

# A case report of immunoglobulin G4-related sclerosing cholangitis with multiple relapse

Xiaoqin Dong, MD<sup>a</sup>, Na Huo, MD<sup>a</sup>, Zhao Wu, MD<sup>a</sup>, Guiqiang Wang, MD<sup>a</sup>, He Wang, MM<sup>b</sup>, Hong Zhao, MD<sup>a,\*</sup>

## Abstract

**Rationale:** Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is classified as a biliary tract manifestation of immunoglobulin G4-related disease (IgG4-RD). Glucocorticoid is the first-line therapy for most patients, but the optimal starting dose, adequate maintaining dose and withdrawal time remain disputable.

**Patient concerns:** An elderly male patient presented to our hospital with neoplasms of the bile duct and pancreas at first visit in December 2011. Further examination revealed bile duct stenosis and obstruction, and elevated serum IgG4 level.

**Diagnoses:** A diagnosis of IgG4-SC was established by examination results and effectiveness of steroid therapy, although IgG4-positive plasma cells were seldom seen in the liver sample.

**Interventions:** Prednisolone was started from 40 mg daily, tapered gradually, and totally withdrawn after 22 months of treatment.

**Outcomes:** A new-onset cholangitis was detected 2 months later. Prednisolone 10 mg daily was administered again. Prednisolone was reduced to 5 mg every other day without consultation with his doctor 1 year ago in May 2017, then he presented to our hospital again with recurrent abdominal pain and jaundice.

**Lessons:** IgG4-SC is a protean condition and can be distinguished from primary sclerosing cholangitis, malignancy, and other inflammatory disorders based on 4 clinical criteria. Serum IgG4/IgG1 ratio is a practicable diagnostic algorithm to distinguish PSC from IgG4-SC. The dose and duration of glucocorticoid for treatment should be adjusted according to clinical situations, and proper maintaining dose is essential for a better prognosis.

**Abbreviations:** AIP = autoimmune pancreatitis, ALP = alanine aminotransferase, alkaline phosphatase, ALT = alanine aminotransferase, AMA = antimicrobial antibody, AMY = amylase, ANA = antinuclear antibody, ANCA = antineutrophilic cytoplasmic antibody, AST = aspartate aminotransferase, CA19-9 = carbohydrate antigen 19-9, ERCP = endoscopic retrograde cholangiopancreatography, GGT = gamma glutamyl transpeptidase, HPF = high-power field, IgG4 = immunoglobulin G4, IgG4-RD = immunoglobulin G4-related disease, IgG4-SC = immunoglobulin G4-related sclerosing cholangitis, IgM = immunoglobulin M, MRCP = magnetic resonance cholangiopancreatography, PPV = positive predictive value, PSC = primary sclerosing cholangitis, SMA = anti-smooth muscle antibody, TBIL = total bilirubin.

**Keywords:** immunoglobulin G4-related sclerosing cholangitis, immunoglobulin G4-related disease, primary sclerosing cholangitis, relapse

## 1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a newly recognized fibro-inflammatory condition characterized by a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, elevated serum (IgG4) levels, and the involvement of various organs including pancreas, bile duct, salivary glands, kidney, lung, retroperitoneum, and even the

thyroid gland.<sup>[1]</sup> IgG4-related sclerosing cholangitis (IgG4-SC) is a recently described biliary disease of unknown etiology<sup>[2]</sup> that frequently involves the intrahepatic and extrahepatic bile ducts, responds to steroid therapy, and is characterized by elevated serum IgG4 levels, massive infiltration of IgG4-positive plasma cells with storiform fibrosis, and/or obliterative phlebitis in the thickened bile duct wall. IgG4-SC is most common in elderly men, frequently being observed with obstructive jaundice and associated with autoimmune pancreatitis (AIP).<sup>[3,4]</sup> IgG4-SC needs to be differentiated from primary sclerosing cholangitis (PSC), pancreatic cancer, and cholangiocarcinoma on the basis of cholangiographic findings alone.<sup>[2]</sup> Glucocorticoid treatment is the first-line therapy for IgG4-SC; however, the duration of steroid therapy is still controversial.<sup>[1]</sup> This study reported a case of IgG4-SC with multiple relapse and supported persistent and sufficient steroid therapy for IgG4-SC.

## 2. Case report

A 68-year-old man, weighing 65 kg, with intermittent upper abdominal pain and jaundice was admitted to a local hospital in June 2010. Initial laboratory results are shown in Table 1. The amylase level in the urine was 936 U/L. Contrast-enhanced computed tomography of the abdomen showed a significant enlargement of the pancreatic head and dilatation of the proximal

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<sup>a</sup> Department of Infectious Diseases, Center for Liver Disease, <sup>b</sup> Department of Radiology, Peking University First Hospital, Beijing, China.

