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Case Report

Mass-forming immunoglobulin G4-related cholangitis with atypical pancreatic lesions: a case report of difficult diagnosis

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Abstract: Background: Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is a systemic immune-mediated fibroinflammatory disease that results in the tissue destruction of multiple organs. IgG4-RD is often underdiagnosed or misdiagnosed as malignant, infectious, or other inflammatory disorder. Case presentation: We describe a 56-year-old woman presented with jaundice and weight loss. Radiological imaging showed common hepatic duct wall thickening and nodular lesions in the pancreas, which was highly suspicious of malignancy. However, she was contraindicated for biopsy; hence, the diagnosis of IgG4-RD was made based on her high serum IgG4 level, multiorgan involvement, and steroid response. The effect of steroid therapy was significant, although the disease relapsed during the maintenance treatment. The dosage of steroid was re-increased, and the patient was under close follow-up. Conclusions: The diagnosis of IgG4-RD is challenging due to its diverse manifestations. Therefore, a careful systematic assessment is necessary to improve the accuracy of IgG4-RD diagnosis, and a close follow-up is important to monitor the disease development as well as adjust the treatment strategy accordingly.

Keywords: IgG4-related disease, IgG4-related sclerosing cholangitis, autoimmune pancreatitis, jaundice

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated condition associated with fibroinflammatory lesions that can occur at nearly any anatomic site [1]. It often presents as a multiorgan disease and tends to be misdiagnosed as malignancy, infection, or other immune-related diseases. The diagnosis of IgG4-RD is challenging due to its diverse manifestations, especially when the radiological results are atypical, or the biopsy cannot be performed. Therefore, the accurate differentiation of IgG4-RD from malignancy is crucial to avoid unnecessary surgery. Here, we report a case of IgG4-RD presented as mass-forming IgG4-related sclerosing cholangitis (IgG4-SC) mimicking hilar cholangiocarcinoma and multiple nodular lesions in the pancreas. The patient also had contraindication for obtaining biopsy; as a result, the diagnosis of IgG4-RD was made based on the serological features, multiorgan involvement, and good response to steroids.

Case presentation

A 56-year-old afebrile woman was admitted to our hospital on December 17, 2021, with anorexia, abdominal pain, jaundice, skin pruritus, and dark urine during the prior week. She also had unintentional weight loss of 5 kg during the prior month.

The patient had a prior history of coronary heart disease, aortic valve stenosis and diabetes mellitus, but no family history of autoimmune diseases or cancer. She received percutaneous coronary intervention 9 years ago as well as aortic valve replacement 7 years ago and was under warfarin medication since then.

Laboratory tests showed markedly elevated biliary enzymes and tumor markers as follows (**Table 1**): total bilirubin (T-Bil), 488.46 umol/L; direct bilirubin (D-Bil), 244.26 umol/L; aspartate aminotransferase (AST), 57.9 U/L; alanine aminotransferase (ALT), 62 U/L; alkaline phos-

Table 1. Laboratory test results in the present case

Laboratory Test	Results (Normal Range)
Peripheral blood counts	
White blood cell ($\times 10^9$/L)	7.83 (3.5-9.5)
Hemoglobin (g/L)	150 (115-150)
Eosinophil (%)	1.7 (0.4-8)
Platelet ($\times 10^9$/L)	182 (125-350)
Inflammatory markers	
C-reactive protein (mg/L)	7.43 (0-8)
Erythrocyte sedimentation rate (mm/h)	44 (0-20)
Biochemistry	
T-Bil (umol/L)	488.46 (3.42-17.1)
D-Bil (umol/L)	244.26 (0-6.84)
AST (U/L)	57.9 (13-35)
ALT (U/L)	62 (7-40)
ALP (U/L)	392 (50-135)
GGT (U/L)	543 (7-45)
Coagulation	
Prothrombin time activity (%)	39 (80-120)
International normalized ratio	2.08 (0.8-1.2)
Tumor markers	
CA19-9 (U/ml)	555.4 (0-35)
CA-242 (U/ml)	42.43 (0-25)
CA-50 (U/ml)	339.76 (0-30)
Immunology	
IgG (g/L)	34.6 (20-40)
IgG4 (g/L)	12.8 (0.03-2.01)
Antinuclear antibody	Negative
Antineutrophil cytoplasmic antibody	Negative

T-Bil: total bilirubin; D-Bil: direct bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyl transpeptidase; CA19-9: carbohydrate antigen 19-9; CA-242: carbohydrate antigen-242; CA-50: carbohydrate antigen-50; IgG: immunoglobulin; IgG4: immunoglobulin G4.

phatase (ALP), 392 U/L; γ-glutamyl transpeptidase (GGT), 543 U/L; carbohydrate antigen 19-9 (CA19-9), 555.4 U/ml.

