the distinction between chronic hepatitis and liver cirrhosis in patients with HCV infection[5]. Then, he was enrolled in a phase 3, randomized, open-label study with OBV/PTV/r+RBV. He received the same dosage and administration of OBV/PTV/r and 800 mg RBV, which was administered orally twice daily. He was assigned to the 16w-treatment arm in the open-label study. He did not achieve an RVR. The HCV RNA disappeared at week 6 of the therapy and reappeared at the end of treatment. The serum ALT level of the patient increased

Table 1 Laboratory findings at baseline, and the treatments and outcomes of the patients

Parameters	Patient 1	Patient 2
Age (yr)	61	50
Sex	Female	Male
BMI (kg/m^2)	25.1	29.7
HCV genotype	2a	2a
IFN-based therapy: Outcome	Peginterferon/ribavirin: Intolerance: discontinuation due to erythema and itching	Naive: NA
DAA-based therapy: Outcome	12-wk ombitasvir/paritaprevir/ritonavir plus ribavirin: relapse at PTW8	16-wk ombitasvir/paritaprevir/ritonavir plus ribavirin: breakthrough at the end of treatment
At the start of therapy		
HCV RNA (log IU/mL)	4.7	6.9
AST (IU/L)	81	31
ALT (IU/L)	60	31
WBC (cells/μL)	4100	4900
Hemoglobin (g/dL)	11.3	15.5
Platelets (cells/μL)	118000	81000
AFP (ng/mL)	62	13.1
FIB4 index	5.41	3.44
APRI	2.08	1.16
RAVs at baseline[1]	None	None
IL28B SNP rs12979860	C/T	C/C
Severity of liver disease	Chronic hepatitis	Chronic hepatitis
Treatment and outcome		
Sofosbuvir/ribavirin dosage (mg)	400/600	400/800
Achievement of a rapid virological response	Yes	Yes
Adherence to sofosbuvir/ribavirin	100%	100%
Weeks of therapy	12	12
Response	SVR24	SVR24
Concomitant drugs	Amlodipine besilate and eplerenone	None
Adverse events	Itching, chill, dull feeling in the throat, hypertension, cough, and increase of transaminases	Headache, blurring vision and light aversion probably due to recurrence of Vogt-Koyanagi-Harada disease, arthralgia and morning stiffness probably due to the development of rheumatoid arthralgia

[1] RAVs against NS3, NS5A or NS5B. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AFP: Alpha-fetoprotein; APRI: AST-to-platelet ratio index; BMI: Body mass index; DAA: Direct-acting antiviral agent; HCV: Hepatitis C virus; IFN: Interferon; IL: Interleukin; NA: Not applicable; PTW: Post treatment week; RAVs: Resistance-associated variations; SNP: Single nucleotide polymorphism; SVR: Sustained virological response; WBC: White blood cells.

again at PTW 4. Regarding the AEs, he became aware of being easily defocused near week 1 of the therapy. He was referred to an ophthalmologist. He was diagnosed with a recurrence of VKH disease at week 2 of the therapy due to choroidal thickening. He received a subtenon capsule injection of triamcinolone acetonide at week 2, week 12 and PTW 9. Then, he had a remission of the symptoms of VKH disease.

FINAL DIGNOSIS

Both patients were diagnosed with HCV genotype 2 with failure of OBV/PTV/r+RBV therapy based on laboratory findings and DAA treatment history.

TREATMENT

Patient 1

We tried to administer a different DAA-based regimen that is SOF/RBV. She did not have any RAVs regarding NS3, NS5A and NS5B before the treatment with SOF/RBV.

Table 2 Primers used for the amplification of the NS3, NS5A and NS5B regions of the genotype 2a hepatitis C virus genome

Primer name	Sequence (5' to 3')[1]	Nucleotide position[2]	Notes
HCV/2a-NS3 region			
HC686	GTGGARCCYATYATCTTCAGTC	3263-3284	1st sense
HC687	GYACAGCHGGYGGYGTGCTG	3991-4010	RT and 1st antisense
HC688	TYATCTTCAGTCCGATGGAG	3273-3292	2nd sense
HC689	HGGYGGYGTGCTGTTGTCAC	3984-4003	2nd antisense
HCV/2a-NS5A region			
HC694	YGCTTCCAGAGGAAACCACG	6118-6137	1st sense
HC695	AGCCCRACGCWRAACGAGAC	6785-6804	RT and 1st antisense
HC696	ACYCAYTACGTGACGGAGTC	6146-6165	2nd sense
HC697	CWRAACGAGACCTCRTCCCG	6776-6795	2nd antisense
HCV/2a-NS5B region			
HC673	TGCTGCTCYATGTCWTACTCC	7661-7681	1st sense
HC669	GARTACCTRGTCATRGCCTCC	8686-8706	RT and 1st antisense
HC674	GCTCYATGTCWTACTCCTGGAC	7665-7686	2nd sense
HC670	CATRGCCTCCGTGAAGRCTC	8676-8695	2nd antisense

[1] R=A/G, D=G/A/T, H=A/C/T, W=A/T and Y=T/C.
[2] Nucleotide positions are numbered in accordance with the HC-J6 strain (D00944) as the HCV/2a reference.
HCV: Hepatitis C virus.

Then, she received the combination therapy of SOF/RBV.

Patient 2

As we considered that the recurrence of VKH disease associated with DAA-based therapy can be controllable, we tried to administer a different DAA-based regimen that is SOF/RBV. He did not have any RAVs regarding NS3, NS5A and NS5B before the treatment with SOF/RBV. He received the combination therapy of SOF/RBV.

OUTCOME AND FOLLOW-UP

Patient 1

She achieved an RVR, SVR12 and SVR24. However, she developed itching, chill, a dull feeling in the throat, hypertension and cough. Her transaminases were temporarily increased. We considered elevation of transaminases as AE, but it may be due to discontinuation of ursodeoxycholic acid and Monoammonium glycyrrhizinate, Glycine, Aminoacetic acid, L-Cysteine hydrochloride hydrate (Stronger Neo Minophagen C®) just before the start of SOF/RBV. Although this is applied to Patinet 2 as well, the effect may vary in patients. After the treatment, these AEs disappeared completely.

Patient 2

He achieved an RVR, SVR12 and SVR24. Regarding the AEs, he developed a headache at week 1 and week 6 of the therapy. The recurrence of VKH disease was diagnosed at week 5 of the therapy on a regular clinical visit to his primary care ophthalmologist, and he was referred to the ophthalmologist in our hospital. Then, he received a subtenon capsule injection of triamcinolone acetonide, and resultantly, he had remission of light aversion. We retrospectively found that he had noticed a slightly blurring vision and light aversion one month before the combination therapy with SOF/RBV according to the detailed medical interview. As it remains a possibility that the symptom was deteriorated after the start of the combination therapy, this AE was however considered as being a treatment-emergent AE. Fortunately, the severity of the recurrence was mild because the single subtenon injection caused the remission of the disease. However, he developed arthralgia and morning stiffness approximately 7 wk after the end of treatment and turned out to have rheumatoid arthralgia (RA). The ultrasonography findings of the right ulnar intercarpal joints in patient 2 are shown in Figure 1. The RA was considered as being a treatment-emergent AE. The symptoms due to RA were improved using corticosteroid and disease modified anti-rheumatic

drugs. HLA DNA typing showed that this patient had the DRB1*04:05:01, DQB1*04:01:01, and DQA1*03:03 genotypes. Serum HCV RNA levels remain negative even after treatment of RA.

The clinical course of both patients is shown in Figure 2. The laboratory findings, treatments and outcomes of both patients are shown in Table 1.

DISCUSSION

The major finding from this case series is that the combination therapy of SOF/RBV may have promise as an efficacious therapy in patients infected with HCV genotype 2 who could not achieve a SVR by the combination therapy with OBV/PTV/r+RBV. This is the first report showing the efficacy of the combination therapy with SOF/RBV for patients with failure of the combination therapy with OBV/PTV/r+RBV. OBV/PTV/r+RBV has been performed until very recently and was replaced by GLE/PIB combination therapy in Japan. However, there might be cases of treatment failure with OBV/PTV/r+RBV, and we believe that our study is useful for this current setting.

However, patient 1 received once-daily co-formulated OBV/PTV/r+RBV (25 mg/150 mg/100 mg) with twice-daily weight-based RBV for 12 wk but not the 16 wk that are covered by insurance at the present. The virological response for the combination therapy with OBV/PTV/r+RBV for patient 1 was a relapse. If she received this regimen for 16 weeks, she might have achieved SVR12 and SVR24. In fact, this regimen could achieve a numerically higher SVR12 rate in the 16-wk regimen compared to the 12-wk regimen[2]. In addition, the SVR12 rates based on this regimen were higher in patients with the HCV genotype 2a than in those with the HCV genotype 2b. However, both cases were HCV genotype 2a and were susceptible to this regimen, even the 12-wk regimen[2]. In this regard, patient 1, who received the 12-wk regimen, was considered relatively treatment-resistant. The reasons for the treatment failure due to the combination therapy with OBV/PTV/r+RBV were unclear. The patient characteristics that were statistically associated with virologic failure for the combination therapy with OBV/PTV/r+RBV were a prior treatment experience and male gender[2]. Patient 1 had a prior treatment experience and patient 2 is male. The RBV dose modification was a factor that was potentially but not statistically associated with virologic failure[2]. Neither of the patients had an RBV dose modification. RAVs before the combination therapy of SOF/RBV were not detected in NS3/4A, NS5A or NS5B in either patient. Patient 1 had no RAVs in NS3/4A or NS5A at the time of failure based on the clinical trial[2]. Regarding patient 2, the information about RAVs was not available at the time of failure. The genotypes of IL28B SNP rs12979860 were C/T and C/C in patient 1 and patient 2, respectively. Although, for the combination therapy with LDV plus sofosbuvir for patients with chronic HCV genotype 1, the multivariate analysis identified the FIB4 index (< 3.25), IL28B rs8099917 (TT type), and NS5A-L31 (wild-type) as significant determinants of SVR12[8]. The genotype C/T of IL 28B SNP in patient 1 might contribute to the failure of the combination therapy with OBV/PTV/r+RBV, although both of the cases were genotype 2a. The reason why SVR was achieved by SOF/RBV combination therapy but not OBV/PTV/r+RBV combination therapy was unclear but may have been due to the different functional mechanisms between each regimen. For example, the host innate and adaptive immune systems are closely associated with nearly every step of HCV infection[9]. In addition to viral factors, the host responses are critical for viral clearance[9]. The different regimens may cause the difference of host responses such as host cytokine cascade and resultantly affect viral clearance.

Regarding the safety of the combination therapy of SOF/RBV, the patient was generally well-tolerated in the phase 3 clinical trial[1]. Patient 2 might have had a recurrence of VKH disease caused by the combination therapy with OBV/PTV/r+RBV or SOF/RBV. Although the recurrence was not severe and was controllable by a subtenon capsule injection of triamcinolone acetonide, either therapy might have played a causal role in the deterioration from the VKH disease. IFN or IFN+RBV reportedly leads to the development of VKH disease or can cause a recurrence of VKH disease[10-17]. The assumed causes include a shift towards a predominant T-helper 1-type immune response, an alteration of the expression of histocompatibility class I and II antigens[12,18], and an increase in the production of endogeneous IFN-gamma that is induced by IFN-alpha[19,20], in addition to immunomodulation effects of IFN. In patient 2, however, IFN was not used. RBV may have an immunomodulatory effect by favoring the T-helper 1 cytokine response[21-23], as well as by enhancing the expression of IFN-stimulated genes[24], possibly leading to the development of VKH disease. In addition, RBV directly increases IL-8 expression

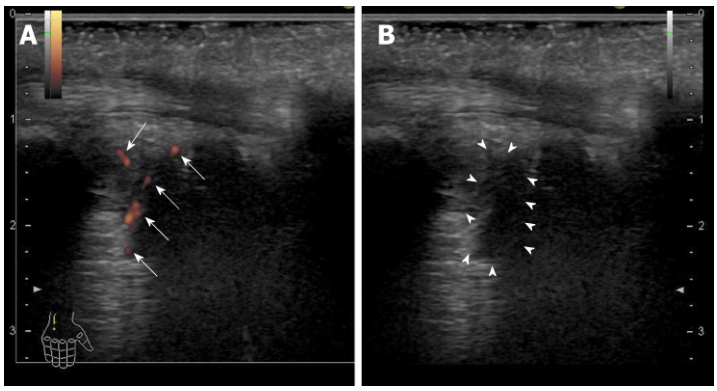

Figure 1 Ultrasonography findings of the right ulnar intercarpal joints in patient 2. A: Power Doppler imaging. There were clear synovial blood flow signals (arrows) with localization of the synovial thickening; B: B-mode imaging. Synovial thickening was observed as a low echoic lesion (surrounded by arrowheads).

in human hepatoma cell lines[25]. On the other hand, the high levels of IL-8 were observed in both the aqueous humor and plasma of the patient with VKH disease[26], and there is a significant correlation between the incidence of IL-8 detection in aqueous humor samples from patients with uveitis, including VKH disease and an increased disease activity[27]. The role of IL-8 levels on the pathogenesis of VKH disease or the action of RBV should be investigated in future studies.

Patient 2 developed arthralgia and morning stiffness approximately 7 wk after the end of the treatment. Rheumatoid factor, anti-nuclear antibody, and anti-cyclic citrullinated peptide antibody were negative. Serum matrix metalloproteinase-3, IgG, and C-reactive protein levels were within normal range. However, the ultrasound detected active synovitis in the right and left carpal joints and peritenon of the flexor muscle. RA was diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism criteria[28]. Thus, our case was seronegative RA. As with the VKH disease, RA associated with IFN or PEG-IFN plus RBV treatment for chronic hepatitis C has been reported[29-33]. The possible reasons for the relationship between RA and IFN-based therapy were assumed to be similar to that with VKH disease and IFN-based therapy[29-33]. IFN-alpha reportedly induces the production of B-lymphocyte activation factor of which levels correlate with the autoantibody levels and synovitis in a subset of patients with early RA[34]. Interestingly, there are reports showing an association between VKD disease and RA[35-37]. One case of this is myasthenia gravis complicated with RA and VKH disease[36]. The case had DR4, Bw54 and MT3 as subtypes of the HLA-DR antigen, which are frequently recognized in RA and VKH disease in common[36]. At the genomic level, our case had the DRB1*04:05:01, DQB1*04:01:01, and DQA1*03:03 genotypes. DRB1*04:05 is significantly increased compared to the healthy controls and is in a strong linkage disequilibrium with DQB1*04:01 in VKH patients[38]. DRB1*04:05 is also associated with a susceptibility to RA[39]. Thus, the development of RA and deterioration of VKH disease in our case were assumed to be associated with these genetic predispositions to autoimmune diseases.

The deterioration or development of autoimmune disease in our case may be affected by immune reconstitution/restoration due to HCV eradication with DAA-based therapy. DAA-based therapy reportedly improves innate immune function with restoration of type I IFN responses and normalization of NK cell function[40-43] and ameliorates various defective T cell functions[44,45]. This immune reconstitution/restoration may generate a harmful effect in patients with genetic predispositions to autoimmune diseases.

