IgG4-related sclerosing cholangitis: not always an obvious entity

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Abstract

Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is a distinct type of cholangitis, currently recognized as a biliary manifestation of IgG4-related disease. We present a case of type 3 IgG4-SC in a patient with normal IgG4 serum levels, surgically treated for suspicion of cholangiocarcinoma. This case highlights that differentiating between isolated IgG4-SC and cholangiocarcinoma can present a challenging diagnostic dilemma.

Keywords IgG4-related sclerosing cholangitis, cholangiocarcinoma

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Introduction

Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is a distinct type of cholangitis, frequently associated with autoimmune pancreatitis (AIP) and currently recognized as a biliary manifestation of a systemic disorder termed IgG4-related disease (IgG4-RD) [1]. The characteristic features of IgG4-RD are enlargement of the affected organ(s) with lymphoplasmacytic infiltrations composed of IgG+ plasma cells, storiform fibrosis, obliterator phlebitis and high serum IgG and IgG4 levels [2]. Here, we report a patient who presented with weight loss and elevated cholestatic enzymes. Two segmental stenoses in both the hilar hepatic duct and the common bile duct (CBD) were demonstrated, and were finally attributed to type 3 IgG4-SC, after being surgically resected on suspicion of cholangiocarcinoma.

Case report

A 70-year-old male with no significant past medical history presented in March 2019 with fatigue and an 8-kg weight loss over the previous 6 months. At admission, he was afebrile without any symptoms or signs of abdominal origin. Laboratory tests revealed normochromic, normocytic anemia (hemoglobin at 12.5 g/dL, normal range [NR] 13.4-17.4), and an elevation of γ-glutamyltransferase (γ-GT) (202 U/L, NR 0-50) and alkaline phosphatase (ALP) (184 U/L, NR 40-150). Magnetic resonance cholangiopancreatography (MRCP) demonstrated choledolithiasis, biliary sludge and a short stricture at the distal end of the CBD with upstream dilation 12 mm in diameter. The biliary tract was otherwise unremarkable. No pancreatic enlargement or narrowing of the main pancreatic duct was observed. An endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy was performed. The presence of the above-mentioned CBD stricture was confirmed but no filling defects were observed. A straight plastic biliary stent (10 Fr, 7 cm) was placed. The brush cytology obtained from the stricture was negative for malignancy.

The patient was admitted 6 months later, having undergone cholecystectomy, in order to undergo repeat ERCP for stent removal. In the meantime, he remained asymptomatic. Besides the known stricture, a hilar hepatic stricture was also demonstrated during the ERCP procedure. Cholangioscopy (SpyGlass™, Boston Scientific, Marlborough, USA) revealed an irregular pattern, mucosal friability and anarchic vascularization (Fig. 1; Video 1) while targeted biopsies from the strictures showed non-specific signs of chronic inflammation. A new MRCP scan confirmed the ERCP findings (Fig. 2). Quantification of serum immunoglobulins showed normal levels of IgG4 (76.9 mg/dL, NR 8-140). Viral serology, cancer antigen 19-9, α-fetoprotein, carcinoembryonic antigen, anti-nuclear antibodies, antineutrophil cytoplasmic antibodies, anti-smooth muscle antibodies, and anti-mitochondrial antibodies were all negative.

In view of the persistent elevated levels of γ-GT and ALP, although the patient had experienced no symptoms, a new ERCP procedure was performed 2 months later. The cholangioscopic features of the strictures remained unchanged.
Multiple targeted biopsies were again obtained and were negative for malignancy. A straight plastic biliary stent (11.5 Fr, 10 cm) was positioned in the CBD. The patient’s serum IgG4 levels were reexamined and remained within normal levels (81 mg/dL, NR 8-140). Based on the absence of elevated serum IgG4 concentrations, along with the non-involvement of other organs related with IgG4-RD, immunohistochemical stain for IgG4 on bile duct biopsies was not requested. In the following 3-month period, the patient was twice readmitted because of episodes of cholangitis and underwent 2 ERCP procedures. Both cholangiographic and cholangioscopic findings as well as histopathology of the lesions remained invariable (Fig. 3; Video 2). A liver biopsy was performed with findings suggestive of non-specific cholestatic hepatitis.