Contrast enhanced abdominal computed tomography (CT) showed a soft tissue mass in the common hepatic duct causing the dilation of upstream intrahepatic bile ducts. The lesion was significantly enhanced with the density levels of the pre-contrast, arterial, and venous phases as 34, 89, and 93 Hounsfield Unit (HU), respectively (**Figure 1**). The CT also revealed multiple nodular masses in the body and the tail of the pancreas which showed equal density in plain scan (43 HU) but had a significantly increased enhancement in the arterial phase (93 HU) and a delayed enhancement in the venous phase (101 HU) (**Figure 2**). Magnetic Resonance Cholangiopancreatography (MRCP) also revealed strictures at common hepatic duct with upstream intrahepatic biliary tree dilation, while no sign of pancreatic duct involvement was observed. Given the age, clinical presentation, weight loss, elevated tumor markers, and imaging characteristics of this patient, hilar cholangiocarcinoma or pancreatic cancer was the primary suspected disease. Although percutaneous transhepatic drainage (PTCD) was performed to relieve jaundice, it was ineffective and the patient's percutaneous puncture site continued to leak blood due to her poor coagulation function. Further examination such as endoscopic retrograde cholangiopancreatography (ERCP) with bile duct biopsy or endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) to obtain samples for tissue pathology was called off for the risk of uncontrollable internal hemorrhage.

The diagnosis for the mass forming lesions in the extrahepatic bile duct and the multiple nodular masses on the pancreas was difficult with the contraindication to obtain biopsies. We carefully reviewed her chest as well as abdominal CT and found bilateral hilar and mediastinum lymph node enlargement with uniform enhancement, slightly thickening in bilateral renal pelvic walls, and possible inflammation in the perirenal fat, which suggested a possible IgG4-RD. Serum immunological tests revealed a significantly elevated serum IgG4 level (12.8 g/L, >5× the upper limit of normal); however, lacrimal and salivary gland involvement, peripheral lymphadenopathy, clues of retroperitoneal fibrosis, or aortic wall thickening was not observed. According to the 2019 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for IgG4-RD, this patient had a total point of 19 (11 points for serum IgG4 level, and 8 points for renal pelvis thickening), which did not