There is a case series study of DAA-based therapy for 12 patients with chronic hepatitis C complicated with autoimmune liver disease[46]. One cirrhotic patient with autoimmune hepatitis developed serum ALT elevation and was obliged to receive prednisolone during the therapy with SOF/LDV. Their report supports our study in which special caution regarding AEs should be taken in case of DAA-based therapy for patients with chronic hepatitis C complicated with autoimmune disease.

Several limitations associated with the present case series warrant mentioning. The sample size of our case series was very small, and the duration of combination therapy with OBV/PTV/r+RBV in one case was short compared to what is currently approved in Japan.

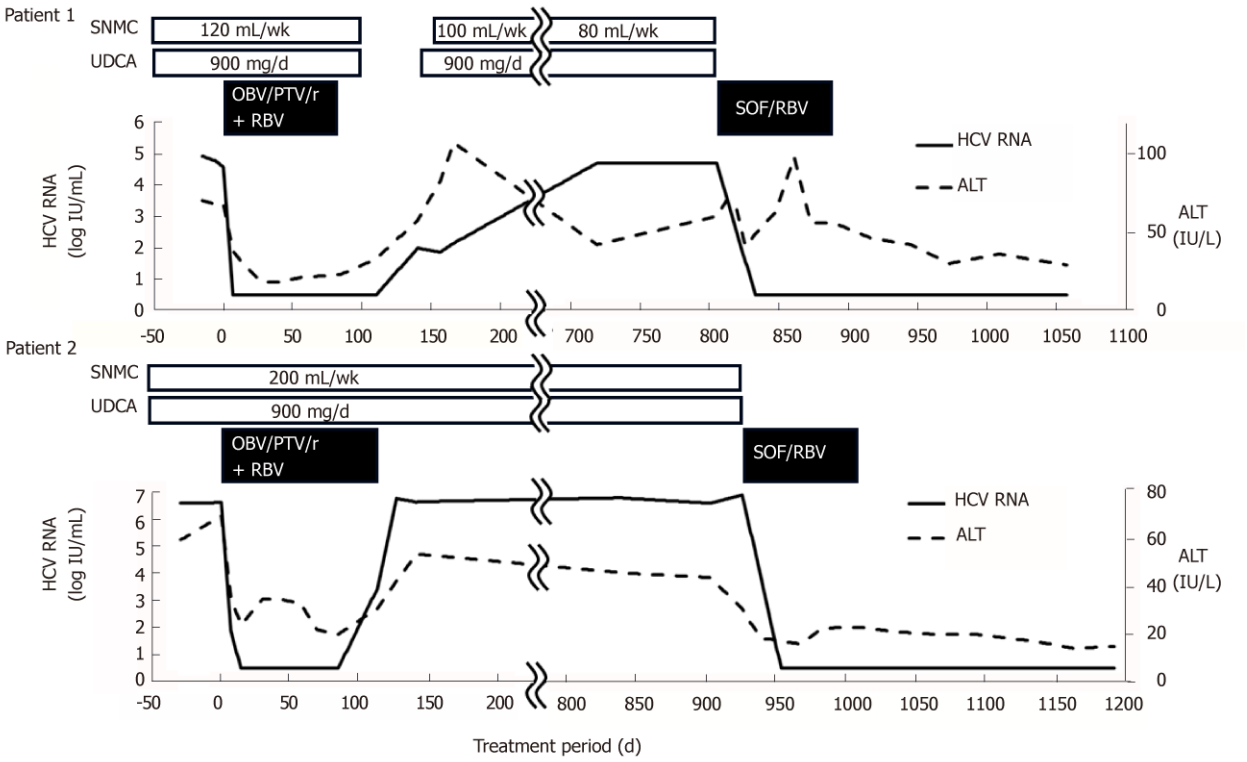

Figure 2 Clinical course of patient 1 and patient 2. The serum hepatitis C virus RNA levels rapidly decreased and became undetectable in both of the cases. Both of the cases achieved a sustained virological response at 12 wk after the treatment. In Patient 2, the serum alanine aminotransferase (ALT) level transiently increased during the combination therapy with sofosbuvir and ribavirin. In Patient 2, the serum ALT levels decreased compared to the pretreatment levels after the start of the combination therapy. HCV: Hepatitis C virus; ALT: Alanine aminotransferase; SOF/RBV: Sofosbuvir and ribavirin; OBV/PTV/r+RBV: ombitasvir/paritaprevir/ritonavir plus ribavirin.

CONCLUSION

The combination therapy with SOF/RBV might have promise as an efficacious therapy, but caution regarding AEs should be practiced. Larger prospective studies of combination therapy with SOF/RBV for those with treatment failure for OBV/PTV/r+RBV are needed in the near future to confirm the findings in our case series.

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CASE REPORT

Management of the late effects of disconnected pancreatic duct syndrome: A case report

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Author contributions: Yamada R contributed to the conception of the study, drafting of the article, critical revision of the article for important intellectual content, and final approval of the article; Tanaka K contributed to the critical revision of the article for important intellectual content, and final approval of the article; Umeda Y, Shiono Y, Okuse H, Kuroda N, Tsuboi J, Inoue H, Hamada Y, Horiki N and Takei Y contributed to the technical and material support and final approval of the article.

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

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2013), and the

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Abstract

BACKGROUND

There have been few reports about the late effects of disconnected pancreatic duct syndrome (DPDS). Although few reports have described the recurrence interval of pancreatitis, it might be rare for recurrence to occur more than 5 years later. Herein, we describe a case of recurrence in an 81-year-old man after the treatment of walled-off necrosis (WON) with pancreatic transection 7 years ago.

CASE SUMMARY

An 81-year-old man visited our hospital with chief complaints of fever and abdominal pain 7 years after the onset of WON due to severe necrotic pancreatitis. His medical history included an abdominal aortic aneurysm (AAA), hypertension, dyslipidemia, and chronic kidney disease. Computed tomography (CT) scan showed that the pancreatic fluid collection (PFC) had spread to the aorta with inflammation surrounding it, and CT findings suggested that bleeding occurred from the vasodilation due to splenic vein occlusion. First, we attempted to perform transpapillary drainage because of venous dilation around the residual stomach and the PFC. However, pancreatic duct drainage failed because of complete main pancreatic duct disruption. Second, we performed endoscopic ultrasound-guided drainage. After transmural drainage, the inflammation improved and stenting for the AAA was performed successfully. The inflammation was resolved, and he has been free from infection for more than 2 years after the procedure.

CONCLUSION

This case highlights the importance of continued follow-up of patients for

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recurrence after the treatment of WON with pancreatic transection.

Key words: Case report; Endoscopy; Necrosis; Pancreas; Walled-off necrosis; Disconnected pancreatic duct syndrome

Core tip: There have been a few reports about the late effects of disconnected pancreatic duct syndrome. We describe a case of recurrence in an 81-year-old man after the treatment of walled-off necrosis (WON) with pancreatic transection 7 years ago. Endoscopic transpapillary drainage was attempted first but failed. Thereafter, endoscopic ultrasound-guided drainage was performed. Subsequently, pancreatic inflammation resolved, and abdominal aortic stenting for the aneurysm was performed successfully. The patient has been infection free for more than 2 years post-procedure. This case highlights the importance of continued follow-up of patients for recurrence after the treatment of WON with pancreatic transection.

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INTRODUCTION

Disconnected pancreatic duct syndrome (DPDS) is characterized by disruption of the main pancreatic duct (MPD), resulting in various upstream pancreatic glands becoming isolated from the MPD downstream[1]. A recent retrospective study reported that DPDS occurred more frequently in patients with walled-off necrosis (WON) than in those with other pancreatic fluid collections (PFCs) (68.3% *vs* 31.7%)[2]. It was also reported that DPDS due to WON is disadvantageous compared to that due to other PFCs because of the increased need for re-interventions (30% *vs* 18.5%; P = 0.03), rescue surgery (13.2% *vs* 4.8%; P = 0.02), and a longer length of admission[2]. However, there have been few reports about the late adverse effects of DPDS. Currently, endoscopic intervention is increasingly considered as a less invasive alternative to surgery for managing DPDS[3]. Thus, endoscopic intervention is considered to be effective for the late effects of DPDS. We describe a case of endoscopic management for the late effects of DPDS with complete duct disruption and pancreatic transection following severe acute pancreatitis.

CASE PRESENTATION

Chief complaints

An 81-year-old man with a medical history of abdominal aortic aneurysm (AAA), hypertension, dyslipidemia, and chronic kidney disease visited our hospital with fever and abdominal pain.

History of past and present illnesses

The patient reported having severe acute necrotizing pancreatitis due to a gallstone 7 years prior. He did not drink alcohol. He was referred to our hospital 42 d after onset because of the development of WON in the pancreatic neck region (Figure 1). The patient underwent endoscopic ultrasound (EUS)-guided drainage and necrosectomy eight times. Subsequently, he recovered from WON, his nutritional status improved, and he was discharged from our hospital after 79 d. After discharge, we performed endoscopic choledocholithotomy. Cholecystectomy was not performed because the gallbladder had already shrunk. Although he had a pancreatic fistula due to pancreatic transection following severe pancreatitis, he had been asymptomatic for 6 years. Four years after WON onset, he underwent distal gastrectomy with Roux-en-Y reconstruction for invasive gastric cancer.

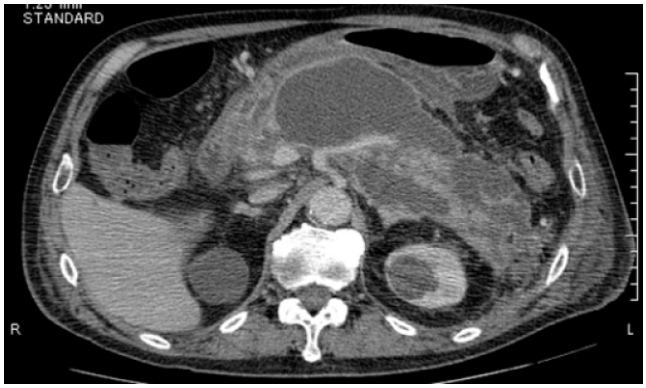

Figure 1 Computed tomography image showing the development of walled-off necrosis in the pancreatic neck region when severe acute necrotizing pancreatitis occurred 7 years prior.

Physical examination

On examination, upper abdominal tenderness and gastrointestinal bleeding were noted.

Imaging examinations

Computed tomography (CT) scan was suggestive of PFC in the pancreatic tail due to pancreatic transection that had spread to the aorta with surrounding inflammation. Inflammation was also found around the aorta and ulcer-like blood flow appeared in the aortic aneurysmal thrombus (Figure 2A). Gastrointestinal bleeding was present, but no active bleeding was observed through the endoscope. The CT scan showed venous dilation mainly around the residual stomach, and it was thought that bleeding occurred from the vasodilator due to splenic vein occlusion (Figure 2B). Because there was a risk of rupture of the AAA owing to the spread of inflammation from the PFC, drainage was deemed necessary.

FINAL DIAGNOSIS

The final diagnosis of the presented case is late effects of DPDS and infected PFC due to severe acute pancreatitis and WON.

TREATMENT

First, we attempted transpapillary drainage via double-balloon endoscopy (DBE) due to difficulty in EUS-guided puncture secondary to venous dilation around the residual stomach and the distribution of the PFC, which was extensive but narrow around the stomach (Figure 2C). DBE retrograde pancreatography showed complete pancreatic duct disruption (Figure 3). Pancreatic duct drainage failed because of complete MPD disruption. Thereafter, we performed EUS-guided drainage. The linear array echo-endoscope showed many vessels surrounding the PFC and stomach. We punctured the PFC using a 19-gauge needle, carefully avoiding the vessels and inserted a double pig catheter (6 French/4 cm) transmurally (Figure 4). After transmural drainage, the inflammation was resolved and stenting for the AAA was performed successfully.

OUTCOME AND FOLLOW-UP

The inflammation further improved after the procedure (Figure 5). The patient has been free from WON infection for more than 2 years after the procedure.

DISCUSSION

Previously, surgery was the first therapeutic choice for DPDS. Fischer *et al*[4] retrospectively reviewed operated cases of DPDS; distal pancreatectomy had been performed in whole delayed DPDS cases. They concluded that fluid collection often is

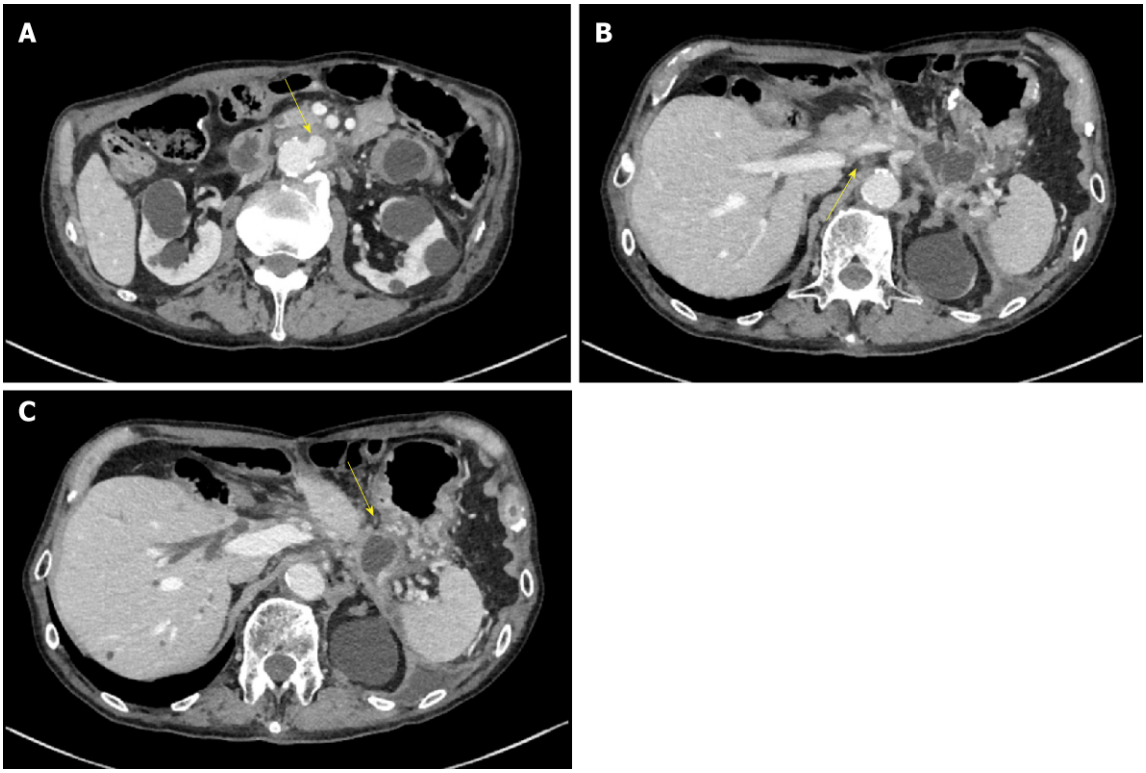

Figure 2 Computed tomography scan taken at 7 years after severe acute necrotizing pancreatitis. A: Computed tomography (CT) scan showing spread of the pancreatic fluid collection to the aorta with surrounding inflammation and the appearance of ulcer-like blood flow in the aortic aneurysm thrombus (yellow arrow); B: The CT scan also shows splenic vein occlusion (yellow arrow; B) and venous dilation around the residual stomach; C: The shape of the pancreatic fluid collection is narrow around the stomach (yellow arrow), although it shows extensive spread.

not accessible endoscopically and that no long-term data support the patency of the endoscopic approach. However, endoscopic intervention is increasingly considered as a less invasive alternative to surgery in the management of DPDS[3]. Furthermore, guidelines were developed for endoscopic management of acute necrotizing pancreatitis, including the management of DPDS[5].

