Clinical Case Report

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# The importance of IgG4 screening in patients diagnosed with primary sclerosing cholangitis in the past

## A case rediagnosed as IgG4-SC after 10 years

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**Abstract**

**Rationale:** While primary sclerosing cholangitis (PSC) has been recognized for decades, immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) has been correctly diagnosed only in recent years. PSC and IgG4-SC show similar clinical symptoms, serologic markers, and imaging results, but the treatment strategies and prognosis of patients differ.

**Patient concerns:** Here, we present the case report of a patient diagnosed with PSC for 10 years and rediagnosed with IgG4-SC recently, to emphasize the importance of screening serum IgG4 levels in patients with previous diagnosis of PSC.

**Diagnoses:** A 57-year-old woman with 10-year history of PSC was hospitalized due to pruritus. In 2004, the patient underwent cholecystectomy and cholangioenterostomy because of unexplained jaundice with pancreatic swelling. In the last 10 years, her liver enzyme levels were continuously elevated. The latest liver function profile showed elevated alanine aminotransferase, aspartate aminotransferase, and total bilirubin. IgG4 was 3.69 (0.03–2.01 g/L). Immunohistochemical staining of the surgical specimen showed >10 IgG4-positive plasma cells per high-power field, and IgG4+/IgG+ plasma cells >40%.

**Interventions and outcomes:** She was treated with prednisone 40 mg once-daily and the dose was gradually tapered. The patient remains well after 18 months.

**Lessons subsections:** Patients with IgG4-SC may be misdiagnosed as PSC due to lack of IgG4 screening. It is important to perform IgG4 screening in patients diagnosed as PSC. Steroid is effective to prevent disease progression in these patients.

**Abbreviations:** ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma-glutamyl transferase, HISORt = histology, imaging, serology, other organ involvement, and response to therapy, IgG4-RD = IgG4-related disease, IgG4-SC = IgG4-related sclerosing cholangitis, MRCP = magnetic resonance cholangiography, PSC = primary sclerosing cholangitis.

**Keywords:** diagnosis differential, IgG4-related sclerosing cholangitis, primary sclerosing cholangitis

### 1. Introduction

Although the American Association guideline for the Study of Liver Diseases for primary sclerosing cholangitis (PSC) suggested screening for serum immunoglobulin G4 (IgG4) in all patients with suspected PSC, the direct clinical evidence is limited.[1] IgG4-related sclerosing cholangitis (IgG4-SC) is characterized by sclerosing cholangitis and its pathogenic mechanism remains unknown. Microscopy shows the infiltration of abundant IgG4-

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*Ethical approval was not necessary as our study was focused on the retrospective observation of a patient's hospital course, which in no way affected his treatment. Informed consent was obtained from the patient regarding the reporting and publication of this case report. Because this article does not involve any human or animal trials, it did not require institutional ethical review and approval.*

*LZ diagnosed and treated the patient. YL performed the literature review and prepared the manuscript. XZ reviewed the images, prepared figure. LZ and NK reviewed and edited the manuscript. BW supervised the treatment of the patient specified in report. All authors approved manuscript to be published.*

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positive plasma cells. PSC and IgG4-SC present similar clinical manifestations and imaging results. However, the treatment strategies and the prognosis of patients differ. There is no effective treatment for PSC, whereas patients with IgG4-SC generally respond well to corticosteroid treatment. Therefore, the differential diagnosis between PSC and IgG4-SC is crucial. The diagnostic criteria of IgG4-SC are now available. It is plausible to predict that some patients with IgG4-SC were misdiagnosed as PSC, thus causing delayed treatment. Herein, we presented the case of a patient diagnosed with PSC for 10 years and rediagnosed with IgG4-SC recently, to emphasize the importance of screening serum IgG4 levels in patients with suspected PSC.