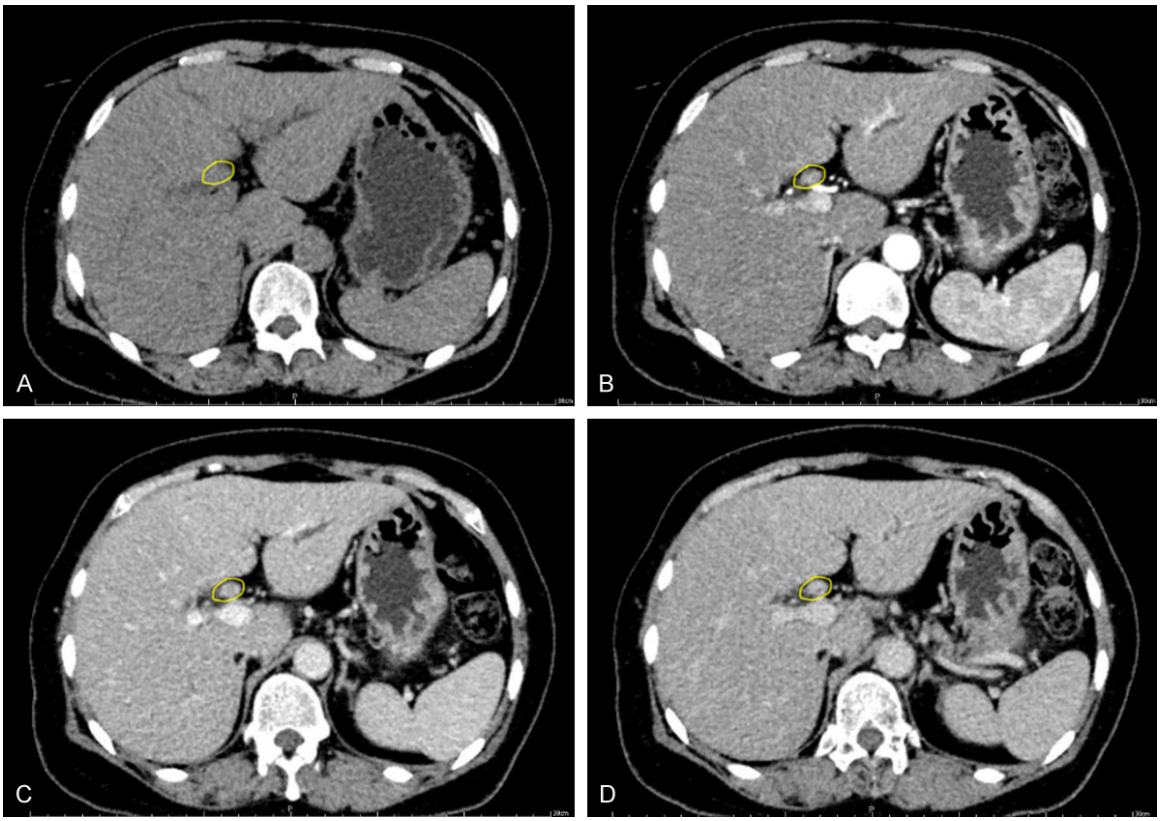

Figure 1. Abdominal CT showed a significantly enhanced soft tissue mass in the common hepatic duct, which caused the dilation of upstream intrahepatic bile ducts. The yellow circles indicated the lesions in plain scan (A), arterial phase (B), portal venous phase (C) and delay phase (D), respectively.

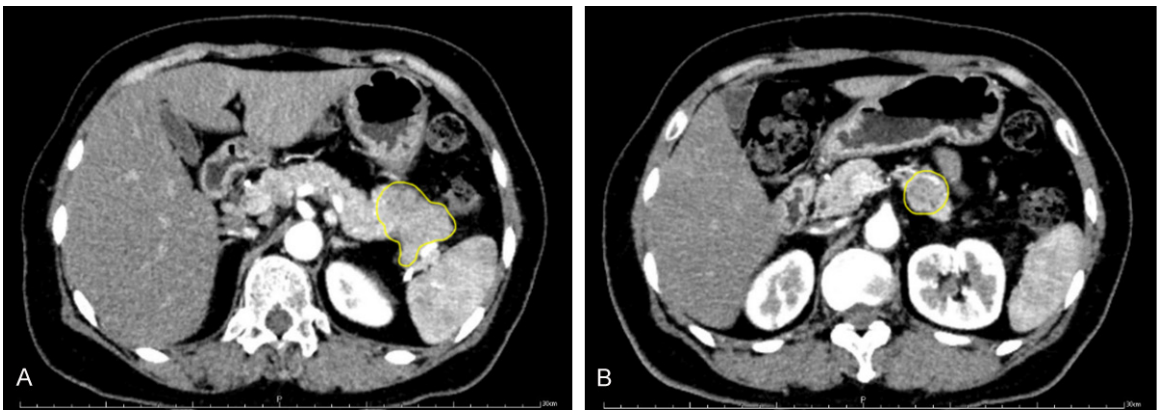

Figure 2. Abdominal CT revealed multiple nodular masses in the body (B) and the tail (A) of the pancreas (arterial phase), as indicated by yellow circles.

reach the diagnostic threshold of ≥20 points. Because of the high suspicion of IgG4-RD, we started her on 32 mg methylprednisolone orally once a day for 2 weeks, and then reduced the dose by 4 mg every 2 weeks until the dose of 12 mg/day. This dosage was further reduced gradually to 4 mg/day for maintenance. The patient showed a swift response to steroids as the 2-week follow-up already exhibited reduced thickening of biliary wall. After six weeks of treatment, her hepatic enzyme levels were normal, T-Bil was decreased to 29.67 umol/L, and

