Published online: 2019-09-16

Case Report

Difficulties in Diagnosing Isolated IgG4-associated Sclerosing Cholangitis

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Abstract

The most common causes of recurrent cholangitis are biliary stones and neoplasia. Primary types of sclerosing cholangitis such as IgG4-associated sclerosing cholangitis (IgG4-SC) and primary sclerosing cholangitis (PSC) are rare causes of recurrent cholangitis. Differentiating diagnoses for IgG4-SC and PSC is essential because of the significant difference in treatment. We report a challenging case of recurrent cholangitis.

Keywords: *IgG4-associated sclerosing cholangitis, primary sclerosing cholangitis, recurrent cholangitis*

Introduction

Cholangitis is a result of bacterial superinfection of stagnant bile caused by bile flow disturbances. It may recur, causing significant morbidity and mortality if the etiology is not resolved.[1] Primary types of sclerosing cholangitis such as IgG4-associated sclerosing cholangitis (IgG4-SC) and primary sclerosing cholangitis (PSC) are rare causes of recurrent cholangitis.[2,3] IgG4-SC is a distinctive type of cholangitis of unknown origin, which is characterized by increased serum levels of IgG4, massive infiltration of IgG4-positive plasma cells with storiform fibrosis and/or obliterative phlebitis in the bile duct wall, and a good response to steroids. IgG4-SC is considered as a biliary manifestation of IgG4-related disease and it is frequently associated with autoimmune pancreatitis.[3,4]

PSC is an unknown chronic inflammation of the biliary epithelium resulting in multifocal intra- and/or extra-hepatic biliary strictures and fibrosis eventually leading to biliary cirrhosis and malignancy.[3,5]

We report a case of intrahepatic primary recurrent cholangitis and the difficulties of diagnosing it.

Case Report

A 59-year-old man with an unremarkable past medical history presented at our emergency department with upper abdominal pain in April 2015. Laboratory analysis demonstrated the following results: aspartate aminotransferase (AST) 22 U/L (<37); alanine aminotransferase (ALT) 24 U/L (<40); gamma-glutamyl transferase (GGT) 344 U/L (<50), alkaline phosphatase (ALP) 126 U/L (<129), total bilirubin (Bi) 0.6 mg/dl (<1.9), white blood cells (WBCs) 13.6 × 10^9/L (<9.5), C-reactive protein (CRP) 7.2 mg/L (<5), and normal electrolytes and renal function. He underwent abdominal ultrasonography (US) with normal findings. Cholangitis was the indication of endoscopic retrograde cholangiopancreatography (ERCP), which produced a normal cholangiopancreatogram [Figure 1]. An endoscopic sphincterotomy was performed, and debris was removed from the extrahepatic bile ducts. The laboratory parameters improved after the intervention, and the patient became symptom free.

The serum level of liver enzymes increased again in September 2015. The antibody to hepatitis C virus, hepatitis B surface antigen, antinuclear antibody, antimitochondrial antibody, antineutrophil cytoplasmic antibody, antiliver/kidney microsomal antibody, and antismooth muscle antibody were negative. Abdominal computed tomography (CT) was normal. Liver function further deteriorated (AST 186 U/L; ALT 200 U/L;

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Access this article online

Quick Response Code:

Website: www.jdeonline.in

DOI: 10.4103/jde.JDE_39_17

How to cite this article: Zsóri G, Illés D, Tiszlavicz L, Czakó L. Difficulties in diagnosing isolated IgG4-associated sclerosing cholangitis. J Dig Endosc 2019;XX:XX-XX.

GGT 1247 U/L, ALP 404 U/L, Bi 1.7 mg/dl, WBC 13.9 × 10^9/L, CRP 12.5 mg/L) in March 2016. US showed a relatively thick ductus choledochus wall and mild intrahepatic bile duct dilatation [Figure 2]. ERCP found a subtle dilatation of the left hepatic duct with a short stenosis of its subsegmental branch without prestenotic dilatation [Figure 3]. Retrospective analysis of the previous ERCP performed by another doctor discovered subtle changes at the same location. The sampled bile culture revealed *Actinomyces odontolyticus*. Cholangitis was cured with targeted antibiotic therapy.