## 2. Case presentation

A 57-year-old woman with a 10-year history of abnormal liver function was hospitalized in July 2015. In 2004, the patient underwent a cholecystectomy due to the presence of gallstones. She developed an unexplained jaundice 3 months after the operation. Magnetic resonance cholangiography (MRCP) showed the dilation of intrahepatic bile duct and space-occupying lesions on head of pancreas. She underwent a cholangioenterostomy due to the jaundice. At that time, the histopathological diagnosis of the surgical specimen suggested PSC (Fig. 1). In the last 10 years, her liver enzyme levels were elevated continuously, with alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) approximately 300 U/L, and the patient did not receive any treatment during these 10 years. Currently, the liver function profile showed alanine aminotransferase (ALT) 244 U/L, aspartate aminotransferase (AST) 141 U/L, ALP 164 U/L, GGT 635.6 U/L, and total bilirubin 39.8 μmol/L. She had a 10-year medical history of hypertension and 7-year history of diabetes. Antibodies against hepatitis B virus and hepatitis C antigen were negative. Liver autoantibodies profiled positive antinuclear antibody (1:100). Indirect immunofluorescence for the presence of other liver autoantibodies was negative, including antismooth muscle antibodies, antimitochondrial antibody, antineutrophil cytoplasmic antibody, liver/kidney microsomal autoantibodies, anti-SLA autoantibodies, anti-sp100 antibody, anti-gp210 antibody, and antimitochondrial antibody—M2. Immunoglobulin levels were normal excluding IgG4 3.69 (0.03–2.01 g/L). Tumor markers including cancer antigen 19-9 and carcinoembryonic antigen were normal. MRCP demonstrated postoperative biliary intestinal anastomosis, anastomotic stenosis, and intrahepatic bile duct dilation (Fig. 2). Immunohistochemical staining of the surgical specimen (common bile duct) from the cholangioenterostomy 10 years earlier showed the infiltrate of CD38 and CD138 positive cells. Importantly, the number of IgG4-positive plasma cells was more than 10 per high-power field with IgG4+/IgG+ plasma cells >40% (Fig. 3). Therefore, according to the HISORt criteria (histology, imaging, serology, other organ involvement, and response to therapy), the patient was rediagnosed with IgG4-SC. She was treated with prednisone 40 mg once daily and ursodeoxycholic acid 250 mg 3 times a day. The dose of prednisone was tapered to 10 mg 1 time a day within 12 weeks and maintenance till now. The liver profile after 2 months of prednisone treatment showed ALT 36 U/L, AST 28 U/L, ALP 90 U/L, GGT 38 U/L, and total bilirubin 10.3 μmol/L. The serum level of IgG4 reduced to 1.1 g/L after 3 months of treatment. The patient performed well and her liver function remained normal during 18-month follow-up.

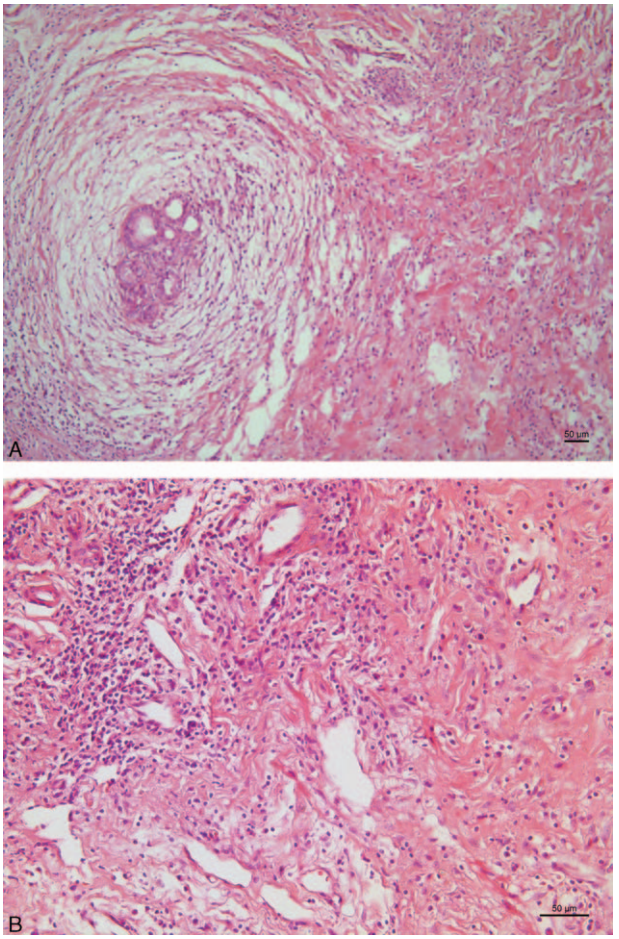


**Figure 1.** Histopathology of biliary biopsy specimen. (A) Periductal concentric fibrosis, loose connective tissue around the small bile duct (magnification ×200). (B) Lymphocytic and plasma cell infiltration (magnification ×200).