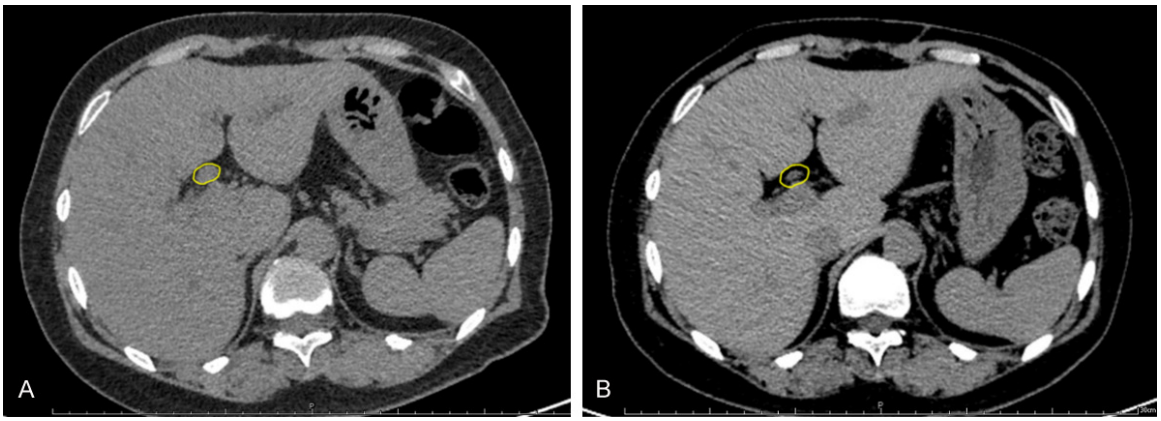

Figure 3. Significant reduction in the size of soft tissue mass (yellow circles) in the hilar, indicating the reduced thickening of the common hepatic duct wall after steroid therapy for 6 weeks. A. Before treatment; B. 6 weeks after therapy.

the serum level of IgG4 was decreased to 11.9 g/L. Additionally, abdominal CT showed a reduction of the soft tissue mass surrounding the hilar and an improvement in the dilatation of intrahepatic bile duct (**Figure 3**), although changes in the pancreatic lesions were not obvious at that time.

She was on 4 mg/day methylprednisolone by the time of 6-month follow-up, and her laboratory tests showed normal biliary enzymes and a significant decrease in CA19-9 level (38.7 U/ml). However, at her 8-month follow-up, she was admitted to the emergency room due to mesenteric hematoma after colonoscopy examination. The imaging results showed that although the thickening of the bile duct wall had been significantly reduced, nodular lesions in the pancreas were still remarkable. In addition, the thickening of the renal pelvic wall was also decreased, but multiple small patchy hypointense lesions appeared in the parenchyma of both kidneys (**Figure 4**). Notably, the serum level of IgG4 rebounded to 12.6 g/L. According to the 2019 ACR/EULAR criteria, this patient now had a total point of 21 (11 points for serum IgG4 level, and 10 points for bilateral renal cortex low-density areas), confirming the diagnosis of IgG4-RD [1]. Given that the patient had developed new renal lesions during low dose steroid maintenance therapy, we increased the dose of methylprednisolone to reinduce remission. The patient is currently under close follow-up.

Discussion

The diagnosis of IgG4-RD is challenging due to its diverse manifestations. A misdiagnosis can lead to steroid treatment for malignancies or unnecessary surgery for an autoimmune disease. Although pathological diagnosis is the gold standard to differentiate IgG4-SC from malignant tumors in most cases, the sensitivity of bile duct biopsy for detecting malignancy was only 55-72%, and the sensitivity for IgG4 staining was only 18-52% in biopsy specimens [2-4]. In addition, we confront many patients who have contraindications to biopsy, such as coagulation dysfunction in our case. Therefore, our current report is significant in that we provide both common and unusual radiologic features of pancreatobiliary manifestations of IgG4-RD to improve the accuracy of the noninvasive diagnosis of IgG4-RD.

The most frequently encountered manifestation of IgG4-RD in the digestive system is type 1 autoimmune pancreatitis (AIP) [5], which is characterized by the diffuse sausage-shaped enlargement of the pancreas with a peripheral rim of hypoattenuation on CT imaging [6]. Delayed enhancement is a specific feature of AIP, which can be used to distinguish AIP from pancreatic cancer [7]. In addition, long narrow strictures (>1/3 the length of the pancreatic duct) and the lack of upstream dilatation from the stricture (<5 mm) are also characteristics of AIP, which can be detected by ERCP [8]. In contrast, pancreatic duct dilatation and abrupt cut-off are more frequently seen in pancreatic adenocarcinoma [9]. Approximately 25-40% of patients demonstrate mass forming lesions, seen as focal enlargement of the pancreas with hypo- or iso-attenuated area, which may be indistinguishable from pancreatic cancer [10].

