IgG4-associated Cholangitis Mimicking Cholangiocarcinoma – Report of A Case

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Abstract

Immunoglobulin G4 (IgG4)-associated cholangitis is a novel clinicopathological disease entity. It was formerly recognized as one of extrapancreatic diseases of autoimmune pancreatitis. Now, it is redesignated as one of the IgG4- associated sclerosing diseases, which are characterized by high serum IgG4 concentrations and extensive infiltration of IgG4-positive plasma cells into the involved organs. We described a case of obstructive jaundice had a clinical presentation resembling cholangiocarcinoma proved to be IgG4-associated cholangitis after surgery. (J Intern Med Taiwan 2013; 24: 137-141)

Key Words: Autoimmune pancreatitis; Cholangiocarcinoma; Immunoglobulin G4-associated cholangitis

Introduction

Autoimmune pancreatitis (AIP) was firstly described in Japan in 1995 by Yoshida et al.[1]. But it was not recognized as a worldwide disease entity until 10 years later[2-4]. Sclerosing cholangitis with intra and extrahepatic biliary stricture is a common combination in AIP, and it was classified as one of the extrapancreatic diseases of AIP formerly[5-7]. However, many cases of sclerosing cholangitis associated with immunoglobulin G4 (IgG4) had been presented with isolated biliary tract involvement in the absence of pancreatic disease[8,9]. With several emerging evidences, Bjornsson et al. have suggested that the biliary change of AIP might be a distinct disease entitiy and should be redesignated as IgG4-associated cholangitis (IAC)[10]. We presented a patient with IAC mimicking cholangiocarcinoma. The diagnosis and treatment were discussed also.

Case Report

This is a 58 years old male patient. He had cholecystectomy for gallbladder stones with acute cholecystitis 10 years ago. He had no diabetes mellitus or hypertension. He complained of epigastric fullness and anorexia for a week. Tea-colored urine occurred 3 days before he visited our emergency service department. He had no fever during this period of time. He had no generalized pruritus. Physical examinations revealed icteric sclera. The abdomen was soft and flat and with no tenderness. The laboratory tests showed

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normal white blood cell count, 4290 /ul, elevated serum bilirubin, total 8.2 mg/dl (0.4 – 1.4), direct 3.1 mg/dl (< 0.4), high alanine aminotransferase (ALT) 308 U/L (3 – 30) and high aspartate aminotransferase (AST) 194 U/L (10 – 35). Under the tentative diagnosis of obstructive jaundice, he was admitted. He underwent abdominal ultrasonography and dilatation of bilateral intrahepatic bile ducts was noted. Recurrent choledocholithiasis with obstruction was suspected, so endoscopic retrograde cholangio- pancreatography (ERCP) was performed. A short segment of stenosis in common hepatic duct with marked poststenotic dilatation was revealed [Fig. 1]. Cholangiocarcinoma was highly suspected and internal drainage was done by endoscopic retrograde biliary drainage (ERBD). Then, he underwent abdominal computed tomography (CT), which showed bilateral intrahepatic bile duct dilatation and a normal pancreas but no definite extrahepatic bile duct lesion. The tumor markers were checked after ERBD and showed CEA 3.95 ng/ml (< 3.4) and CA-199 384 U/ml (0 – 33). The serum total bilirubin was declined to 3.6 mg/dl 3 days after ERBD. Under the provisional diagnosis of cholangiocarcinoma, surgical exploration was done. Intraoperatively, thickening of bile duct near the hilum was noted. The extrahepatic bile duct was excised and a Roux-en-Y hepaticojejunostomy and lymph node dissection were performed. A yellowish tense tumor with ulceration was noted in the bile duct after explored the excised specimen [Fig. 2]. However, the pathological examination revealed no malignancy but a fibroinflammatory lesion composed of numerous lymphocytes, plasma cells and eosinophils infiltrated in a background of sclerosing fibrosis [Fig. 3]. The IgG4-positive plasma cells account for 80 – 100 per high-power field and IgG4/IgG ratio is about 70 percent. And the lymph nodes taken from the surgery showed focal IgG4-positive plasma cells and plasmatoid cells infiltrated in the germinal center and interfollicular region. These features are compatible with IAC. The surgical course was uneventful, but he was complicated with obstructive pneumonitis after surgery. After endotracheal tube intubation with mechanical ventilator support and antibiotic treatment, he recovered. The laboratory tests later

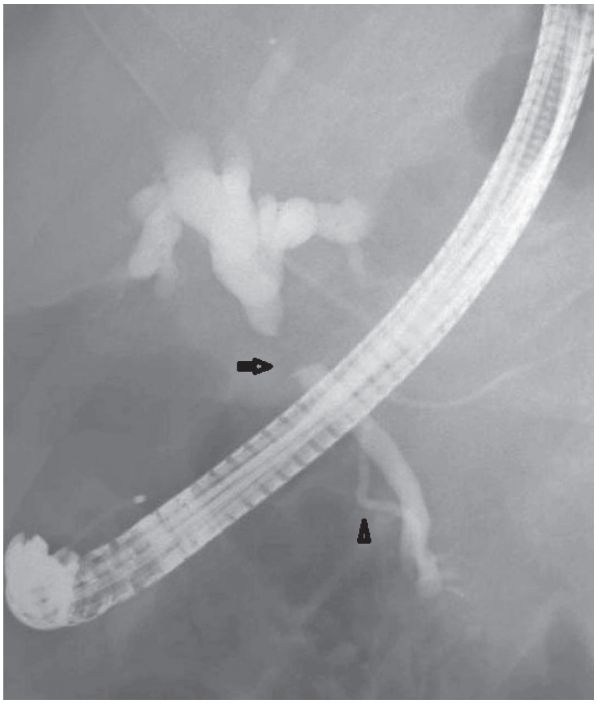

Figure 1. The cholangiogram showed a short segment of stenosis in hilum and poststentic dilatation of intrahepatic ducts (arrow). The main pancreatic duct was normal (arrow head).