There are two endoscopic strategies for treating DPDS: Transpapillary placement of the drainage stent and endoscopic transmural drainage of the PFC. The evidence-based multidisciplinary guidelines of the European Society of Gastrointestinal Endoscopy suggested that transpapillary stenting can be considered where partial MPD disruption has occurred[5]. Even though widely practiced in the management of DPDS, transpapillary stenting sometimes results in failure. However, successful transmural drainage does not depend on the presence of communication between the proximal MPD and the disconnected upstream segment. Bang *et al*[6] reported that the best indication of EUS-guided drainage for DPDS is when WON or PFC is larger than 4 cm at its largest dimension and located within 15 mm of the gastrointestinal lumen. In this case, the PFC distribution was narrow and surrounded the stomach, although it had spread extensively. Thus, we attempted to perform transpapillary drainage first but discontinued the drainage because of complete MPD disruption. Although the width of the PFC was less than 4 cm, transmural drainage was performed safely and successfully.

The present patient showed recurrence of pancreatitis in the form of PFC after a prolonged period of 7 years. Recurrence in the form of a necrotic cavity or pseudocyst has been reported in approximately 10% of patients, even after successful endoscopic treatments. For WON, the recurrence rates were reported to be 9.4% after endoscopic transmural drainage (the single or multiple transluminal gateway technique) in 53 patients[7], 7.8% after combined percutaneous and endoscopic drainage in 103 patients[8], and 10.9% (7%-15%) after endoscopic necrosectomy in a meta-analysis (8 studies, 233 patients)[9]. Although few reports have described the recurrence interval of pancreatitis, Yasuda *et al*[10] reported that 7.0% of 43 patients showed recurrence within 2-8 months after endoscopic treatment.

CONCLUSION

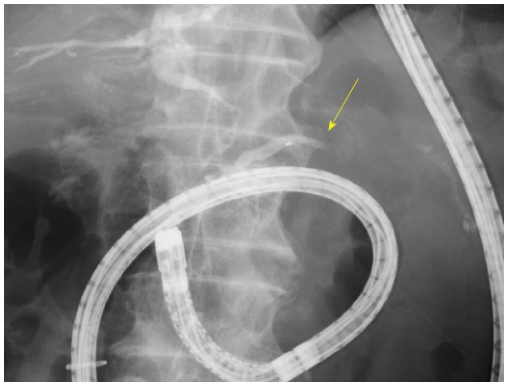

Figure 3 Pancreatogram during a double-balloon endoscopic retrograde cholangiopancreatography shows complete pancreatic duct disruption (yellow arrow).

Based on the literature, it might be rare for recurrence to occur more than 5 years later. Nevertheless, it is important to continue following patients after the treatment of WON with pancreatic transection because late recurrence due to DPDS may occur.

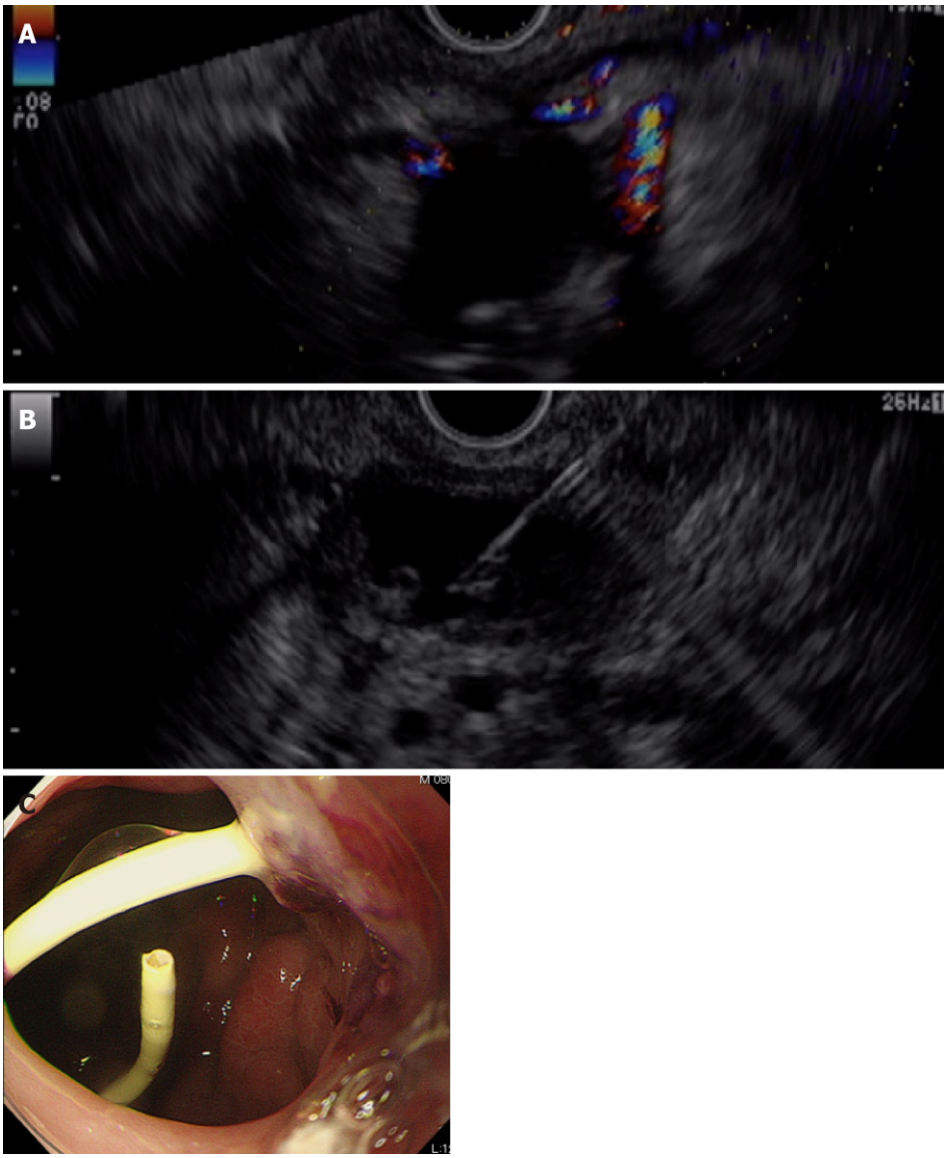

Figure 4 Endoscopic ultrasound-guided drainage. A: A linear array echo-endoscope shows many vessels surrounding the pancreatic fluid collection and stomach; B, C: The pancreatic fluid collection is punctured using a 19-gauge needle, carefully avoiding the vessels (B), and a double pigtail catheter (6 French/4 cm) is inserted transmurally (C).

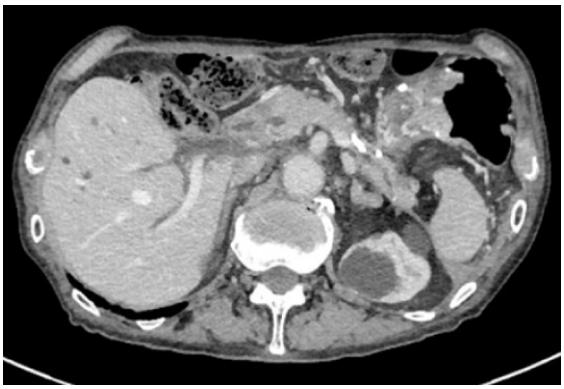

Figure 5 The inflammation further improved after the procedure.

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CASE REPORT

Nerve coblation for treatment of trigeminal neuralgia: A case report

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Abstract

BACKGROUND

Trigeminal neuralgia (TN) is a severe type of neuropathic pain which is often inadequately managed using conventional therapies. In this report, we present the first case of TN treated with gasserian ganglion nerve coblation (NC).

CASE SUMMARY

A 58-year-old man presented with right facial pain, mostly localized in the right zygomatic zone, alveolar region, and jaws. Similar to acupuncture and shock pain, the pain lasted about five seconds after each attack before resolving unaided. A diagnosis of TN was made, after which treatment with acupuncture therapy and oral carbamazepine was given. However, the pain was not satisfactorily controlled. Subsequently, gasserian ganglion NC of the right trigeminal nerve guided by computed tomography (CT) was performed on the patient. Following this procedure, the right zygomatic, alveolar, submandibular, and cheek pain disappeared completely. The right zygomatic and alveolar areas experienced mild numbness (level II). At 1-, 2-, 3-, and 6-mo follow-ups after surgery, the patient was painless and the numbness score was level I.

CONCLUSION

CT-guided gasserian ganglion (NC) is an effective treatment for TN and is associated with less or no postoperative numbness or hypoesthesia in comparison with current standard-of-care approaches.

Key words: Nerve coblation; Trigeminal neuralgia; Gasserian ganglion; Computed tomography guided; Case report

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Core tip: Pain due to diseases or injuries affecting the trigeminal nerve can be devastating. Conventional drug-based therapies are often ineffective in controlling advanced trigeminal neuralgia (TN). On the other hand, surgical interventions, although showing better success than most drugs, are at times accompanied by numbness and relapsing pain. In this case, we report the treatment of a patient who presented with signs of TN using an innovative technique, computed tomography (CT)-guided nerve coblation (NC). The patient reported neither feeling pain nor numbness when followed for up to a period of six months. CT-NC, therefore, is a minimally invasive technique for the treatment of TN bearing the advantages of inducing little trauma and being effective in alleviating pain without causing postoperative numbness.

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INTRODUCTION

Trigeminal neuralgia (TN) is characterized by sudden, severe, brief, stabbing, and recurrent pain, with a reported incidence of about 13/100000 persons every year[1]. The etiology of the disease remains unclear and its clinical management, comprising medicinal and surgical approaches, is similarly inadequate. Technological advancements have paved the way for the application of minimally invasive interventional therapy, such as the treatment of TN. Benefits of these moments include little trauma, quick recovery, and adequate pain control.

However, postoperative numbness or hypoesthesia is the most common complication after treatment using the invasive techniques[2]. We therefore explored the gasserian ganglion nerve coblation (NC) technique to treat a patient with TN in the Department of Pain Medicine, Xuanwu Hospital, Beijing, China.

CASE PRESENTATION

Chief complaints

A 58-year-old man presented with chronic right facial pain and was followed at our hospital for about eight years. The pain was described as paroxysmal puncture with no obvious cause, mostly located in the right zygomatic zone, upper alveolar region, and jaws. Moreover, the pain, with a VAS score of 7-8 points, continued for about five seconds during each attack and resolved without intervention.

History of present illness

Identifiable triggers for the pain included activities such as eating, talking, brushing of the teeth, washing the face, and touching. Initially, the patient was started on acupuncture therapy together with oral carbamazepine (100 mg, once per day but still complained of right facial pain.

Physical examination upon admission

On further examination, we found that there was a trigger point on the right side of the zygomatic zone. However, muscles involved in mastication and movement of the mouth were normal and their functions were not limited.

Imaging examinations

Furthermore, examination of the skull base using magnetic resonance angiography (MRA) returned normal results.

FINAL DIAGNOSIS

The treatment presented in this Case Report was undertaken after obtaining the

relevant ethical approval by the institutional review board of Xuanwu Hospital. Additionally, we obtained a signed informed consent form from the patient towards publishing this case report.

TREATMENT

On November 23, 2017, the patient received gasserian ganglion NC of the right trigeminal nerve guided by computed tomography (CT) at the positron-emission tomography-CT room of Xuanwu Hospital. As there was no standardized technique procedure, we adopted the method of CT-guided percutaneous radiofrequency thermocoagulation[1].

Prior to the procedure, the CT examination room was disinfected and the patient placed in a supine position with his head overhanging on the CT scanner bed. Vital signs were monitored during the entire procedure. First, access to the gasserian ganglion was explored following the Hartel's anterior route. The target was confirmed by CT scan to find the foramen ovale and mark the best puncture path (Figures 1 and 2). The route from the puncture point to the target was measured as a predetermined distance to ensure that skeletal obstacles were circumvented. An intravenous drip of 5 μg of sufentanil was conducted to relieve pain before puncture. After sterilization, the insertion point was anesthetized with 2 mL of 1% lidocaine. Second, a 150 mm 18G puncture needle was inserted. The angle and depth of insertion of the needle to the foramen ovale followed the best puncture approach. While piercing the needle into the foramen ovale, a repeat CT scan was done to ascertain the position of the needle tip (Figures 3 and 4). Third, the needle core was pulled out, and the coblation wand was inserted into the introducer needle and extended approximately 5 mm beyond the introducer needle. Stimuplex HNS 11 Nerve Stimulator (B. Braun Co. Ltd, Melsungen, Germany) was then connected. Electrical stimulation was induced while observing the patient's response to the stimulation. This guided the adjustment of the positioning of the wand until the target was accessed. Fourth, intravenous anesthesia comprising propofol (1–2 mg/kg) supplemented with facemask oxygen was administered after certifying the proper location. No tracheal intubation was performed. The coblation wand was changed to connect with a low temperature plasma multi-function operating system SM-D380C (GaoTon Co. Ltd, Xi'an, China). Fifth, the target nerve was ablated by the coblation wand using the following settings: ablation intensity at mode 2 and operation temperature at 40 to 50 °C. Ablation cycle lasted approximately 30 s. Thereafter, the coblation wand was retracted to 3 mm. Finally, the wand and puncture needle were pulled out. After the procedure, dressing was applied to the patient who, after regaining consciousness, was returned to the ward and instructed to rest for 24 h.

OUTCOME AND FOLLOW-UP

The patient was followed for 3 d after the surgery. On examination, the right zygomatic, alveolar, submandibular, and cheek pain had disappeared completely with a VAS score of 0. The right zygomatic and alveolar regions manifested some mild numbness (level II). During follow-ups at 1, 2, 3, and 6 mo after surgery, the VAS score for pain was 0 and the numbness score was level I. The patient reported no other adverse effects during the follow-up examinations.

DISCUSSION

Early TN treatment is dominated by the use of drugs with carbamazepine as the drug of choice achieved pain control in 70% to 98% of patients[3,4]. With progression of the disease, carbamazepine, even at high doses, becomes ineffective in alleviating pain. In fact, higher doses of the drug can cause side effects, such as dizziness, drowsiness, fatigue, nausea, rashes, vomiting, occasional granulocytopenia, reversible thrombocytopenia, and even aplastic anemia and toxic hepatitis. Many patients, therefore, cannot tolerate high dose medication[5,6].