\* Correspondence: Hong Zhao, Department of Infectious Diseases, Center for Liver Diseases, Peking University First Hospital, No.8 Xishiku Street, Xicheng District, Beijing, 100034 China (e-mails: minmin2001@126.com, zhaohong\_pulh@bjmu.edu.cn).

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**Table 1****Liver biochemical tests of the patient.**

	ALT (IU/L)	AST (IU/L)	GGT (IU/L)	TBIL (umol/L)	Serum AMY (IU/L)	Treatment
June 2010	453		859	78.7		Stent implantation
February 2011	211	135	550	126	35	Stent implantation
December 2011	35	31	114	14.5	53	Stent implantation Prednisolone 40 mg
March 27, 2018	101	55	506	21.5	26	Prednisolone 5 mg
March 31, 2018	55	29	353	13.0		Prednisolone 25 mg

ALT = alanine aminotransferase, AMY = amylase, AST = aspartate aminotransferase, GGT = gamma-glutamyl transferase, TBIL = total bilirubin.

bile duct. Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated obstruction of the distal extrahepatic bile duct, and the stent was implanted simultaneously. The symptoms were relieved, and the liver function returned to normal after stent implantation.

However, the patient experienced recurrence in February 2011. Examinations are shown in Table 1. Ultrasonography of the abdomen demonstrated the swelling of the pancreas and intrahepatic and extrahepatic bile duct dilatation. Stent implantation was again performed considering bile duct stent obstruction, and the patient felt better.

The patient was first shown in our hospital in December 2011 with recurrent abdominal pain. Laboratory examinations are shown in Table 1. Negative serology excluded viral hepatitis, and anti-nuclear antibody (ANA), anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (SMA), and anti-neutrophilic cytoplasmic antibody (ANCA) were all negative. The concentration of carbohydrate antigen 19-9 (CA19-9) was 14.1 U/mL (normal, <39 U/mL). The serum levels of IgG, IgG1, and IgG4 were 10.4 g/L (normal, 7.23–16.85 g/L), 6.54 g/L (normal, 4.90–11.40 g/L), and 3.25 g/L (normal, 0.03–2.00 g/L), respectively. The ratio of IgG4 to IgG was 0.31 and IgG4 to IgG1 was 0.50. Contrast-enhanced magnetic resonance cholangiopancreatography (MRCP) showed swelling of the pancreas, delayed enhancement of pancreas, stricture of the pancreatic and duodenal segments of the common bile duct, intrahepatic bile duct dilation, wall thickening, and enhancement of bile duct (Fig. 1). ERCP revealed obstruction of common bile duct stent and stenosis of the distal common bile duct. Stent implantation was performed again. The liver biopsy sample showed fibrous hyperplasia around the bile duct, disappearance of bile duct epithelium, and sclerosing cholangitis, without filtration of IgG4-positive plasma cells (Fig. 2). The patient was diagnosed with

IgG4-SC with the characteristics of elevated IgG4 level, typical imaging, and involvement of pancreas.

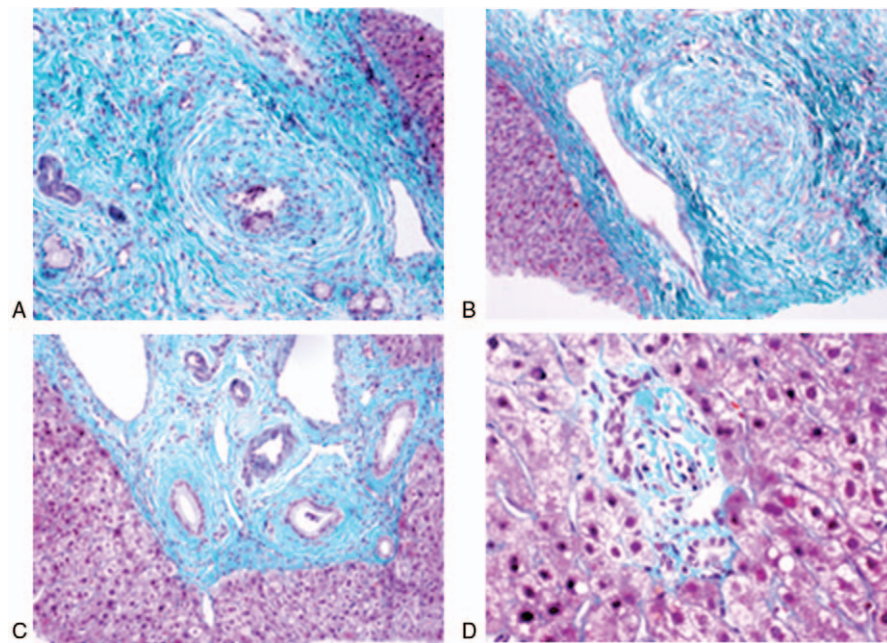
Prednisolone was started from 40 mg daily, tapered gradually, and totally withdrawn in October 2013. Liver biochemical tests and IgG4 level returned to normal, and the MRCP scan showed a significant improvement (Fig. 3) in follow-up examinations.