The patient was admitted to our department again in May 2016 with cholangitis. Abdominal US demonstrated thickening of the common bile duct and gallbladder wall and a 1.5 cm gallbladder polyp. ERCP produced the same cholangiogram as shown in Figure 3. *Enterobacter cloacae* was cultured from bile. The cholangitis was cured with targeted parenteral antibiotic treatment.

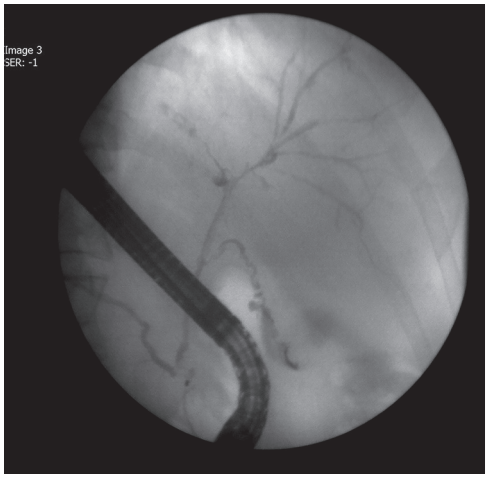

Figure 1: Endoscopic retrograde cholangiopancreatography. A normal cholangiopancreatogram was revealed by the examiner

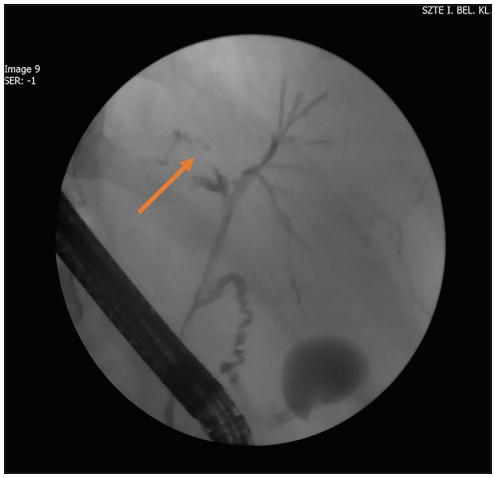

Figure 3: Endoscopic retrograde cholangiopancreatography estimated short stenosis of the subsegmental branch of the left hepatic duct without prestenotic dilatation

Repeated abdominal CT scans demonstrated a thickening of the gallbladder wall, but no mass [Figure 4]. Elective cholecystectomy was performed because of the 1.5 cm polyp in the gallbladder.

The patient was hospitalized again with upper abdominal discomfort and cholestasis in December 2016. Magnetic resonance cholangiography revealed dilatation of two subsegmental branches in the left lobe of liver [Figure 5]. *Achromobacter* was cultured from the bile, and the patient recovered after targeted antibiotic therapy. The patient was rehospitalized in January 2017 with upper abdominal pain and cholestasis (AST 43 U/L; ALT 83 U/L; GGT 599 U/L, ALP 295 U/L, Bi 1.0 mg/dl, WBC 10.2 × 10^9/L, CRP 8.1 mg/L, CA19-9 164.6 U/ml [<27]; CEA 1.61 ng/ml [<4.7]). ERCP demonstrated multiple stenosis and dilatation on one segmental branch of the left hepatic duct [Figure 6]. Tissue sampling was taken with biopsy forceps from the bifurcation of the common hepatic duct [Figure 7]. A histological examination