## 3. Discussion

PSC is a chronic cholestatic liver and biliary tract disease characterized by fibrosis and strictures involving intra- and extrahepatic bile ducts.[2] PSC may be asymptomatic for a long time but it may also have an aggressive course, leading to recurrent biliary tract obstruction potentially progressing to end-stage liver disease or cholangiocarcinoma (CCA).[3] ACG Clinical Guideline reported that characteristic human leukocyte antigen haplotype associations have long been recognized in PSC.[3] In addition, autoimmunity, mutations in the gene encoding the cystic fibrosis transmembrane receptor and immunologic priming in a genetically predisposed individual also been suggested. To date, liver transplantation as the only treatment is available for patients with PSC. Tanaka demonstrated with respect to complications, inflammatory bowel disease (IBD) was detected in 34% (68/197) PSC patients, CCA was found in 7.3% (14/197) PSC. While neither IBD nor CCA was noted in patients with IgG4-SC.[4]

IgG4-SC is characterized by microscopic findings of sclerosing inflammation with the infiltration of abundant IgG4-positive plasma cells, autoimmune pancreatitis is associated in most cases.[5–7] The biochemical tests and bile duct images are similar between PSC and IgG4-SC, which makes the differential diagnosis of the 2 conditions challenging. In 2010, Koyabu reported 3 cases with PSC that showed elevated serum IgG4 levels

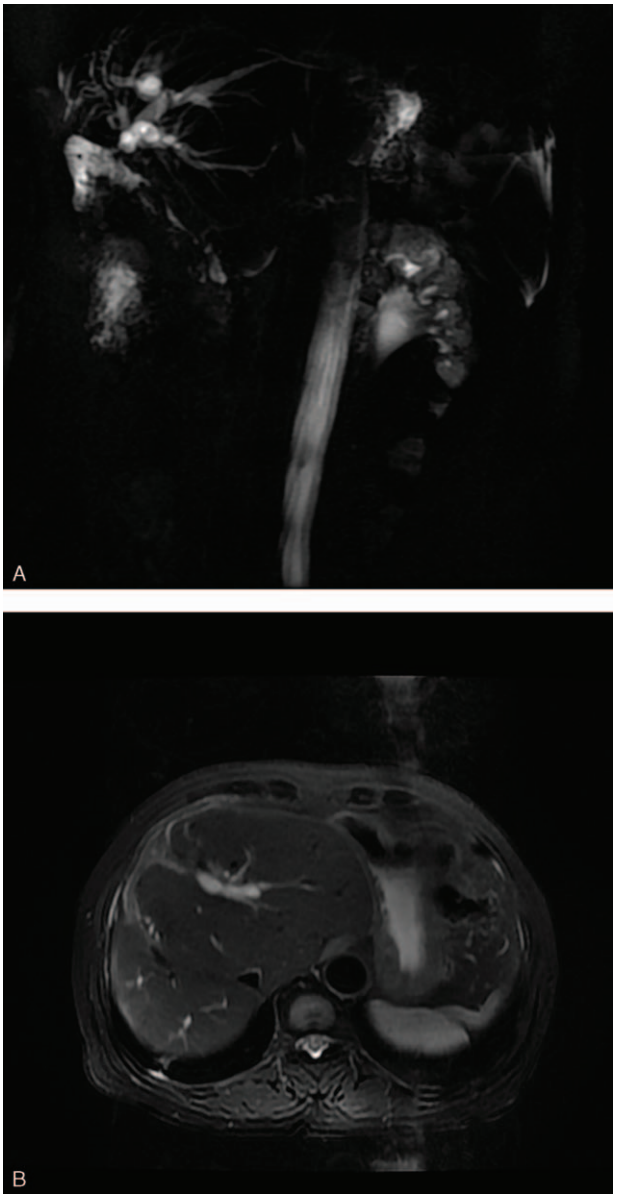


**Figure 2.** (A) Magnetic resonance cholangiography demonstrating dilation of intrahepatic bile ducts. Arrows show anastomotic stenosis. (B) The axial T2-weighted image fat-suppression image shows cholestatic cirrhosis with intrahepatic bile duct dilation, irregular edge of liver, and hypertrophic lateral segment of left lobe of liver.