Two months later in December 2013, MRCP showed abnormal perfusion foci of liver S5, together with atrophic pancreas (Fig. 4). Liver function tests and serum IgG4 level were within normal range. Combining with laboratory examinations and MRCP signs, the patient could be diagnosed as new-onset cholangitis. Prednisolone 10 mg daily was administered again and maintained three years without recurrence and new lesions by regularly checking liver function tests, serum IgG4 level (every 0.5 year) and MRCP (every 1 year). The patient reduced prednisolone to 5 mg every other day without consultation with his doctor in May 2017.

Four years after his initial admission, he presented to our hospital again with recurrent abdominal pain and jaundice in March 27, 2018. The patient was diagnosed with esophageal and gastric cancer 5 months ago, and received the first chemotherapy treatment in March 8, 2018. The laboratory studies revealed unbalanced liver function test (gamma glutamyl transpeptidase [GGT]=506 IU/L, alanine aminotransferase [ALT]=101 IU/L, aspartate transaminase [AST]=55 IU/L, and total bilirubin in serum [TBil]=21.5 umol/L) (Table 1). The serum levels of IgG, IgG1, and IgG4 were 12.7 g/L, 7.17 g/L, and 2.19 g/L, respectively. The ratio of IgG4 to IgG was 0.17 and IgG4 to IgG1 was 0.31. Contrast-enhanced MRCP showed irregular dilation and wall thickening of the intrahepatic bile ducts, enhancement of partial bile duct, and atrophic pancreas without pancreatic duct dilation. Given that the patient was in an immunosuppressive state, prednisolone was added to 25 mg daily.



**Figure 1.** Contrast-enhanced magnetic resonance cholangiopancreatography (MRCP) showed swelling of the pancreas, delayed enhancement of pancreas, stricture of the pancreatic and duodenal segments of the common bile duct, intrahepatic bile duct dilation, wall thickening, and enhancement of bile duct.



**Figure 2.** Liver biopsy sample displayed sclerosing cholangitis and IgG4-positive plasma cells were rarely seen.

A 4-day treatment with prednisolone helped improve his liver function (GGT=353 IU/L, ALT=55 IU/L, AST=29 IU/L and TBIL=13.0  $\mu$ mol/L) (Table 1). The drug dosage will be reduced gradually after 2 weeks and maintained at 10 mg daily at last.

### 3. Discussion

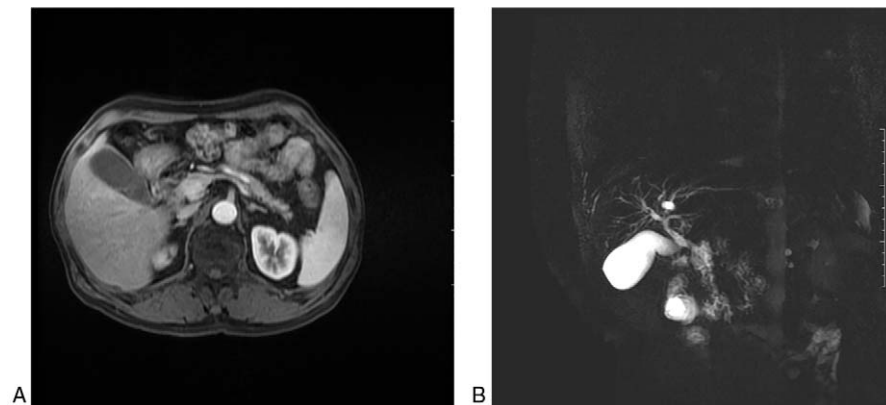
IgG4-SC is most common in elderly men, being observed with obstructive jaundice. Japanese Biliary Association established the clinical diagnostic criteria in 2012, which included 4 criteria to diagnosis IgG4-SC: typical biliary imaging findings, elevated level of serum IgG4 (1.35 g/L or higher), the coexistence of other IgG4-related diseases, and characteristic histopathological features.<sup>[4]</sup>