Surgical intervention becomes an alternative to treat TN when drug therapy fails. Presently, surgical methods are mainly divided into minimally invasive intervention and open surgery. The former includes the radiofrequency thermal coagulation of the trigeminal nerve[7], glycerol neurolysis[8], and percutaneous ganglion balloon compression[9]. On the other hand, open surgery includes trigeminal nerve root microvascular decompression[10], posterior root amputation of trigeminal nerve, and

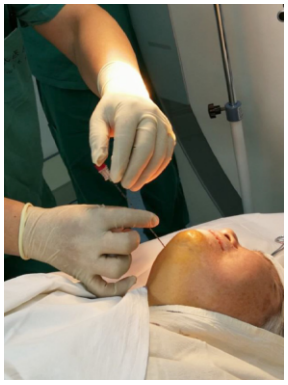

Figure 1 Accessing the gasserian ganglion according to the Hartel anterior route.

spinal cord amputation. A notable disadvantage of open surgery is that it requires craniotomy under general anesthesia, which may cause significant trauma. Greater risks and, in some cases, higher mortality rate have been associated with open surgery[10,11]. Minimally invasive interventional therapy has therefore become a preferred approach in the treatment of TN since it elicits little trauma, allows for quick recovery, and achieves effective relief of pain .

The case reported here was characterized by typical symptoms leading to a clear diagnosis of TN. The latest NC technology guided by CT was employed. The patient did not report feeling any pain three days after the surgery; a VAS score of 0 was recorded. The same results were observed at 1, 2, 3, and 6 mo after the surgery. From the foregoing observation, the pain-relieving effect of CT-guided NC is significantly distinct, and consistent with that reported for radiofrequency thermal coagulation in treating TN[12]. We are conscious, however, that there is need to observe the long-term effects of this procedure on pain relief and numbness. From a mechanistic point of view, NC does not rely on thermal effect as does radiofrequency thermal coagulation[13,14]. However, with 100-500 kHz and special bipolar radiofrequency electric field segment, the high-frequency oscillating tip locally generates a low-temperature plasma layer. The activated ionic layer can break down the molecular bonds (layer thick 1 mm[15]), cut or ablate the nerve tissue, cause it to decompose and vaporize and drain out of the body from the puncture channel, block the pain signal transduction, and do not produce numbness at the same time. The patient had mild numbness 3 d after surgery, which was scored as level II. At 1, 2, 3, and 6 mo after surgery, numbness disappeared completely and was scored as level I. Postoperative numbness scores were significantly lower than those for the other case reported[2]. Based on the techniques, it may be that the fine fibers (Aδ and C fibers), which transmit temperature sensation and pain, are damaged when ablating nerve tissue. However, there is little damage to the crude fibers (Aα and Aβ fibers) that transmit the sense of touch. Therefore, the incidence of postoperative numbness is low.

As an emerging technology, NC for the treatment of TN has not been extensively explored globally. This is a very promising minimally invasive interventional technique that holds multiple benefits to the patient not least because of effective pain control. A larger patient sample and longer follow-up period are warranted to ascertain the effectiveness of NC in the management of TN.

CONCLUSION

We conclude that CT-guided gasserian ganglion NC is a promising, effective treatment for TN and associated with minimal or non-postoperative numbness or hypoesthesia.

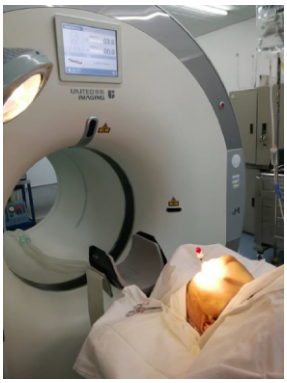

Figure 2 Target confirmation by a computed tomographic scan.

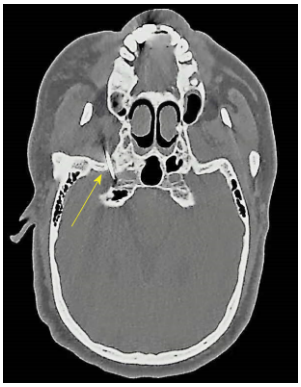

Figure 3 Computed tomographic image showing the introducer needle and coblation wand (yellow arrow). The coblation wand extended approximately 5 mm beyond the introducer needle.

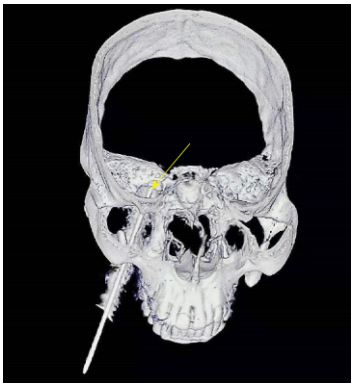

Figure 4 Computed tomographic three-dimensional skull reconstruction image showing the introducer needle and coblation wand (yellow arrow), which pierced the needle into the foramen ovale and reached the target nerve.

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CASE REPORT

Adult-onset mitochondrial encephalopathy in association with the *MT-ND3* T10158C mutation exhibits unique characteristics: A case report

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Abstract

BACKGROUND

Mitochondrial diseases are a heterogenous group of multisystemic disorders caused by genetic mutations affecting mitochondrial oxidation function. Brain involvement is commonly found in most cases but rarely as the unique clinical manifestation. Since the knowledge of its clinical manifestation combined with genetic testing is important for preventing misdiagnosis and delay in treatment, we report here how we diagnosed and managed a very unusual case of mitochondrial encephalopathy.

CASE SUMMARY

We report a 52-year-old woman with recurrent stroke-like episodes carrying the m.10158T>C mutation in the *MT-ND3* gene, which is also responsible for fatal infant-onset Leigh syndrome. Despite the common mutation, the present case featured a distinct clinical and neuroimaging manifestation from Leigh syndrome. This patient presented with sudden onset of right-sided hemiparesis and hemilateral sensory disturbance accompanied by a left temporal cluster-like headache and later developed epilepsy during hospitalization, with no other signs suggestive of myopathy, lactate acidosis, or other systemic symptoms. Brain magnetic resonance imaging revealed variable lesions involving multiple cortical and subcortical regions. Furthermore, a negative genetic test obtained from peripheral blood delayed the diagnosis of mitochondrial disease, which was eventually established through second-generation DNA sequencing using biopsied muscle.

CONCLUSION

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Based on this report, we suggest that clinicians pursue proper genetic testing for patients when the clinical phenotype is suggestive of mitochondrial diseases.

Key words: Mitochondrial disease; Stroke-like episode; Magnetic resonance; diagnosis; Case report

Core tip: An adult-onset stroke-like episode combined with a distinctive magnetic resonance imaging finding serves as a key diagnostic feature indicating mitochondrial disease. A negative peripheral blood genetic test does not necessarily exclude mitochondrial disease, and muscle biopsy is necessary, even with a lack of muscular symptoms.

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INTRODUCTION

Diagnosis of mitochondrial disease is challenging. Symptoms such as a stroke-like episode, lactic acidosis, deafness, diabetes mellitus, short stature, and myopathy, often with a family history showing maternal inheritance, are the most common characteristics of a mitochondrial disease. Additionally, a stroke-like episode often occurs in childhood or adolescence. Nonetheless, a diagnosis of mitochondrial diseases in patients with adult onset is often delayed due to a lack of family history, atypical manifestations, and limited resources for functional, pathologic, and/or genetic testing in routine clinical practice[1]. We report an adult-onset patient with mitochondrial encephalopathy carrying the m.10158T >C mutation in the *MT-ND3* gene. The encephalopathy manifested as isolated recurrent stroke-like episodes without clinical myopathy or other organ dysfunction. In this paper, we focus on how we diagnosed this case and the distinct feature of the brain magnetic resonance imaging (MRI), which is important for preventing misdiagnosis and delay in treatment. Additionally, we summarize the clinical implications of such cases with this mutation.

CASE PRESENTATION

Chief complaints

A 52-year-old female presented with a sudden onset of right-sided numbness and weakness that was accompanied by a left temporal cluster-like headache. No fever or prodromal infection was found at disease onset.

Personal and family history

The family and personal history was unremarkable.

Physical examination upon admission

On physical examination, the height and weight of the patient were 154 cm and 56 kg, respectively. Vital signs were normal, as were heart, lung and abdominal examinations. Neurological examination showed intact mental status, with normal speech and comprehension. Mild 4/5 right-sided hemiparesis was present with normal tone in both the arm and leg, though no other focal neurological deficits were found. After admission, she complained of discomfort and tingling in the right leg, after which a generalized tonic-clonic seizure for 3 min occurred before it was stopped by a bolus of intravenous diazepam.

Laboratory examinations

Laboratory tests, including D-dimer, lactic acid, and serum autoantibody levels, as

well as thyroid function and tumor markers indicated no apparent abnormalities. Glucose tolerance and lactic acid movement tolerance tests were normal. A lumbar puncture was performed, and her open intracranial pressure was 180 mm H_2O. Cerebrospinal fluid (CSF) testing showed that cell counts and protein, glucose, chloride, monoclonal antibody, adenosine deaminase, and lactate dehydrogenas levels were within normal ranges.

Imaging examinations and history of present illness

MRI demonstrated a lamellar left parietal lobe lesion predominantly involving the cortex, with hyperintensity on both diffusion-weighted imaging and fluid-attenuated inversion recovery (Figure 1). The apparent diffusion coefficient map revealed a preserved, isointense signal. No abnormalities were found by susceptibility weighted imaging or magnetic resonance angiography and venography (Figure 1). Due to the stroke-like onset pattern and MRI features, further thrombophilia screening was performed and showed decreased protein S activity. A diagnosis of cortical venous thrombosis was first proposed. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) was also considered but temporarily excluded because of the incomplete manifestation and lack of genetic evidence. Anticoagulation therapy was initiated, and follow-up was performed to maintain the international normalized ratio (INR) within the target range.

Two months later, the patient was readmitted for subacute cognitive impairment. She was unable to identify and communicate with family members; she also had difficulty understanding questions or instructions and instead responded by repeating the word "nothing". During hospitalization, a secondary generalized seizure occurred, initially with eyes gazing to the right and then convulsion developing, which lasted for approximately 10 s before self-alleviation. Neurological examination suggested transcortical sensory aphasia, with fully covered limb strength. Blood tests and CSF examination were normal; INR was 2.21. On repeated MRI, new lesions were identified in the left temporal lobe and were also detected 10 days later in the right temporal lobe on radiological follow-up (Figures 1 and 2). Although the MRI signal characteristics are consistent with the initial findings, the original lesion in the left parietal lobe had been alleviated, with cortical atrophy. We further conducted magnetic resonance spectroscopy (MRS), which revealed markedly elevated lactate (Lac) concentrations in the regions of interest in the left temporal lesion (Figure 1). Mitochondrial encephalopathy was diagnosed, and genetic testing using peripheral blood was performed. However, DNA testing for frequent MELAS and myoclonic epilepsy with ragged red fibers syndrome mutations were negative. Because of the lack of symptoms of muscle weakness or pain, the patient declined our suggestion of performing a muscle biopsy. Anticoagulation therapy was terminated, and levetiracetam (1000 mg/d) was administered.

At 3 mo after her second admission, the patient was experiencing involuntary movement in her left limbs, with repetitive flexion/extension. An MRI scan showed a hyperintense signal abnormality in the right parietal lobe (Figure 2). Brachial biceps biopsy was performed. Histopathology revealed no abnormalities, and no necrotic or regenerating fibers were observed; ragged-red fibers and intense succinate dehydrogenase activity were not detected. Nonetheless, complete sequencing of mitochondrial DNA samples extracted from the biopsied muscle revealed a heteroplasmic m.10158T>C mutation, with a heteroplasmy level of 69.6%, in the mitochondrial complex I subunit gene *MT-ND3*. In contrast, this mutation was not found in her peripheral blood cells.

FINAL DIAGNOSIS

The diagnosis was MELAS syndrome harboring the m.10158T>C mutation.

TREATMENT

We administered levetiracetam (1000 mg/d) and oxcarbazepine (400 mg/d) to control epilepsy. Q10 and L-arginine were also administered.

OUTCOME AND FOLLOW-UP

Over the next 6 mo, the present patient did not manifest any further stroke-like episodes.

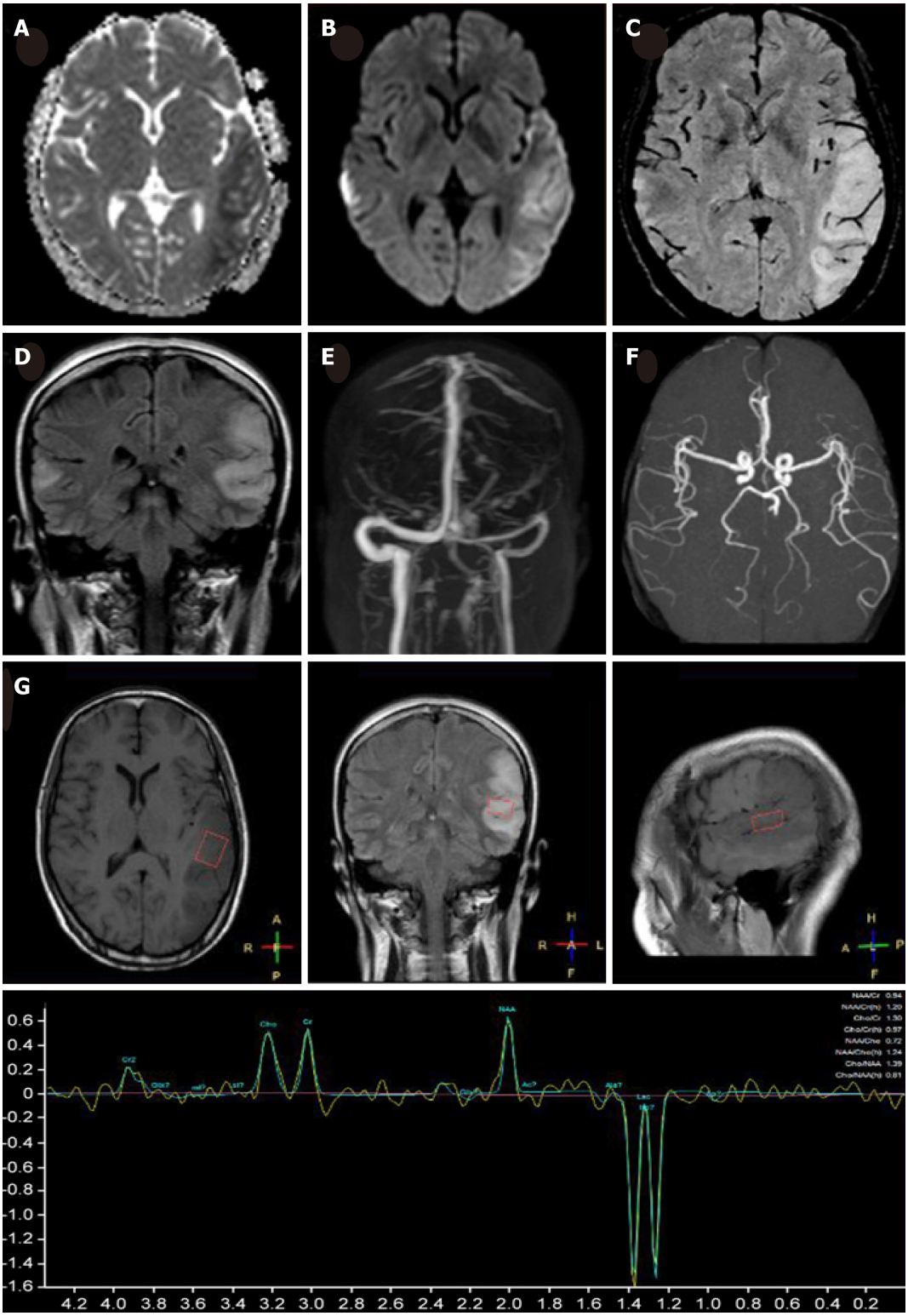

Figure 1 Magnetic resonance imaging of the present patient during her second hospitalization. Axial brain magnetic resonance imaging showed marked hyperintensity on diffusion-weighted imaging (A), slight hypointensity on apparent diffusion coefficient maps (B) in the bilateral temporal cortical regions, predominantly on the left side, with hyperintensity in the corresponding region on coronal fluid-attenuated inversion recovery (D). No hypointensity of dilated intrasulcal venous structures was observed on susceptibility weighted imaging (C), and no abnormalities were observed on magnetic resonance angiography (E) or magnetic resonance venography (F). Magnetic resonance spectroscopy revealed an inverted lactate (Lac) doublet in the subcortical region of the left temporal lesion (G).