We decided to suggest surgical treatment, given the high clinical suspicion of an underlying neoplasia (patient’s weight loss, worrisome endoscopic appearance of the strictures, negative blood workup, recurrent episodes of cholangitis despite the presence of biliary stents). A hepaticojejunostomy with lymphadenectomy was performed. Histopathology of the surgical specimen demonstrated lesions of IgG4-related SC with significant IgG4 infiltration of the CBD and regional lymph nodes. Cholestatic enzymes gradually normalized and the patient has been followed-up for 6 months without recurrence.

Discussion

IgG4-SC is frequently associated with AIP [3] and this association is useful for the diagnosis of IgG4-SC [4]. However, it is particularly difficult to diagnose IgG4-SC in the absence of AIP [5]. An elevation of serum IgG4 levels (≥140 mg/dL) is seen in 90% of all IgG4-SC cases [6]. For type 3 IgG4-SC in particular, where cholangiographic and/or cholangioscopic findings tend to mimic cholangiocarcinoma, a cutoff of ≥206 mg/dL may be useful for the diagnosis of IgG4-SC [6], since some cholangiocarcinomas exhibit high serum IgG4 levels. An even higher cutoff level of 560 mg/dL provides a more reliable marker for the differential diagnosis of IgG4-SC from malignancy [7]. In our case, serum IgG4 concentrations had been evaluated twice and histopathological examination of biopsy specimens did not reveal histologic findings indicative of IgG4-SC, namely, marked lymphoplasmacytic infiltration, storiform fibrosis and obliterator phlebitis. Immunohistochemical stain for IgG4 was not performed. However, in the absence of the aforementioned characteristic histologic findings, the diagnosis of IgG4-SC is not established based on IgG4 immunostaining alone [8]. A thorough diagnostic investigation of cholangiocarcinoma was conducted, including cholangioscopy-guided biopsies from the strictures. Taking into consideration that bile duct samples obtained with SpyGlass™ forceps (SpyBite™, Boston Scientific, Marlborough, USA) are often small, repeated biopsies were taken even though the reported sensitivity of cholangioscopy-guided biopsies for malignant lesions is quite satisfactory (85%) [9].

As an afterthought in this case, despite the fact that the diagnosis of IgG4-SC was not even possible according to the clinical diagnostic criteria for IgG4-SC [8], we could have evaluated the effectiveness of a steroid trial. Treatment with corticosteroids is effective in most IgG4-SC cases [8], although some malignant lesions may improve after steroid
administration [10]. For the time being, our patient is being followed-up with laboratory evaluation every 6-8 weeks. In case of symptoms and/or signs of disease activity (abdominal pain, obstructive jaundice, elevated serum hepatobiliary enzyme levels, new biliary strictures), steroid therapy will be initiated.

In conclusion, this case shows that IgG4-SC should always be considered as part of the differential diagnosis in patients presenting with unclassified intrahepatic and/or extrahepatic biliary strictures, even in the absence of elevated serum IgG4 levels when a thorough work up for malignancy is negative. Our case report highlights the fact that distinguishing IgG4-SC from cholangiocarcinoma may occasionally be remarkably difficult on a clinical basis.

**Video 1** Cholangioscopy demonstrated the presence of 2 segmental strictures at the hilar hepatic and common bile duct with irregular pattern, friability and anarchic vasculatization
You can see https://www.youtube.com/watch?v=X3c_KO8_xx8

**Video 2** Cholangioscopy performed 5 months after the initial one indicated that the features of the strictures remained unchanged
You can see https://www.youtube.com/watch?v=BTCHiF2C5Vw

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