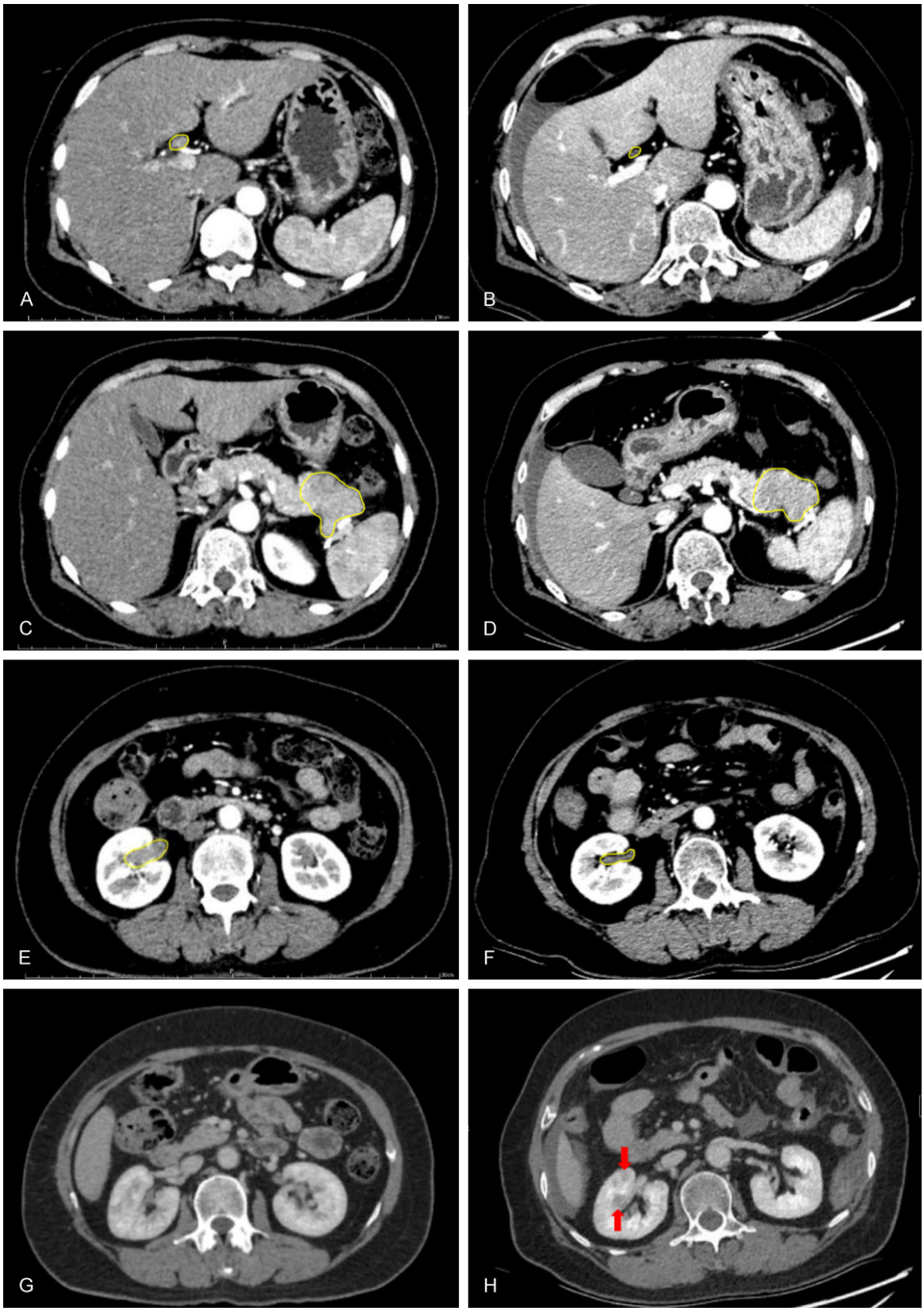

Figure 4. Contrast enhanced abdominal CT at 8-month follow-up after steroid therapy revealed the reduced thickening of the bile duct (yellow circles) (A, B). Nodular masses (yellow circles) in the pancreas were still remarkable (C, D). Reduced thickening of the renal pelvic wall (yellow circles) (E, F). Compared to the CT image before treatment (G), de novo multiple small patchy hypointense lesions (red arrows) appeared in the parenchyma of kidney (H).

Although our patient presented with atypical multiple nodular masses in the body and the tail of the pancreas, which resembled malignancy, the delayed enhancement of the lesion and the absence of pancreatic duct involvement suggested a different disease from pancreatic cancer.