DISCUSSION

We herein report a case of adult-onset mitochondrial encephalopathy, whereby the patient was admitted three times for similar stroke-like episodes before the definitive diagnosis was confirmed. Despite highly suggestive MRI features of MELAS syndrome, the diagnosis of mitochondrial encephalopathy was delayed due to the

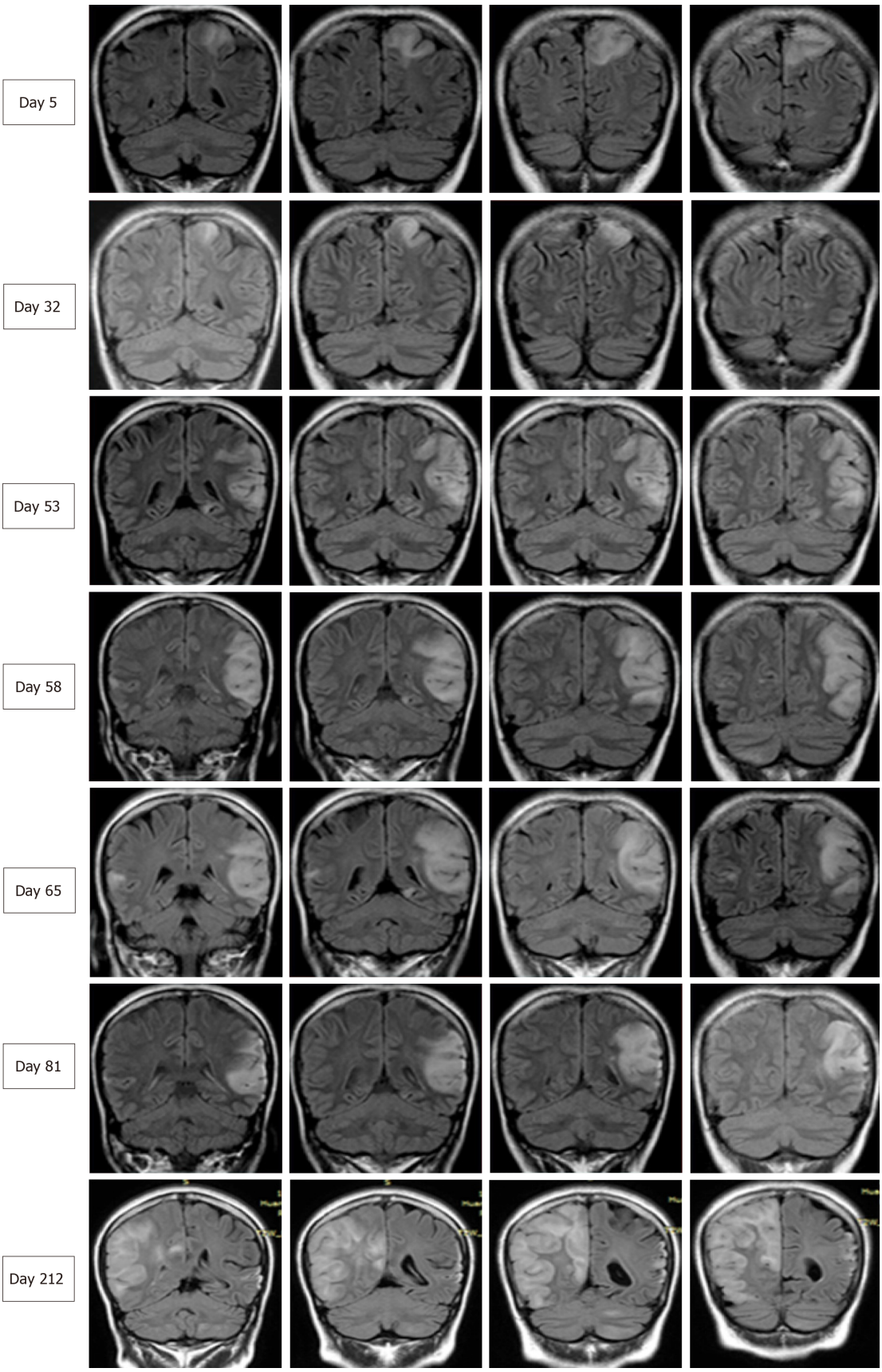

Figure 2 Serial brain images covering three recurrent stroke-like episodes in the present patient over a 7-mo period. Four representative coronal slices were serially shown in chronological order. Fluid-attenuated inversion recovery images on days 5, 32, 58, 65, 81, and 212 revealed hyperintensity signals appearing recurrently in various cortical and subcortical areas, mainly in the parietal and temporal lobes, and the progressive development of cortical atrophy.

following reasons: (1) Lack of family history showing maternal inheritance; (2) Isolated symptoms of CNS impairment, without myopathy, lactic acidosis, or other

systemic disorders; and (3) Negative mitochondrial genetic testing using peripheral blood. Although muscle biopsy revealed no abnormality, genetic testing using the biopsied muscle demonstrated a 69.6% heterozygous T10158C mutation in the *MT-ND3* gene.

Although MELAS is not uncommon in clinical practice, its diagnosis may be challenging because the clinical symptoms are highly variable and genetic findings may be absent. Our patient presented with a headache, seizure, and acute focal lesion observed by MRI, which fit the diagnostic criteria of supportive MELAS by Yatsuga *et al*[2]. Although her level of lactic acid in blood was normal, the presence of an inverted lactate peak was detected in the temporal cortex by MRS, which is a useful tool to detect metabolic dysfunction in the brain[3]. Additionally, despite no obvious myopathy, the biopsied muscle showed a 69.6% heteroplasmic mutation, T10158C, in the *MT-ND3* gene.

The *MT-ND3* protein is a structural component of multimeric enzyme complex I of the mitochondrial respiratory chain, which drives ATP generation in mitochondria[4]. The *MT-ND3* T10158C mutation, which is located in the coding region of the loop domain of the ND3 subunit protein, has been identified in infants and pediatric patients with Leigh syndrome or Leigh-like disease[5]. However, the manifestation of late-onset stroke-like encephalopathy similar to MELAS in our patient harboring the *MT-ND3* T10158C mutation highlights the complicated genotype-phenotype relationship in mitochondrial diseases. In a literature review, we found four similar cases of *MT-ND3* T10158C mutation (in muscle)[6,7], and all of these patients presented with adult-onset, isolated involvement of the central nervous system. Moreover, MRI revealed similar features among these five patients, with lesions predominately in the posterior cortex of the supratentorial region; in contrast, MRI typically shows involvement of the basal ganglia, brainstem, and cerebellum in Leigh syndrome. Thus, adult-onset patients harboring the *MT-ND3* T10158C mutation may exhibit unique clinical features. Although no myopathy symptoms were observed in any of these cases and genetic testing using peripheral blood was negative, muscle specimens should be obtained to establish a definitive diagnosis. This may be explained by heteroplasmic mtDNA mutations in various tissues, in which case, the mutation load in muscles is higher than that in blood[8].

CONCLUSION

Adult-onset mitochondrial encephalopathy in the presence of the *MT-ND3* T10158C mutation shows unique clinical characteristics. Despite a lack of lactic acidosis, myopathy, or other clinical implications, the diagnosis of MELAS needs to be considered for adult-onset patients with a stroke-like episode of encephalopathy. Due to the heteroplasmic mutation load, a negative genetic test obtained when using peripheral blood does not necessarily exclude the diagnosis of mitochondrial disease, and next-generation DNA sequencing using biopsied muscle should be considered.

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CASE REPORT

Rare variant of pancreaticobiliary maljunction associated with pancreas divisum in a child diagnosed and treated by endoscopic retrograde cholangiopancreatography: A case report

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Author contributions: Zhang XF is an advanced endoscopist who performed the ERCP procedure; Cui GX wrote the paper; Yang JF helped to revise the paper; Zhang XF and Huang HT analyzed the special part of the case.

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Abstract

BACKGROUND

Pancreaticobiliary maljunction (PBM) is an uncommon congenital anomaly of the pancreatic and biliary ductal system, defined as a union of the pancreatic and biliary ducts located outside the duodenal wall. According to the Komi classification of PBM, the common bile duct (CBD) directly fuses with the ventral pancreatic duct in all types. Pancreas divisum (PD) occurs when the ventral and dorsal ducts of the embryonic pancreas fail to fuse during the second month of fetal development. The coexistence of PBM and PD is an infrequent condition. Here, we report an unusual variant of PBM associated with PD in a pediatric patient, in whom an anomalous communication existed between the CBD and dorsal pancreatic duct.

CASE SUMMARY

A boy aged 4 years and 2 mo was hospitalized for abdominal pain with nausea and jaundice for 5 d. Abdominal ultrasound showed cholecystitis with cholestasis in the gallbladder, dilated middle-upper CBD, and a strong echo in the lower CBD, indicating biliary stones. The diagnosis was extrahepatic biliary obstruction caused by biliary stones, which is an indication for endoscopic retrograde cholangiopancreatography (ERCP). ERCP was performed to remove biliary stones. During the ERCP, we found a rare communication between the CBD and dorsal pancreatic duct. After clearing the CBD with a balloon, an 8.5 Fr 4-cm pigtail plastic pancreatic stent was placed in the biliary duct through the major papilla. Six months later, his biliary stent was removed after he had no symptoms and normal laboratory tests. In the following 4-year period, the child grew up normally with no more attacks of abdominal pain.

CONCLUSION

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We consider that ERCP is effective and safe in pediatric patients with PBM combined with PD, and can be the initial therapy to manage such cases, especially when it is combined with aberrant communication between the CBD and dorsal pancreatic duct.

Key words: Pancreaticobiliary maljunction; Pancreas divisum; Endoscopic retrograde cholangiopancreatography; Variant; Communication; Children; Case report

Core tip: The coexistence of pancreaticobiliary maljunction (PBM) and pancreas divisum is an infrequent condition. According to the Komi classification of PBM, the common bile duct (CBD) directly fuses with the ventral pancreatic duct in all types. However, we present a case who had an anomalous communication existing between the CBD and dorsal pancreatic duct. There is lack of therapeutic experience for such a case. We successfully diagnosed and treated the little child by endoscopic retrograde cholangiopancreatography. The child remained asymptomatic during 4 yr of follow-up.

Citation: Cui GX, Huang HT, Yang JF, Zhang XF. Rare variant of pancreaticobiliary maljunction associated with pancreas divisum in a child diagnosed and treated by endoscopic retrograde cholangiopancreatography: A case report. *World J Clin Cases* 2019; 7(9): 1073-1079
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INTRODUCTION

Pancreaticobiliary maljunction (PBM) is an uncommon congenital anomaly of the pancreatic and biliary ductal system, defined as a union of the pancreatic and biliary ducts located outside the duodenal wall[1]. Because of this anatomical anomaly, PBM has been frequently associated with cholelithiasis, cholangitis, pancreatitis[2], and increased risk of cholangiocarcinoma[3]. PBM has been classified into three types by Komi *et al*[4], according to the angle of the junction of the common bile duct (CBD) and pancreatic duct, dilatation of the common channel, and the running of the dorsal pancreatic duct. Types I and II have no pancreas divisum (PD). In type III, PD exists in all PBM patients with complete PD in types IIIa and b and incomplete PD in types IIIc1–3. According to the Komi classification of PBM, the CBD directly fuses with the ventral pancreatic duct in all types. PD occurs when the ventral and dorsal ducts of the embryonic pancreas fail to fuse during the second month of fetal development. It is the most common anatomical variant of the pancreas, in which ventral duct drains the minor part of the pancreas through the major papilla, whereas the dorsal duct drains the major part of the pancreatic juice through the minor papilla[5]. The coexistence of PBM and PD is an infrequent condition.

Here, we report an unusual variant of PBM associated with PD in a pediatric patient, in whom an anomalous communication existed between the CBD and dorsal pancreatic duct. Our case was hardly classified into Komi classification of PBM with the special anatomical variant. The patient was successfully diagnosed and managed by endoscopic retrograde cholangiopancreatography (ERCP). Written informed consent was obtained from his parents prior to the endoscopic therapy.

CASE PRESENTATION

Chief complaints

A boy aged 4 years and 2 mo was hospitalized for abdominal pain with nausea and jaundice for 5 d.

History of present illness

He had colic pain located in the right upper abdomen, without radiating to the back or paroxysmal attacks and with no confirmed exacerbating or relieving factors. He was sent to a local hospital after the first attack. Abdominal ultrasound indicated

gallbladder muddy stones and CBD stones. After symptomatic treatment, he was referred to our institution for further diagnosis and therapy.

History of past illness and Personal and family history

Neither he nor his family had any past history of biliaro-pancreatic diseases or other abnormalities.

Physical examination upon admission

Physical examination revealed mild tenderness in the middle upper abdomen without rebound tenderness. Slight jaundice was observed in his sclera.

Laboratory examinations

Routine blood tests showed an inflammatory result: white blood cell count, 11.4 × 10^9/L; neutrophils, 78.9%; and hypersensitive C-reactive protein (hs-CRP), 20 mg/L. Liver biochemical function tests indicated extrahepatic biliary obstruction: alanine aminotransferase, 78 U/L; aspartate aminotransferase, 55 U/L; γ-glutamyl transpeptidase, 210 U/L; alkaline phosphatase, 441 U/L; total bilirubin, 40.5 μmol/L; and direct bilirubin, 33.1 μmol/L. The level of serum amylase was elevated (135 U/L). The serum autoimmune antibody tests including IgG 4 were negative.

Imaging examinations

Abdominal ultrasound showed cholecystitis with cholestasis in the gallbladder, dilated middle-upper CBD with a diameter of 1.1 cm, and a strong echo in the lower CBD, indicating biliary stones. Computed tomography was not performed because of the radiation risk.

Preliminary diagnosis

These findings above supported a diagnosis of extrahepatic biliary obstruction caused by biliary stones, which is an indication for ERCP.