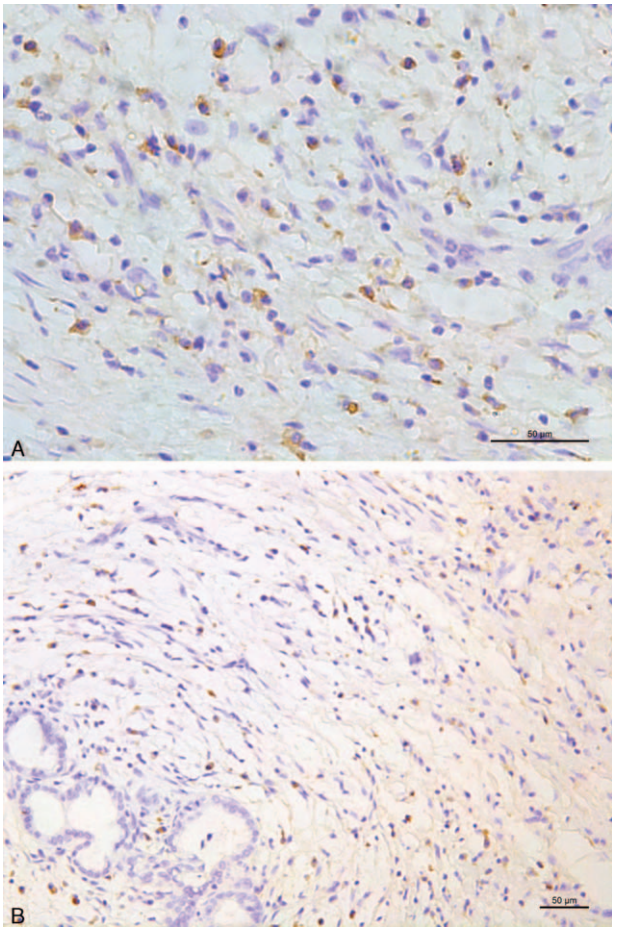


**Figure 3.** (A) IgG4 immunostaining showed abundant IgG4-positive plasma cells (>10/high-power field) (magnification ×400). (B) IgG immunostaining showed abundant IgG-positive plasma cells (magnification ×200).

and/or an infiltration of abundant IgG4-positive plasma cells; they did not fulfill the HISORt criteria because they had no response to steroid therapy.[5] However, the absence of response to steroids is rather rare in IgG4-SC. Therefore, it is very important to distinguish IgG4-SC from PSC for a better prognosis. Recently, Moon et al[8] suggested a new scoring system for differentiating IgG4-SC from PSC. Our study reported a case of a patient diagnosed with PSC for 10 years and rediagnosed with IgG4-SC recently. The findings suggested that it might be worthwhile to screen serum IgG4 levels in all patients diagnosed with PSC.

Table 1 shows the comparison of PSC and IgG4-SC with respect to the clinical manifestations, serology, imaging, and histology.[6,9–12] Patients with PSC often present without symptoms and come to attention by a finding of persistently abnormal liver tests. When symptoms occur, fatigue may be the most commonly noted finding, but it is nonspecific.[3] Approximately 60% to 70% of patients with PSC are men, and age at diagnosis is usually 25 to 45 years.[3] In contrast, patients with IgG4-SC often show chronic progressive obstructive jaundice, and IgG4-SC is rarely reported in patients younger than 45 years.[4] Other symptoms including epigastric discomfort or pain, costovertebral angle tenderness, and fever are often presented in patients with IgG4-SC.[10] A wide range of autoantibodies can be detected in patients with PSC, most are present at low prevalence rates and at relatively low titers.[1] A typical bile duct image of IgG4-SC includes localized or diffuse biliary stenosis, bile duct wall-associated thickening and inflammation, and saccular dilatation of bile ducts, leading to a beaded appearance.[13] Imaging of IgG4-SC can also be associated with inflammatory pseudotumor, which often causes difficulties in distinguishing IgG4-SC from CCA and pancreatic carcinoma.[1] Naitoh et al[14] reported that the sensitivity and specificity of MRCP for identifying IgG4-SC and malignant diseases were more than 90%. To avoid unnecessary surgery, IgG4-related diseases (IgG4-RDs) should be considered when imaging findings of the bile duct demonstrate segmental stenosis or merging with pancreatic lesions.[4,15] Although immunohistochemical analysis is of great significance for diagnosing IgG4-SC, it is difficult to obtain