IgG4-SC is frequently associated with autoimmune pancreatitis, with 80% to 90% of cases accompanied by AIP. It is especially difficult to diagnose IgG4-SC accurately without AIP.<sup>[2,5]</sup> IgG4-related dacryoadenitis/sialadenitis and IgG4-related retroperitoneal fibrosis are also occasionally observed

in IgG4-SC. Our patient was associated with pancreas involvement. However, some IgG4-SC cases do not involve other organs.<sup>[6]</sup>

Elevated level of serum IgG4 (1.35 g/L or higher) is one of the diagnostic criteria for IgG4-SC, which is elevated in about 84% of cases.<sup>[7]</sup> Furthermore, the serum IgG4 cut-off value of 5.4 g/L have been reported to be useful for ruling out almost all PSC, pancreatic cancer, and cholangiocarcinoma (>99%). When setting the cut-off value at 2.7 g/L, it can distinguish IgG4-SC from all cholangiocarcinoma, 98.4% pancreatic cancer, and 96.5% PSC.<sup>[8]</sup> The patient in our report is over 1.35 g/L in both hospitalizations.

Regarding pathological features, infiltration of massive IgG4-positive plasma cells (>10/HPF) is another diagnostic criteria for IgG4-SC, but this criteria is not the necessary one.<sup>[9]</sup> In the present study, our patient implicated extrahepatic bile duct with stent implantation, which might explain the negative result of infiltration with IgG4-positive plasma cells.



**Figure 3.** Magnetic resonance cholangiopancreatography (MRCP) scan showed a significant improvement.



**Figure 4.** Magnetic resonance cholangiopancreatography (MRCP) showed abnormal perfusion of liver S5, together with atrophic pancreas.

There are typical biliary imaging findings in our patient, but discerning IgG4-SC from PSC is challenging on the basis of cholangiographic findings and IgG4 level because various clinical features of IgG4-SC are similar to PSC. Boonstra et al<sup>[10]</sup> pointed out that in patients with serum IgG4 >1.4 and <2.8 g/L, incorporating the serum IgG4/IgG1 ratio with a cutoff at 0.24 in the diagnostic algorithm significantly improved sensitivity and positive predictive value (PPV), by measuring total IgG and IgG subclasses in serum samples of patients with IgG4-SC (n=73) and PSC (n=310), as well as in serum samples of disease controls (primary biliary cirrhosis; n=22). In this subgroup, the serum IgG4/IgG1 ratio cutoff of 0.24 yielded a sensitivity of 80%, a specificity of 74%, a PPV of 55%, and a negative predictive value of 90%. The serum IgG4/IgG1 ratio of our patient was respectively 0.5 and 0.31 in both hospitalizations, supporting the diagnosis of IgG4-SC.

Glucocorticoid treatment as the first-line therapy with an initial dosage of prednisolone 0.6–1.0 mg/kg daily has been shown to exert a marked effect on the inflammatory activity of IgG4-SC.<sup>[11]</sup> However, practice varies as to the duration and initial dosage of steroid therapy. Relapse occurs in 53% of cases after steroid withdrawal. The presence of proximal extrahepatic and intrahepatic bile duct strictures is predictive of relapse.<sup>[6]</sup> Our patient presented with obstructive jaundice at first, relapsed 2 months after steroid withdrawal, and suffered a horrible flare when maintenance dose of glucocorticoid was not enough. Hence, we

hold the opinion that IgG4-SC patients with obstructive jaundice, tending to recrudescence, require an enough initial and maintenance doses, and a long therapeutic course.

In addition, the indicators used to assess the immune state, including the IgG4 level, showed low sensitivity and accuracy. A maintenance therapy with glucocorticoid 2.5 to 5 mg/day for at least 3 years is recommended by the Research Committee for Intractable Pancreatic Disease and Japan Pancreas Society. Here, long-term maintenance therapy with a low-dose steroid (10 mg/d) is recommended because of the lack of accurate indicators reflecting the immune state of patients. At the same time, a longer duration of follow-up is needed to avoid relapse.

In conclusion, the present study reported that our patient did not match all the criteria of IgG4-SC, but steroid therapy were effective. Long-term maintenance therapy with a low and adequate dose steroid should be administered.

### Author contributions

**Data curation:** Xiaoqin Dong, Na Huo, Zhao Wu, He Wang.

**Methodology:** He Wang, Hong Zhao.

**Formal analysis:** Hong Zhao.

**Resources:** Hong Zhao.

**Writing – original draft:** Xiaoqin Dong, Zhao Wu.

**Writing – review & editing:** Xiaoqin Dong, Na Huo, Zhao Wu, Guiqiang Wang, He Wang, Hong Zhao.

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