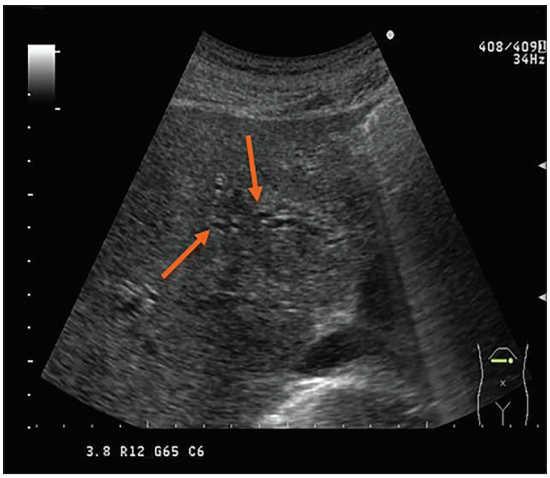

Figure 2: Abdominal ultrasound showed mild intrahepatic bile duct dilatation

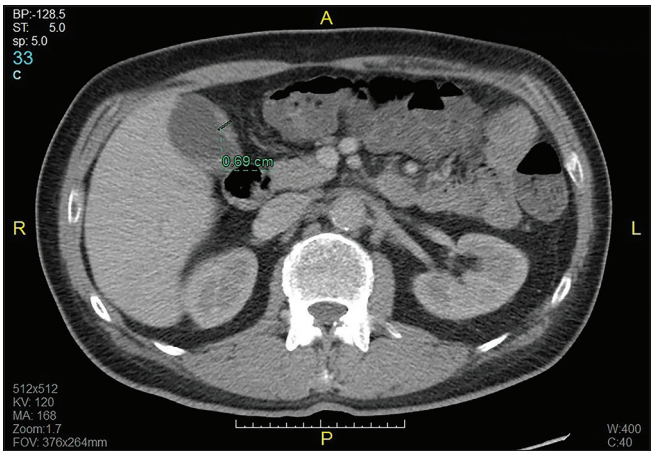

Figure 4: Abdominal computed tomography showed a thickening of the gallbladder wall, but no mass (0.69 cm)

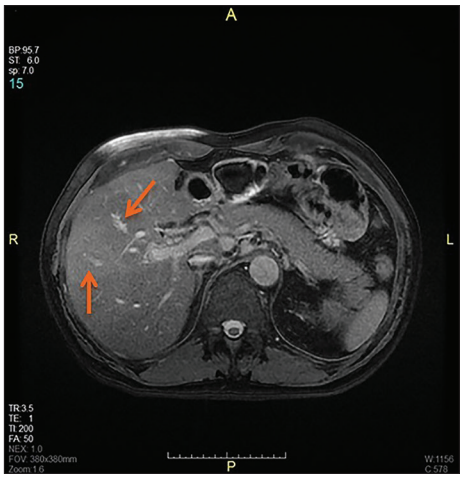

Figure 5: Magnetic resonance cholangiography showed dilatation of two subsegmental branches in the left lobe of liver

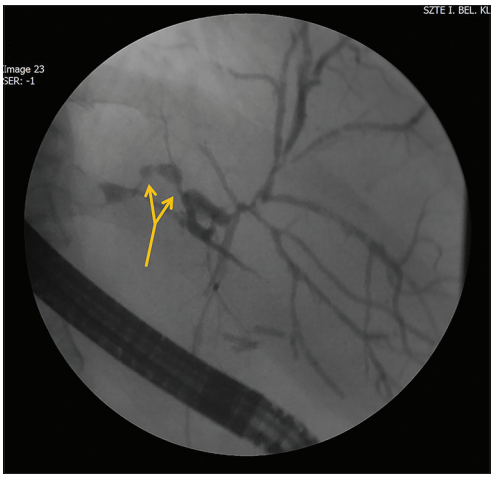

Figure 6: Endoscopic retrograde cholangiopancreatography. Localized strictures and prestenotic dilatations were revealed in the intrahepatic branches of the left lobe

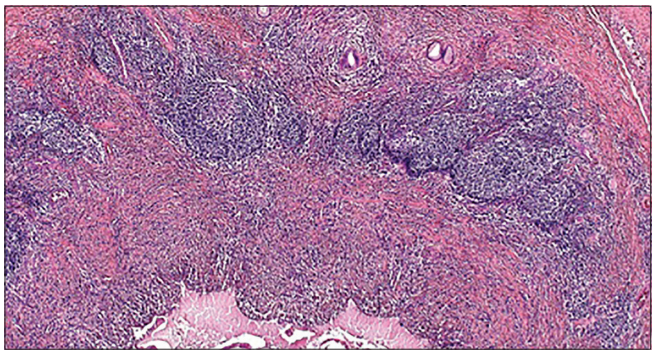

Figure 7: Bile duct biopsy with H and E staining strong lymphoplasmacytic infiltration with lymphoid formation