**Table 1**

**Differences in clinical manifestations, serology, histology, and imaging between PSC and IgG4-SC.**

| | PSC | IgG4-SC |
|---|---|---|
| Pathogenesis | Driven by Th1 | Th2 and regulatory T cells |
| Onset age, y | 25–45 | 50–60 |
| Major symptoms | Fatigue, pruritus | Jaundice |
| With AIP | Generally not | Nearly 90% |
| Other organ involvement | Amyloidosis, IBD | Retroperitoneal fibrosis, salivary gland enlargement |
| Diagnostic criteria | ACG Clinical Guideline[3] | HISORt criteria[20] |
| Cholangiography | Focal stricturing and saccular dilatation of the bile ducts, leading to a beaded appearance | Fleeting/migrating biliary strictures |
| Biopsy | Large- and medium-sized bile duct damage stiffness with concentric periductal onion skin fibrosis | Lymphoplasmacytic infiltrate with >10 IgG4-positive cells/high-power field within and around bile ducts with associated obliterative phlebitis and storiform fibrosis; venous wall inflammation with lymphocytes, plasma cells, and acidophils |
| Prognosis | May progress to end-stage liver disease | Avoid surgery if misdiagnosed as malignant |
| Steroid sensitivity | Rare | Sensitive, but easy to relapse |
| Serum level of IgG4 | Slightly elevated in 9% to 36% of patients | Elevated in 80% of patients |

AIP = autoimmune pancreatitis, IBD = inflammatory bowel disease, HISORt = histology, imaging, serology, other organ involvement, and response to therapy, IgG4-SC = immunoglobulin G4-related sclerosing cholangitis, PSC = primary sclerosing cholangitis.

clinical pathological specimens from bile ducts. Ductular proliferation was conspicuous, and onion skin fibrosis was the typical histological finding of PSC.[5] However, the 4 histological hallmarks of IgG4-SC are lymphocytes/plasma cell infiltration and significant fibrosis, an IgG4-positive lymphoplasmacytic tissue infiltrate (>10 IgG4-positive cells per high-power field), storiform fibrosis, and obliterative phlebitis.[9] Taken together, comprehensive clinical, radiological, and histological examinations are required for differential diagnosis.[16]

It is important to note that the reliability of IgG4 serum levels in diagnosing IgG4-SC and other bile duct diseases has been questioned recently. When a large registry of patients recruited to rigorously defined clinical trials at the Mayo Clinic was evaluated, elevated IgG4 was found in 12 out of 133 patients with PSC (9%).[17] In contrast, serum IgG4 levels can be normal in up to 20% of patients with active IgG4-SC.[9] Therefore, IgG4 cannot be the only biological marker for evaluating the diseases. Recently, Doorenspleet et al proposed that IgG4 + B-cell receptor clones and IgG4/IgG RNA ratio markedly improved delineation, early diagnosis, and differentiation of IgG4-RD from PSC. The new laboratory tests performed better than serum IgG4 levels in sensitivity (94% vs 86%) and specificity (99% vs 73%),[18] but screening serum IgG4 levels is simple and easily available. The effectiveness of corticosteroid therapy is an additional diagnostic method. The estimated 10-year survival for patients with PSC is approximately 65% in a population-based study, but large individual variations exist.[19] A response to steroids can also help in establishing the diagnosis of IgG4-SC. However, the natural history of IgG4-RD and IgG4-SC remains unclear. The patient in the present case study showed a 10-year history of IgG4-SC without corticosteroid therapy. With the establishment of the clinical diagnostic criteria of IgG4-SC in 2012,[20] the necessity of carrying out serum IgG4 screening as part of the examination of patients with PSC is being recognized. However, the information on misdiagnosis rates between PSC and IgG4-SC is still lacking in the literature.

## 4. Conclusion

The present findings suggested that it is worthwhile to screen serum IgG4 levels in all patients diagnosed with PSC. Early diagnosis is crucial to improve the prognosis of patients with IgG4-SC. The measurement of serum IgG4 levels and pathological examinations are not yet the routine examination in primary hospitals. It is important to understand the difference of IgG4-SC and PSC. Except for serum IgG4 screening and effectiveness of steroid treatment, more features could be used for differential diagnosis of IgG4-SC and PSC.

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