FINAL DIAGNOSIS

PBM associated with PD with a communication between the CBD and dorsal pancreatic duct; CBD stones with acute cholangitis

TREATMENT

ERCP was performed to remove biliary stones. When the duodenoscope was advanced to the descending part of the duodenum, a hemispheric papilla with a villus-like opening was seen, which resembled the major papilla in both size and morphology (Figure 1A). This was wrongly considered to be the major papilla and cannulation was successfully carried out. X-ray examination after injecting a contrast agent into the papilla revealed a dilated CBD with a diameter of 0.9 cm, which was indicative of biliary stones (Figure 1B). However, the main pancreatic duct was not revealed. A minor endoscopic sphincterotomy was then performed, after which multiple small biliary stones were discharged from the papilla (Figure 1D). However, in a short distance beneath the papilla, another bigger papilla was detected, which was in fact the real major papilla (Figure 1E). The prior one was the minor papilla. After successful cannulation of the major papilla, the CBD was dilated with multiple filling defects, indicating biliary stones. However, the Wirsung duct was not observed. The middle–lower CBD was narrowed (Figure 1C). An endoscopic balloon was used to remove the biliary stones. During the process of pulling the balloon combined with injecting a contrast agent into the biliary tract, the dorsal pancreatic duct was unexpectedly revealed at the level of the middle–lower part CBD, which is rarely seen under normal conditions (Figure 1F and G). After clearing the CBD with the balloon, an 8.5 Fr 4-cm pigtail plastic pancreatic stent was placed in the biliary duct through the major papilla. Finally, the minor papilla was cannulated again and the guidewire was advanced into the CBD accompanying the biliary stent (Figure 1H), from which a communication between the CBD and dorsal pancreatic duct was created.

OUTCOME AND FOLLOW-UP

After the procedure, the child recovered uneventfully. Six months later, his biliary stent was removed after he had no symptoms and normal laboratory tests. In the following 4-year period with periodic telephone call and outpatient visits, the child grew up normally with no more attacks of abdominal pain.

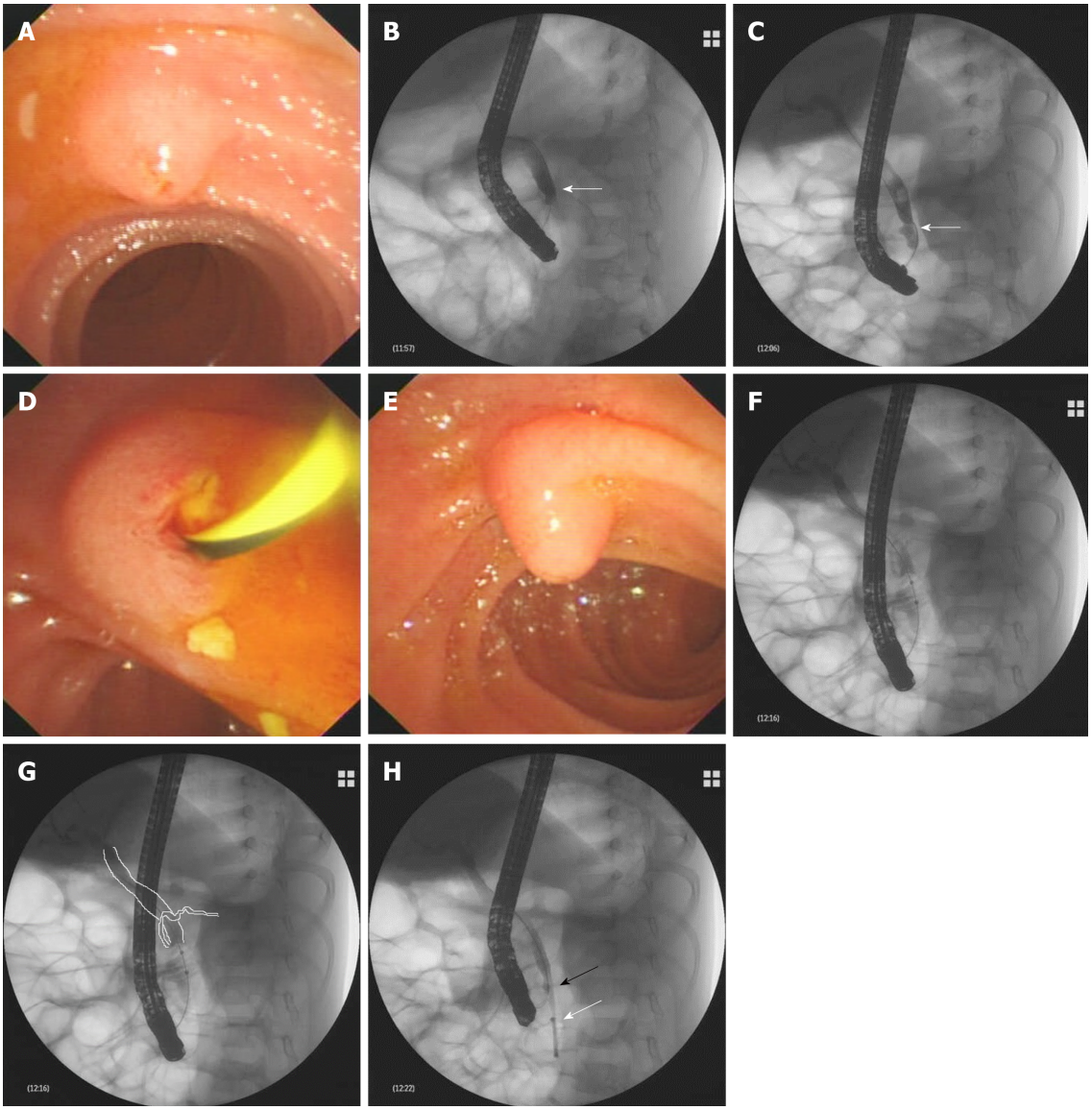

Figure 1 Results of endoscopic retrograde cholangiopancreatography. A: During endoscopic retrograde cholangiopancreatography, a hemispheric papilla with a villus-like opening resembling the major papilla was seen. B-E: Successful cannulation of the papilla and a dilated common bile duct (CBD) detected by X-ray after injection of a contrast agent (B). Multiple small biliary stones were discharged from the papilla after minor endoscopic sphincterotomy (D). Beneath the papilla, the real major papilla was detected (E). After cannulation of the major papilla, the CBD was observed again, which was dilated with multiple filling defects (C), and at the level of the middle–lower CBD, narrowing was observed (arrow); F: During removal of the biliary stones with an endoscopic balloon, unexpectedly, the dorsal pancreatic duct was revealed at the level of the middle–lower part of the CBD; G: Schematic representation of the image of F; H: After clearance of the CBD with the balloon, an 8.5 Fr 4-cm pigtail plastic pancreatic stent was placed in the biliary duct through the major papilla (white arrow); the minor papilla was cannulated again; and the guidewire was advanced into the CBD (black arrow).

DISCUSSION

PBM is a congenital anomaly that occurs when the pancreatic and bile ducts are united outside the duodenal wall. In patients with PBM, the sphincter of Oddi functionally loses its effect on the union of the two ducts. Therefore, continuous reciprocal reflux between pancreatic juice and bile occurs, which can result in various pathological conditions in the biliary tract and pancreas[2]. Under normal circumstances, the hydrostatic pressure in the pancreatic duct is usually higher than that in the bile duct, which means that the pancreatic juice more frequently refluxes into the biliary duct than the pancreatic duct in PBM[6]. This might be an etiological factor in choledocholithiasis, inflammatory ductal epithelial changes, distal common bile duct strictures, and recurrent attacks of acute cholangitis. Additionally, PBM resulting in chronic inflammation of the bile duct is considered to be frequently related to biliary tract malignancy. PD occurs when the ventral and dorsal ducts of the embryonic pancreas fail to fuse during the second month of fetal development[5]. It is the most frequent congenital anomaly of the pancreas in which the dorsal and ventral pancreatic ducts drain separately into the duodenum. The dominant pancreatic juice

is drained by the dorsal pancreatic duct through the minor papilla. Whether PD causes pancreatitis or other complications remains controversial. The co-occurrence of PBM and PD is an uncommon condition. Terui *et al*[7] found that PD was detected in one of 71 cases of PBM, with an incidence rate of 1.4%. In the current study, as shown in the schematic illustration (Figure 2), our case had three pancreaticobiliary abnormalities: PBM, PD, and abnormal communication between the CBD and dorsal pancreatic duct.

Currently, the Komi classification for PBM has been widely accepted and utilized, which influences the selection of type of surgical procedure and prognosis after surgery, especially in patients with complicating cases like type IIIc3[4]. In the Komi classification, all terminal CBDs join the ventral pancreatic duct. Matsumoto *et al*[8] retrospectively analyzed 202 patients with PBM to develop a new concept of the embryonic etiology of PBM. They found no patients in whom the terminal bile duct was joined with the dorsal pancreatic duct, nor was there a communication between the CBD and dorsal pancreatic duct. However, not all PBM cases can be classified according to the Komi classification. A few complicated PBM cases with rare anatomical variants have been reported by a small number of researchers[9-11]. Parlak *et al*[9] reported a 42-year-old woman who underwent ERCP for recurrent biliary pain attacks. During ERCP, the dilated CBD was found to fuse to the dorsal pancreatic duct directly without common channel dilation. Therefore, they thought that it represented a new type of PBM that could not be included in the Komi classification. Zhang *et al*[10] reported four complicated PBM cases, in which the CBD also joined the dorsal pancreatic duct in a direct way. All four cases were female with the youngest aged 11 years. They were successfully treated with intraductal drainage by ERCP. McMahon *et al*[11] reported an anomalous communication between the dorsal pancreatic duct and CBD *via* a small ventral pancreatic duct branch. This patient was a 30-year-old woman who suffered from chronic debilitating pain for several years. The patient's anomaly was indicated by magnetic resonance cholangiopancreatography (MRCP) with intravenous secretin administration. She received a Whipple pancreaticoduodenectomy combined with cholecystectomy. The aberrant ductal communication was confirmed by the resected specimen.

In our case, we found a communication between the CBD and dorsal pancreatic duct, which was similar to that reported by McMahon *et al*[11]. The little difference is that the communication in our case was located closer to the minor papilla. Although no definite communication was delineated by ERCP, the CBD was clearly observed by cannulation of both papillae. Moreover, the dorsal pancreatic duct was developed when removing the biliary stones with the balloon at the middle-lower level of the CBD *via* the major papilla. This may have been caused by high-pressure injection of contrast agent into the dorsal pancreatic duct *via* the communication between the CBD and dorsal pancreatic duct when the balloon was pulled down. We speculated that the communicating pancreatic duct was located at the middle-lower level of the CBD. As indicated earlier, all previously reported cases with this rare anomaly were female, with the youngest being aged 11 years[9-11]. However, in the present case, the child was male and aged 4 years.

To date, MRCP as a noninvasive approach is the first choice for diagnosis of pancreaticobiliary disorders. However, MRCP is limited in diagnosing the common biliopancreatic duct and biliopancreatic junction, compared with ERCP[12-14], even when secretin is used[15]. Diagnostic accuracy may be increased using 3D or dynamic MRCP with secretin stimulation[16]. For diagnosing patients with anatomical maljunction, ERCP remains the gold standard. In the current case, the patient was successfully diagnosed by ERCP.

PBM is generally recognized to be a risk factor for biliary tract malignancy[3]. Here, surgery is considered as radical treatment for patients with PBM. Timely surgical division of the biliary and pancreatic ducts is essential for patients with PBM to prevent free reflux of pancreatic juice into the biliary tract, regardless of the presence or absence of choledochal cyst[17-20]. ERCP is also a useful therapeutic option for patients with PBM, and it can be used to relieve acute biliary obstruction by removing biliary stones, implanting a biliary stent, or sphincterotomy[12-14]. It is helpful to plan the timing and choice of the appropriate surgical procedure. Samavedy *et al*[21] studied the potential benefit of ERCP in patients with PBM and found that 13 of 15 cases presenting with relapsing pancreatitis benefiting from endoscopic therapy. They assumed that ERCP was the logical first step to manage most symptomatic patients with PBM. Until now, only one similar patient with rare variant communication between the CBD and dorsal pancreatic duct has been reported, who underwent surgical treatment at age 30 years[11]. There is lack of therapeutic experience for such cases. In our case, given the factors of age, growth, and surgical trauma to the body, ERCP was chosen as initial therapy. During ERCP, an endoscopic balloon was used to remove the biliary stones and place a biliary stent through the major papilla. The child

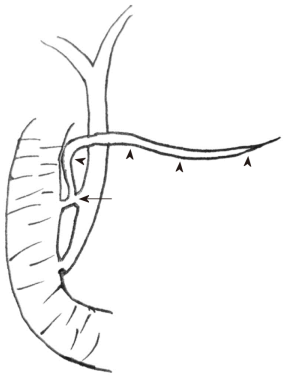

Figure 2 Schematic representation of the pancreaticobiliary system. This child had three anomalies: Pancreaticobiliary maljunction, pancreas divisum (arrowheads indicating dorsal pancreatic duct), and abnormal communication between the common bile duct and dorsal pancreatic duct (arrow).

remains asymptomatic during 4 yr of follow-up. Furthermore, close long-term follow-up is needed to supervise the development of biliary malignancy.

CONCLUSION

In summary, timely diagnosis and treatment of PBM associated with PD are important, especially when it is combined with aberrant communication between the CBD and dorsal pancreatic duct. We consider that ERCP is effective and safe in pediatric patients with PBM combined with PD, and can be the initial therapy to manage such cases. Considering the potential of PBM to develop into biliary malignancy, close follow-up is needed for small children after endoscopic therapy. Once the evidence of neoplastic degeneration is detected during follow-up, timely surgical therapy should be adopted.

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CASE REPORT

Crizotinib-induced acute fatal liver failure in an Asian *ALK*-positive lung adenocarcinoma patient with liver metastasis: A case report

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Author contributions: Zhang Y collected the patient's clinical data and drafted the manuscript; Xu YY reviewed the literature; Chen Y and Li JN contributed to analysis and interpretation of the imaging; Wang Y collected the patient's clinical data and revised the manuscript; all authors issued final approval for the version to be submitted.

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Abstract

BACKGROUND

Crizotinib-induce hepatotoxicity is rare and non-specific, and severe hepatotoxicity can develop into fatal liver failure. Herein, we report a case of fatal crizotinib-induced liver failure in a 37-year-old Asian patient.

CASE SUMMARY

The patient complained of dyspnea and upper abdominal pain for a week in August 2017. He was diagnosed with anaplastic lymphoma kinase-rearranged lung adenocarcinoma combined with multiple distant metastases. Crizotinib was initiated as a first-line treatment at a dosage of 250 mg twice daily. No adverse effects were seen until day 46. On day 55, he was admitted to the hospital with elevated liver enzymes aspartate aminotransferase (AST) (402 IU/L), alanine aminotransferase (ALT) (215 IU/L) and total bilirubin (145 μmol/L) and was diagnosed with crizotinib-induced fulminant liver failure. Despite crizotinib discontinuation and intensive supportive therapy, the level of AST (1075 IU/L), ALT (240 IU/L) and total bilirubin (233 μmol/L) continued to rapidly increase, and he died on day 60.

CONCLUSION

Physicians should be aware of the potential fatal adverse effects of crizotinib.

Key words: Fatal liver failure; Crizotinib hepatotoxicity; Liver metastases; *ALK* rearrangement; Lung adenocarcinoma; Case report

Core tip: Crizotinib-induce hepatotoxicity is rare and non-specific, and severe hepatotoxicity can develop to fatal liver failure. We report a case of fatal crizotinib-induced liver failure in a 37-year-old Asian patient with anaplastic lymphoma kinase-rearranged lung adenocarcinoma combined with hepatic metastasis. Physicians should be

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aware of the potential fatal adverse effect of crizotinib. The King's College Criteria and weekly monitoring of liver enzymes are necessary to diagnose and evaluate crizotinib-induced liver failure.