IgG4-SC is usually associated with AIP; hence IgG4-SC has also been known as AIP-associated sclerosing cholangitis (AIP-SC) [11, 12]. The serum levels of CA19-9 and IgG4 are important markers to distinguish AIP and IgG4-SC from pancreatobiliary malignancy. A previous study has reported that the combination of CA19-9 <74 U/ml and IgG4 >1.0 g/l shows a 94% sensitivity and 100% specificity for the diagnosis of AIP [13]. Furthermore, a study from the United States has revealed that using a 4-fold greater than the upper limit of normal cutoff serum IgG4 level is reliable for IgG4-SC diagnosis [14]. However, significantly high levels of CA19-9 are also observed in AIP [13]. Our patient had serum IgG4 level greater than 4-fold of the upper limit of normal, and her CA19-9 level dropped from 555.4 U/ml to 38.7 U/ml after steroid treatment, which support our diagnosis of IgG4-RD.

IgG4-SC is characterized by relatively long strictures which are the results of the massive lymphoplasmacytic infiltration and the fibrosis of the bile duct wall [15]. Accordingly, imaging examination also reveals a circular and symmetrical thickening of the bile duct wall with a smooth inner margin. Intraductal ultrasonography (IDUS) and endoscopic ultrasonography (EUS) are superior to CT or MRI in detecting such lesions and thus are considered as reliable diagnostic tools for IgG4-SC when pathological analysis is not available [11]. Nevertheless, these techniques are only available in a few tertiary centers, which limits their broad application. In our case, the patient presented with mass-forming thickening of the common hepatic duct wall, which led us to suspect cholangiocarcinoma initially. We didn't perform EUS or IDUS on this patient due to the high cost of the procedure, nor the biopsy due to the patient's condition. Fortunately, multiple organ involvement and significantly elevated serum IgG4 level led us to the correct diagnosis of IgG4-SC.

The concept of "biliary diseases with pancreatic counterparts" has been proposed to describe the biliary and pancreatic conditions that appear simultaneously, such as IgG4-SC and type 1 AIP [16]. It is believed that the close embryologic and anatomic relationship as well as the shared cell signaling pathways during development contribute to the similar histopathologic features between biliary and pancreatic diseases [17]. According to this theory, the clinicopathological information from biliary diseases can provide clues for the evaluation of concurrent pancreatic abnormalities, and vice versa. However, epidemiological data have shown that although more than 90% of IgG4-SC is associated with type 1 AIP and 60-80% of type 1 AIP is associated with IgG4-SC [16], the concurrence of biliary and pancreatic neoplastic diseases is extremely rare [18]. Therefore, when biliary and pancreatic lesions occur simultaneously, it is reasonable to consider IgG4-RD as the most like disease.

Notably, IgG4-RD responds well to steroids; therefore, a swift response to steroids could also help confirm the presence of IgG4-RD. Prednisone at a dosage of 0.6 mg/kg/day has been recommended for the initial treatment [19], and most experts agree that this initial dosage should be maintained for 2-4 weeks and tapered gradually thereafter. The goal of induction therapy is to discontinue steroids 3-6 months after treatment [20]; however, 34% AIP patients experience relapse after the discontinuation of steroids [21]. Multiorgan involvement, elevated serum IgG4 and immunoglobulin E (IgE) at baseline, peripheral eosinophilia, and fast tapering or early discontinuation of steroids are considered to be related to the higher risks of IgG4-RD relapsing [19]. Usually, flares respond well to the same dose of glucocorticoids used for the induction of remission [19]. We started our patient on 32 mg methylprednisolone orally once a day, which is equivalent to the dosage recommended by the current guideline. Although our patient responded well to the initial steroid therapy, considering the high serum IgG4 level and the minimal improvement in the pancreatic lesions, we slowed down the subsequent steroid tapering and maintained her on 4 mg of methylprednisolone daily. Nevertheless, at 8 months after treatment, while the lesions on bile duct and renal pelvic were relieved, the pancreatic lesion persisted,

and new lesions appeared on the renal parenchyma. We believed that our patient experienced a relapse and thus re-increased the dosage of methylprednisolone.

In conclusion, though the imaging of the pancreas and bile duct in this patient was atypical and resembled malignancy, IgG4-RD was finally diagnosed when combining with the high levels of IgG4 and multiorgan involvement (pancreas, extrahepatic bile duct, kidney, hilar and mediastinal lymph nodes). Early recognition of IgG4-RD can save patients from harmful and unnecessary surgeries; however, many cases of IgG4-RD don't meet standard classification criteria due to atypical manifestations and unavailable pathological data, such as focal AIP in our case. Therefore, a careful systematic assessment is critical to improve the accuracy of IgG4-RD diagnosis, and a close follow-up is important to detect and compensate the misdiagnosis.

Disclosure of conflict of interest

None.

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