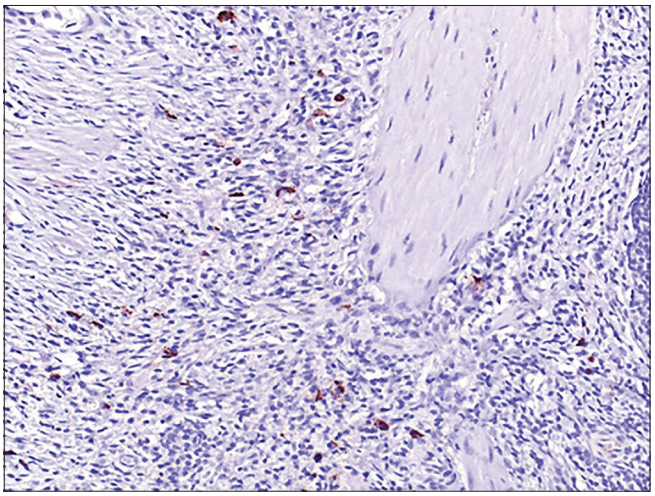

Figure 8: The gallbladder wall with IgG4 immunohistochemical staining IgG4-positive plasma cells are visible in the gallbladder wall

revealed a large number of IgG4-positive plasma cells. The serum IgG4 level was elevated (753 mg/L [<400]). We requested further immunohistochemical analysis of the removed gallbladder, and the results showed a large number of IgG4-positive plasma cells [Figure 8]. A diagnosis of IgG4-related sclerosing cholangitis was finally made. No other organ involvement was found. Methylprednisolone at a dose of 48 mg/day was started. Liver enzymes reduced 6 weeks after the start of steroids (AST 39 U/L; ALT 74 U/L; GGT 359 U/L; ALP 112 U/L; Bi: 0.6 mg/dl; FVS 10.2 × 10^9/L; CRP 8.6 mg/L). Azathioprine was then gradually introduced starting at a dose of 50 mg per day, then 100 mg/day, while steroids were gradually tapered.

Discussion

IgG4-SC needs to be discerned from PSC because they call for different treatments. The diagnosis of IgG4-SC is based on multiple criteria such as (1) characteristic biliary imaging; (2) characteristic serological findings; (3) other organ involvement; (4) histopathological findings; and (5) effectiveness of steroid therapy.[6]

A cholangiogram was not typical in our case. Subtle stenosis was revealed, but only on the branch of the left hepatic duct. This stenosis was visible in Figure 3 but could retrospectively already be seen in Figure 1. Strictures were accompanied by prestenotic dilatation at a later stage [Figure 5]. Circular, symmetrical, and homogeneous thickening of the bile duct wall were demonstrated in our case. This is the most characteristic image of the bile duct and can be seen in the areas without stenosis that appear normal in the cholangiogram or even in the gallbladder.[6] However, isolated intrahepatic localization of IgG4-SC is less frequent.[7]

More than 80% of patients with IgG4-SC show an elevation of serum IgG4 levels.[7] However, elevation of serum IgG4 levels is not specific to IgG4-SC.[7] Moreover, 9%–26% of patients with PSC also have elevated serum IgG4 levels.[8] On the other hand, it is

particularly difficult to diagnose IgG4-SC without other organ involvement as in our case.

Intrahepatic lesions are often unreachable with brushing, and cytological samples are usually not sufficient for immunohistological analysis.[9] In addition, endoscopic transpapillary bile duct biopsy may be recommended.[10] The typical histological findings in the wall of the removed gallbladder facilitated the diagnosis of IgG4 in our case. Moreover, the effectiveness of steroid therapy is a diagnostic criterion but only after excluding the possibility of malignancy.

The isolated IgG4-SC is a rare cause of recurrent cholangitis. The diagnosis could be made with a combination of an increased level of serum IgG4, a large number of IgG4-positive plasma cells with extensive fibrosis in the wall of the bile duct and gallbladder, and a good response to steroid therapy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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