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INTRODUCTION

Lung cancer is one of the most common cancers worldwide, and it is the leading cause of cancer deaths. Non-small-cell lung cancer (NSCLC) accounts for nearly 80%-85% of lung cancers[1-5]. Most NSCLCs are unresectable and are already advanced upon diagnosis[3]. Molecular target therapy is effective for advanced NSCLC patients with related gene mutations. Some specific driver mutations in genes, including epidermal growth factor receptor, Kirsten rat sarcoma viral oncogene and anaplastic lymphoma kinase (*ALK*), have been identified in NSCLC[6]. *ALK* rearrangements are defined as a special molecular subtype of lung cancer and have been found in 5%-7% of NSCLC patients[7].

Crizotinib (Xalkori™, Pfizer) is a multi-target tyrosine kinase inhibitor that targets *ALK*, mesenchymal epithelial transition and c-ros oncogene 1 receptor tyrosine kinase. It was approved as a first-line therapy for the treatment of *ALK*-rearranged NSCLC by the Food and Drug Administration in 2011[8]. Crizotinib showed an improved survival rate compared to conventional chemotherapy in patients with advanced or metastatic *ALK*-positive NSCLC[9-11]. Common adverse effects of crizotinib have been reported, including vision disorders, gastrointestinal disturbances, electrocardiographic abnormalities, hypogonadism and hepatotoxicity. In five clinical trials (PROFILE 1001[12], 1005[13], 1007[10], 1014[14], 1029[15]), elevated aminotransferases were observed in 10%-38% of patients. Among them, 2%-16% of grade 3 or 4 patients had increased aminotransferase levels. However, most transaminase abnormality was reversible. Only 0.4% of patients exhibited irreversible hepatotoxicity, and two of them died[16]. Herein, we report a case of acute fatal crizotinib-induced liver failure when crizotinib was used as a first-line therapy for hepatic metastases in an Asian patient with lung adenocarcinoma. In addition, a literature review on crizotinib-induced hepatitis is presented.

CASE PRESENTATION

Chief complaints

A 37-year-old Asian man complained of dyspnea and upper abdominal pain for a week in August 2017.

History of present illness

The patient was admitted to our hospital in July 2017 due to complaints of fever and severe cough. Positron emission tomography-computed tomography (PET-CT) identified a primary malignant nodule on the right lower lung lobe and mediastinal metastasis without liver metastasis. The patient underwent successful resection of the primary pulmonary nodules. Pathological examination showed a lung adenocarcinoma with echinoderm microtubule associated protein-like 4 and *ALK* rearrangement measured by fluorescence in situ hybridization. The patient did not receive chemotherapy after the operation due to his faint physical condition. In August 2017, he presented with dyspnea and upper abdomen pain for a week and returned to the hospital.

History of past illness

There was no history of past illness.

Personal and family history

He was a non-smoker and non-drinker, also without history of drug allergy.

Physical examination upon admission

A physical examination revealed hepatomegaly and liver tenderness, and the Karnofsky performance status (KPS) was a score of 50.

Laboratory examinations

On examination (day 1), a full panel of liver function tests revealed that the prothrombin time (PT), serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were elevated, as follows: PT: 17.3 s (normal reference < 12.5 s), AST: 95 IU/L (normal reference < 34 IU/L), ALT: 55 IU/L (normal reference < 40 IU/L). However, the total bilirubin (10.6 μmol/L) level was normal (normal reference < 20.5 μmol/L). Biliary obstruction, non-alcoholic fatty liver disease, ischemic hepatitis and hepatitis A, B or C virus infection were excluded. Serum tests were negative for Cytomegalovirus, Epstein-Barr virus, Herpes Simplex, hepatitis E virus antibodies and anti-mitochondrial smooth muscle. Other laboratory data were within normal limits, including serum ferritin, copper and ceruloplasmin.

Imaging examinations

Chest and abdominal CT scans identified an 8.4 cm × 9.8 cm mediastinal metastatic lump and multiple hepatic metastases as a baseline (Figure 1A and D).

FINAL DIAGNOSIS

After consideration of the patient's present history of lung adenocarcinoma and CT scans, the final diagnosis was advanced *ALK*-positive lung adenocarcinoma with multiple distant metastases (cT1N2M1b, Stage IV).

TREATMENT

The patient received 250 mg oral crizotinib twice daily as first-line therapy and 456 mg polyene phosphatidylcholine capsules three times daily for transaminase elevation. On day 10, serum AST (36 IU/L) and ALT (58 IU/L) levels were obviously decreased. Clinical signs of dyspnea were relieved and upper abdomen pain disappeared by day 18. KPS was reevaluated, and the score was 90. Chest and abdominal CT scans identified the stable mediastinal lump and multiple hepatic nodules. On day 25, liver enzyme levels had decreased to normal values. On day 35, chest and abdominal CT scans revealed a slight decrease in volume of mediastinal and liver metastases (Figure 1B, 1E). The therapeutic effect was classified as stable disease according to the Response Evaluation Criteria in Solid Tumors. On day 46, the patient was found to have icteric sclera and abnormal liver enzyme levels during his outpatient follow-up, but he refused treatment. On day 55, he began to appear drowsy but with normal vital signs. Physical examination showed icteric sclera and asterixis. Laboratory data indicated liver function impairment, as follows: AST: 402 IU/L, ALT: 215 IU/L, total bilirubin: 145 μmol/L; PT: 18 s. ALT level, AST level and total bilirubin were evaluated as toxicity grade 3. The plasma NH3 (63 μmol/L) level accumulated (9 < normal reference < 33 μmol/L). Chest CT scan showed that the mediastinal lump was unchanged (Figure 1C) and head CT scan was normal. However, abdominal CT scan revealed acute intrahepatic bile duct dilatation, massive ascites and an increase in liver volume by 20% with unvaried metastatic nodules (Figure 1F). According to the King's College Criteria, fulminant liver failure and hepatic encephalopathy were diagnosed. Crizotinib-induced liver failure was strongly suspected, and crizotinib treatment was discontinued from the evening of day 55. The patient was given intensive treatments for acute hepatic failure, including lactulose against encephalopathy, prophylactic antibiotics, proton pump inhibitor, human albumin and plasma, according to the practice guidelines. On day 57, his disturbed consciousness improved, and the level of AST (150 IU/L), ALT (129 IU/L) and total bilirubin (99.1 μmol/L) decreased. Although these intensive therapies were continued, his liver function rapidly deteriorated, as follows: AST: 1075 IU/L, ALT: 240 IU/L, total bilirubin: 233 μmol/L; PT: 29 s, NH3: 163 μmol/L. The changes in AST, ALT and total bilirubin from day 1 to day 59 are shown in Figure 2. He went comatose on day 59.

OUTCOME AND FOLLOW-UP

On day 60, the patient died. Autopsy or liver biopsy could not be conducted.

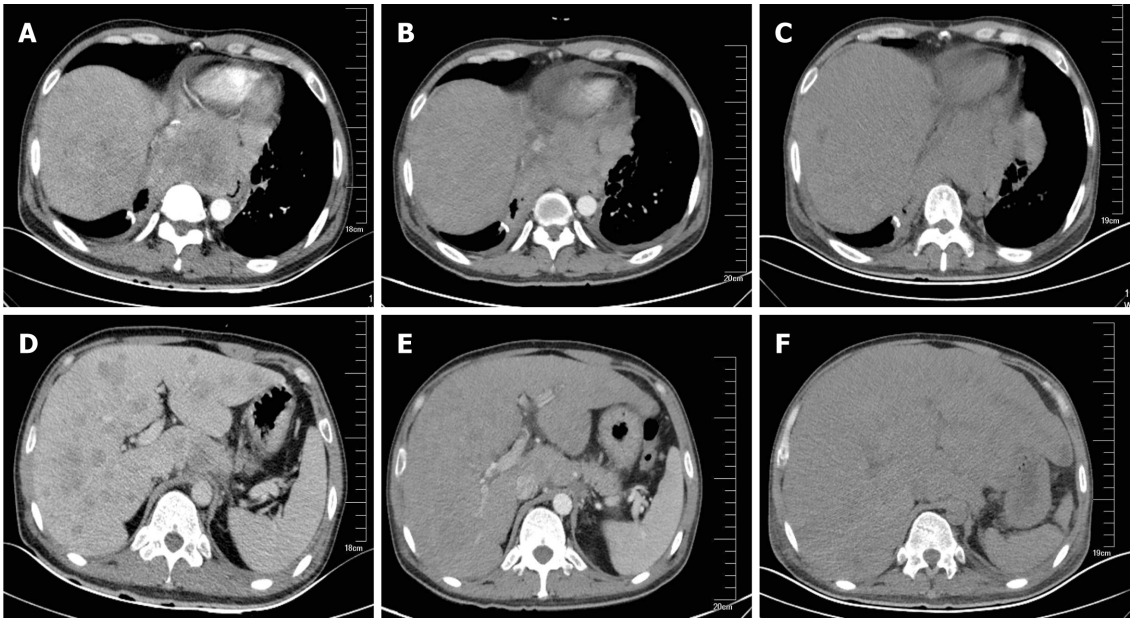

Figure 1 Computed tomography indicated mediastinal and hepatic metastatic changes. A: Chest computed tomography (CT) showed a 8.4 × 9.8 cm mediastinal metastatic lump; B: Chest CT on day 35 showed a slight shrink in mediastinal metastasis; C: Chest CT on day 55 showed unchanged mediastinal lump compared to B; D: Abdominal CT showed multiple metastases; E: Liver metastasis slightly shrank after 35 d of crizotinib therapy; F: Liver volume increased by 20% and acute intrahepatic bile were revealed on day 55.

DISCUSSION

This report describes the first case of fatal crizotinib-induced fulminant liver failure in an Asian patient with liver metastasis. Other causes of liver failure were eliminated, including hepatic metastasis, viral hepatitis infection, biliary obstruction, alcoholic liver disease and concomitant medication. In the beginning, the slightly increased transaminase levels decreased to normal levels after 25 d of oral crizotinib, which indicates that the improvement in liver function was closely related to crizotinib therapy for liver metastasis[17]. However, ALT and AST levels and liver volume suddenly increased on day 55. Although transaminase and total bilirubin levels decreased after two days of crizotinib discontinuation, it increased rapidly again over the next two days, which may have been caused by massive necrosis of liver cells. Based on these findings, crizotinib-induced acute liver injury was strongly suspected.

To better understand the current status of crizotinibinduced fulminant hepatitis, we reviewed and summarized the published literature (Table 1). Four cases of crizotinibinduced hepatitis have been reported, which occurred within a few months after crizotinib treatment. Among these patients, two of them died of hepatic encephalopathy caused by liver failure and one of them died of respiratory failure with carcinomatous pleurisy[18-21]. Consistent with these two cases, the patient in our report also died of crizotinib-induced fulminant liver failure. However, our case was an advanced lung cancer patient with liver metastasis, which is distinct from the reported cases. Thus, early diagnosis and treatment are critical for crizotinib-induced hepatotoxicity, which could help *ALK*-positive lung cancer patients to obtain survival benefits and avoid fatal events. Weekly liver function tests including transaminases and total bilirubin are insufficient to estimate sporadic crizotinib-induced hepatotoxicity. The King's College Criteria was used to evaluate acute liver failure and poor prognosis. The sensitivity and the specificity of King's College Criteria have been shown to be 68%-69% and 82%-92%, respectively[22]. Therefore, drug-induced liver dysfunction could be diagnosed early and accurately by using the King's College Criteria. Altogether, the King's College Criteria should also be used weekly to evaluate crizotinib-induced acute liver failure.

The mechanism of crizotinib-induced hepatotoxicity remains unclear. Crizotinib is extensively metabolized in the liver by *CYP450* 3A. Consequently, crizotinib and *CYP450* 3A inducers or inhibitors should be avoided at the same time so as not to increase plasma concentrations of crizotinib[23]. Moreover, Yasuda *et al*[21] have suggested that the underlying mechanism of hepatotoxicity is a partial allergic reaction to crizotinib or its metabolite. Oral desensitization could be considered a viable option after crizotinib-induced hepatitis. In addition, as a novel *ALK* inhibitor, ceritinib could be also used as an alternative agent when crizotinib causes hepatitis[24].

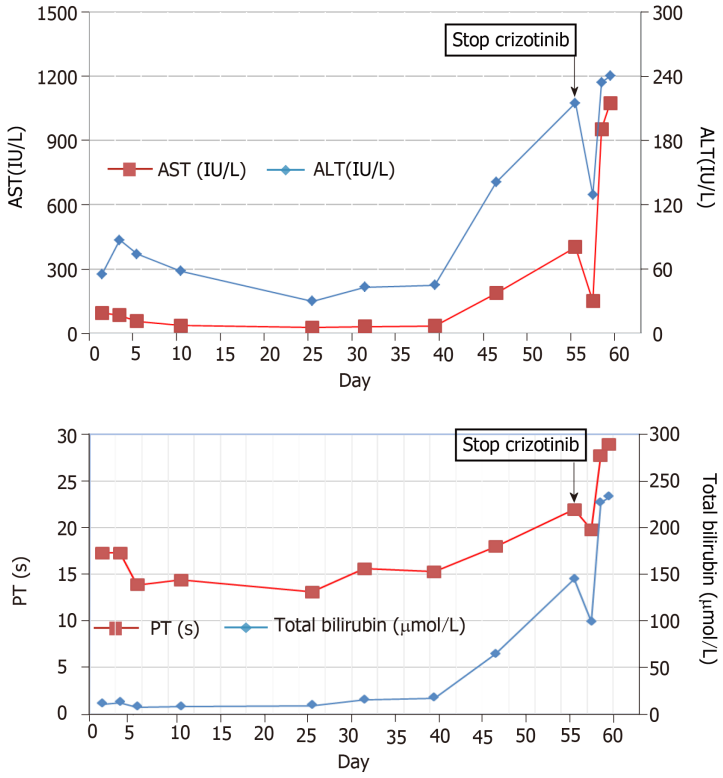

Figure 2 Detailed changes of liver enzymes during crizotinib therapy (day 1–55) and after crizotinib discontinuation (day 56–59). A: Upper graph: aspartate aminotransferase and alanine aminotransferase; B: Lower graph: total bilirubin and prothrombin time. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin time.

Generally, the initial dose of crizotinib was given at 250 mg twice-daily, which does not account for the patient's age, sex, race, body weight, or hepatic function impairment. Therefore, physicians should be aware of serious adverse reactions caused by individual differences[25].

CONCLUSION

This study indicates that crizotinib can cause fulminant liver failure in lung cancer patient with liver metastasis. Clinicians should be highly aware of the potential fatal adverse effect induced by crizotinib, especially for patients with liver metastasis. Liver enzyme testing should be carried out at least once a week during the first 2 mo of crizotinib treatment. It is strongly suggested that the King's College Criteria be used to prevent acute liver failure during crizotinib administration in the clinic.

Table 1 Case reports of crizotinib-induced fulminant hepatitis, 2013-2017

Author	Therapy line	Initial dose	Liver injury	Occurrence time	Outcome
Ripault *et al*[18], 2013	Not mentioned	500 mg Qd	Acute hepatitis	Day 60	Transaminases returned to normal
Sato *et al*[19], 2014	First-line	400 mg Qd	Fulminant hepatitis	Day 29	Died of liver failure
Van Geel *et al*[20], 2016	Second-line	250 mg Bid	Fulminant liver failure	Day 24	Died of liver failure
Yasuda *et al*[21], 2017	Second-line	250 mg Bid	Hepatitis	Day 16	Died of respiratory failure
Present case	First-line	250 mg Bid	Fulminant liver failure	Day 46	Died of liver failure

Qd: Every day; Bid: Twice a day.

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CASE REPORT

Coexistence of breakpoint cluster region-Abelson1 rearrangement and Janus kinase 2 V617F mutation in chronic myeloid leukemia: A case report

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Author contributions: Shi XB participated in patient treatment, collection and analysis of the clinical data and writing of the manuscript; Jiang JF participated in patient treatment, data analysis and manuscript revision; Jin FX helped guide the treatment of the patient and research design; Cheng W took part in the patient's therapy; All authors read and approved the final manuscript.

Informed consent statement: Written informed consent was obtained from both the patient and her spouse for publication of this case report.

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Abstract

BACKGROUND

The Janus kinase 2 (*JAK2*) V617F mutation is common in patients with breakpoint cluster region-Abelson1 (*BCR-ABL1*)-negative myeloproliferative neoplasms, including polycythemia vera, essential thrombocythemia and primary myelofibrosis, but is rarely detected in *BCR-ABL1*-positive chronic myeloid leukemia (CML) patients. Here, we report a CML patient with both a *BCR-ABL1* rearrangement and *JAK2* V617F mutation.

CASE SUMMARY

A 45-year-old Chinese woman was admitted to our department with a history of significant thrombocytosis for 20 d. Color Doppler ultrasound examination showed mild splenomegaly. Bone marrow aspiration revealed a karyotype of 46, XX, t(9;22)(q34;q11.2) in 20/20 metaphases by cytogenetic analysis, rearrangement of *BCR-ABL*1 (32.31%) by fluorescent polymerase chain reaction (PCR) and mutation of *JAK2* V617F (10%) by PCR and Sanger DNA sequencing. The patient was diagnosed with CML and *JAK2 V617F* mutation. Following treatment with imatinib for 3 mo, the patient had an optimal response and *BCR-ABL1* (IS) was 0.143%, while the mutation rate of *JAK2* V617F rose to 15%.

CONCLUSION

Emphasis should be placed on the detection of *JAK2* mutation when CML is diagnosed to distinguish *JAK2* mutation-positive CML and formulate treatment strategies.

Key words: Chronic myeloid leukemia; *JAK2* V617F; *BCR-ABL1*; Imatinib; Myeloproliferative neoplasm; Case report

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Core tip: The Janus kinase 2 (*JAK2*) V617F mutation is rare in breakpoint cluster region-Abelson1 (BCR-ABL1)-positive chronic myeloid leukemia (CML). We report a female CML patient with a *JAK2* V617F mutation. This rare subset of CML patients often have notable thrombocythemia in addition to more typical CML features. The patient achieved complete hematological response following 2 mo imatinib treatment. After 3 mo of imatinib treatment, the value of BCR-ABL1 (IS) was 0.143%, but the *JAK2* V617F mutation rate rose from 10% to 15%.

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INTRODUCTION

Chronic myeloid leukemia (CML) is a hematologic malignant neoplasm with clonal proliferation of hematopoietic cells. The specific molecular biologic feature of typical CML corresponds to a translocation between chromosome 9 and chromosome 22 [t(9;22)(q34;q11)], named the Philadelphia (Ph) chromosome, which leads to breakpoint cluster region-Abelson1 (*BCR-ABL1*) rearrangement[1]. The Ph chromosome and/or *BCR-ABL1* rearrangement are necessary for the diagnosis of typical CML[1]. Janus kinase 2 (*JAK2*) V617F mutation is an important biomarker in the diagnosis of myeloproliferative neoplasms (MPNs). According to the literature, the mutation rate of *JAK2* V617F is 90%-95% in polycythemia vera (PV) and about 60% in both essential thrombocythemia (ET) and primary myelofibrosis (PMF)[2]. However, *BCR-ABL1*-positive CML with *JAK2* V617F mutation is very uncommon. Herein, we present a case of CML with both the *BCR-ABL1* rearrangement and *JAK2* V617F mutation.

CASE PRESENTATON

Chief complaints

On May 29, 2018, a 45-year-old Chinese woman with a history of marked thrombocytosis for 20 d was admitted to the Department of Hematology and Oncology, Tongling People's Hospital (Anhui Province, China).

History of present illness

She had been treated with antibiotics for 3 wk for lobar pneumonia in another hospital before admission to our hospital. Peripheral blood count showed a platelet count of 586 × 10^9/L at the beginning of anti-infective therapy, which increased to 1109 × 10^9/L when her pneumonia resolved. She attended our department for hematological evaluation.

History of past illness

She had no past history of surgery, anemia or malignant neoplasms and was not taking any medication.

Personal and family history

She was married, and her spouse and daughter were both healthy. The family history was unremarkable.

Physical examination upon admission

Physical examination showed that the splenic inferior margin was 2 cm under the left arcus costarum.

Laboratory examinations

The concentration of lactate dehydrogenase was 364 U/L. Peripheral blood count showed a leukocyte count of 11.46 × 10^9/L, hemoglobin of 121 g/L, platelet count of 1582 × 10^9/L and neutrophil count of 7.63 × 10^9/L. Peripheral blood smear examination showed 2% blasts, 1% myelocytes, 70% mature neutrophils, 3%

eosinophils, 7% basophils, 13% lymphocytes and 4% monocytes (Table 1). Bone marrow cytomorphologic examination revealed mild granulocytic hyperplasia of 49%, including 1.5% myelocytes, 5.5% metamyelocytes, 10.5% stab nuclear neutrophils, 22% segmented neutrophils, 1.5% eosinophils, 3% basophils and 5% blasts (Table 1). The leukocyte alkaline phosphatase score was 135 and leukocyte alkaline phosphatase positivity was 92%. Immunophenotyping analysis by flow cytometry revealed 5% blast cells. The reagents applied in flow cytometry mainly consisted of antibodies against CD10, CD19, CD5, CD7, CD13, CD33, HLA-DR, CD38, CD34, CD16, CD11b, CD117, CD36, CD64, CD56, CD14, CD20, CD8, CD3, CD2, CD4, cMPO, cCD22, cCD3, TCRab, TCRgd, CD45RA, CD45RO, CD15,CD11c, CD43 and CD45. Cytogenetic analysis using both the G-banding and R-banding technique demonstrated a karyotype of 46, XX, t(9:22)(q34;q11.2) in 20/20 metaphases examined. The rearrangement of *BCR-ABL1* (P210) was detected by fluorescent polymerase chain reaction (commonly known as PCR), and the *BCR-ABL1/ABL1* ratio was 32.31%. Moreover, the *JAK2* V617F mutation was identified by PCR and Sanger DNA sequencing, and the mutation percentage, which was calculated as [copy-number$_{JAK2V617F}$ / (copy-number$_{JAK2V617F}$ + copy-number$_{wild\text{-}type\ JAK2}$)], was 10%. Bone marrow biopsy examination showed active proliferation of granulocytic cells and marked hyperplasia of megakaryocytes (Figure 1A). The proliferative megakaryocytes had small cell bodies and decreased karyolobism. Additional immunohistochemistry of bone marrow cells exhibited CD34 (2%+), CD117 (5%+), MPO partial +, CD235a minority +, CD61 + for megakaryocytes and a few scattered CD138 +. Gomori staining was positive (++ - +++) (Figure 1B).

Imaging examinations

Color Doppler ultrasound examination showed mild splenomegaly.

FINAL DIAGNOSIS

The patient was diagnosed with CML (chronic phase, Sokal 1.68, high risk) and *JAK2* V617F mutation.

TREATMENT

Due to severe thrombocytosis, the patient was treated with hydroxyurea (0.5-2.0 g/d), aspirin (0.1 g/d) and platelet separation. On the sixth day of hospitalization, she was administered imatinib (0.4 g/d) due to the detection of the *BCR-ABL1* rearrangement. Her platelet count rapidly decreased, and hydroxyurea and aspirin were discontinued successively.

OUTCOME AND FOLLOW-UP

On July 11, 2018, her peripheral blood counts were as follows: leukocytes 3.44 × 10^9/L, neutrophils 2.11 × 10^9/L, hemoglobin 117 g/L and platelets 130 × 10^9/L, and she was discharged from the hospital. After leaving hospital, she continued to take imatinib (0.4 g/d). During regular follow-up, her peripheral blood counts were in the normal reference range, and spleen size returned to normal within 2 mo. After 3 mo of imatinib therapy, bone marrow aspiration was reexamined. Mutation of the *ABL1* kinase domain was negative. Chromosomal karyotype was 46, XX in all 20 metaphases by G-banding, while the karyotype of 46, XX, t(9;22)(q34;q11.2) was identified in 1/16 metaphases by R-banding. The *BCR-ABL1/ABL1* ratio decreased to 0.216% and *BCR-ABL1* (IS) was 0.143%, but the percentage of *JAK2* V617F mutation increased to 15%. The patient had an optimal response to imatinib therapy and is continuing to take imatinib.

DISCUSSION

MPNs are clonal disorders of hematopoietic stem cells, and they can be divided into *BCR-ABL1*-negative MPN and Ph chromosome and/or *BCR-ABL1* positive CML according to the 2016 World Health Organization classification system for hematopoietic and lymphoid tissue tumors. The former mainly includes *JAK2*/*CALR*/*MPL* mutated MPNs (PV, ET and PMF), chronic neutrophilic leukemia, chronic eosinophilic leukemia and unclassified MPN[2]. As an important marker in the

Table 1 Differential cell counts in peripheral blood and bone marrow

Cell types	Peripheral blood	Bone marrow
	Cell counts, %	Cell counts, %
Blast	2	5
Myelocyte	1	1.5
Metamyelocyte	NA	5.5
Mature neutrophil	70	32.5
Stab nuclear neutrophil	NA	10.5
Segmented neutrophil	NA	22
Eosinophil	3	1.5
Basophil	7	3
Lymphocyte	13	10.5
Monocyte	4	1

NA: Not applicable.

diagnosis of *JAK2*/*CALR*/*MPL* mutated MPNs, the *JAK2* V617F mutation has often been reported in PV, ET and PMF, but rarely in typical CML.

In recent years, a few studies have reported that *BCR-ABL1* rearrangement/Ph chromosome and *JAK2* V617F mutation can coexist in CML patients[3-14]. However, some of these studies failed to examine *JAK2* status at the time of initial diagnosis of CML, but detected *JAK2* V617F mutation with a decrease in *BCR-ABL1* translocation level during treatment with tyrosine kinase inhibitors (TKIs)[3-9], while others discovered concomitant *BCR-ABL1* rearrangement and *JAK2* V617F mutation when CML was diagnosed and before administration of TKIs[5,10-14]. The CML patients with a *JAK2* V617F mutation not only had typical CML characteristics but also had notable thrombocythemia[5-7,9-11], and thrombocytosis even persisted in some patients after obtaining a complete cytogenetic response, major molecular response or deep molecular response after TKI therapy[5,7,11]. Most studies indicated that following TKI treatment, the mutation rate of *JAK2* V617F increased with a decrease in *BCR-ABL1* transcript level in this category of CML patients[7,8,12,13]. Only one study showed that *JAK2* V617F mutation gradually decreased and then disappeared, accompanied by a reduction in *BCR-ABL1* rearrangement[10]. As reported in the literature, *JAK2* V617F mutation affected the curative effect in CML patients, and *JAK2 V617F*-positive CML patients often had a suboptimal response to TKIs[9,10,13]. Pahore *et al*[14] demonstrated that 26.7% of 45 CML patients had a *JAK2* V617F mutation, and the risk of early disease progression in patients with a *JAK2* V617F mutation was significantly higher than that in patients without the *JAK2* V617F mutation.

There is no optimal treatment strategy for *JAK2* V617F-positive CML patients. As described in published reports, TKIs are preferentially administered in this subset of patients[3-12]. To our knowledge, it is unclear whether such cases can benefit from the *JAK2* inhibitor ruxolitinib.

In our patient, bone marrow examination revealed the coexistence of *BCR-ABL1* rearrangement and *JAK2* V617F mutation before imatinib was administered, and the patient also presented with marked megakaryocytic hyperplasia and myelofibrosis. Following hospitalization, peripheral blood primarily showed a marked increase in platelet count. The patient achieved complete hematological response following 2 mo of imatinib treatment. After 3 mo of imatinib treatment, the proportion of Ph chromosome-positive cells was 6.25% in all metaphases and *BCR-ABL1* (IS) was 0.143%, which suggested that the optimum response had been obtained. However, the *JAK2* V617F mutation rate rose from 10% to 15%. The marked thrombocytosis observed at diagnosis and identification of the *JAK2* V617F mutation level increasing in pace with the decrease in *BCR-ABL1* transcript level during imatinib therapy were consistent with previously reported observations[5-9,11-13]. We hypothesize that the coexistence of *BCR-ABL1* rearrangement and *JAK2* V617F mutation originates from two different clones that grow independently. Although our patient has favorable treatment efficacy at present, the *JAK2* V617F mutation level is still increasing and bone marrow fibrosis is still present. Thus, the long-term prognosis of this patient may be poor, and extended follow-up is required.

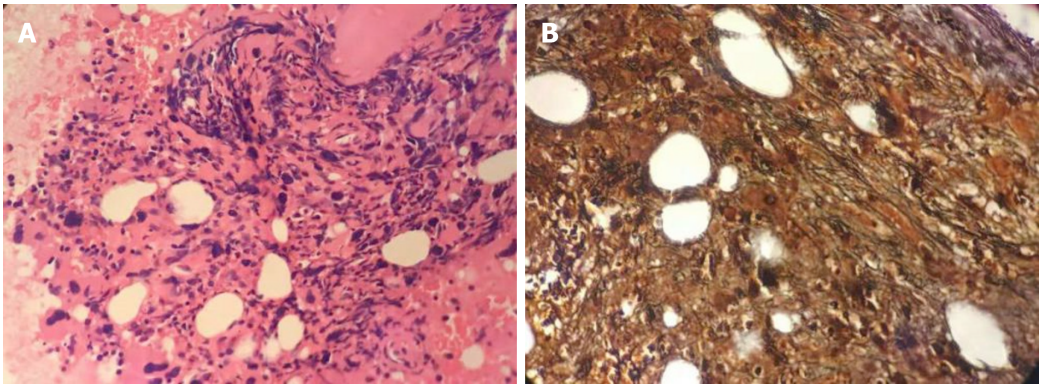

Figure 1 Bone marrow biopsy. A: Hematoxylin and eosin staining shows active proliferation of granulocytic cells and marked megakaryocytic hyperplasia (400 ×); B: Gomori staining is positive (++ to +++) (400 ×).

CONCLUSION

With the rapid development of molecular biology, a few CML patients with a *JAK2* V617F mutation have been reported recently, but such cases are relatively rare. The specific pathogenesis, optimal treatment and prognosis of this special type of CML are currently still ambiguous, and further large-sample studies are urgently needed. Moreover, further research to determine whether the *JAK2* mutation is associated with *BCR-ABL1* translocation in these patients is required. Attention should be paid to the detection of the *JAK2* mutation during the diagnosis and treatment of CML in order to timely identify *JAK2* mutation-positive CML patients and guide the formulation of treatment strategies.

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