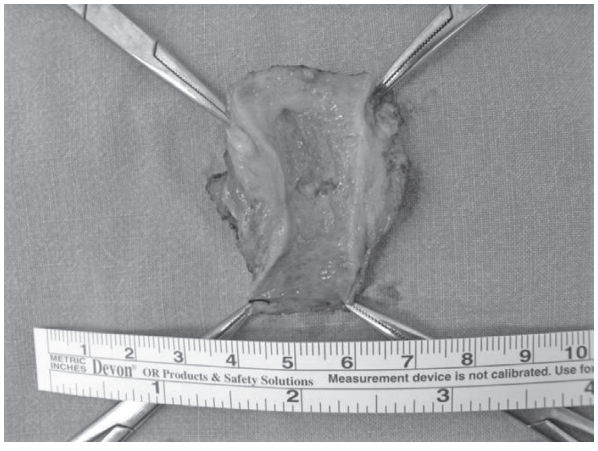

Figure 2. The excised specimen showed a yellowish tense tumor with ulceration in it.

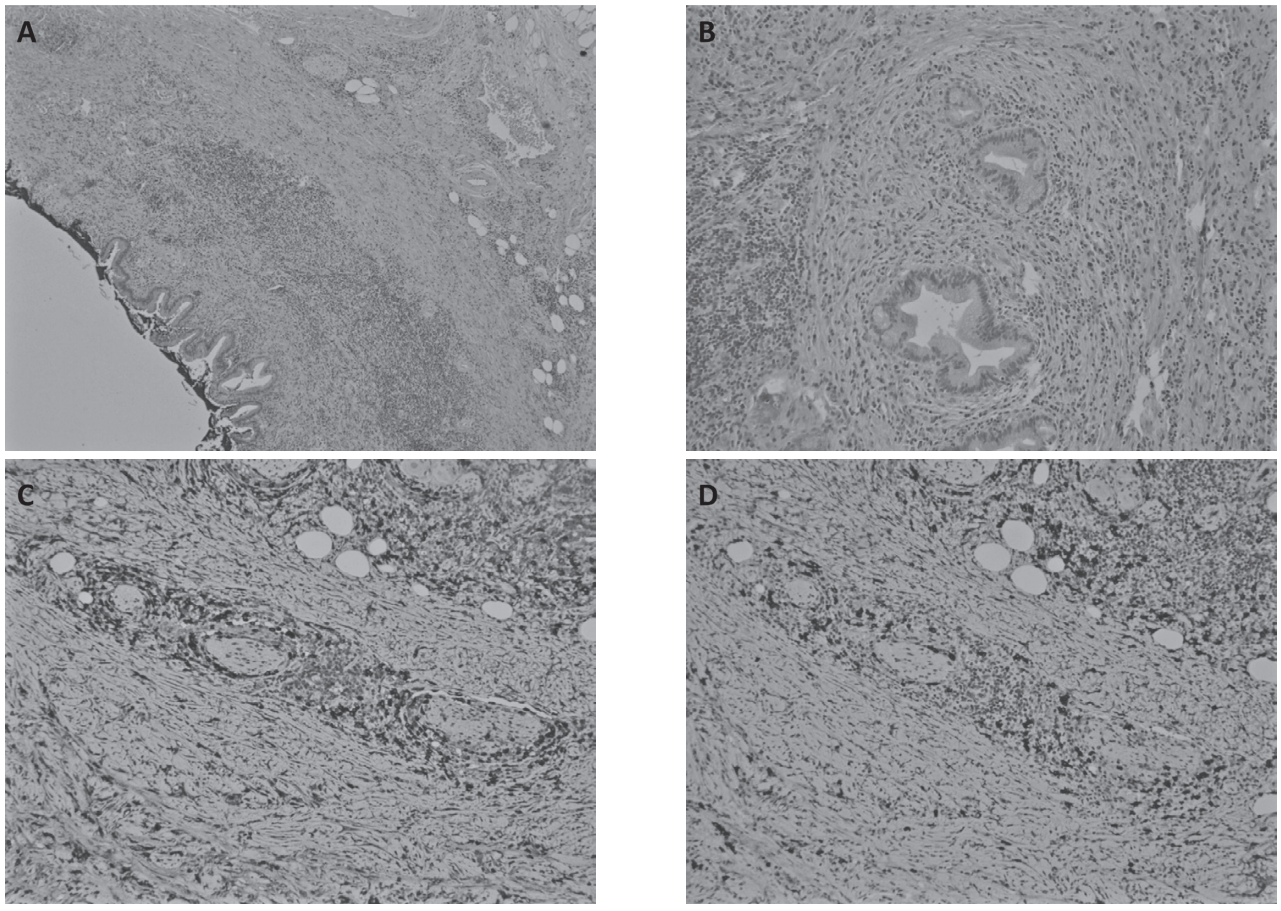

Figure 3. (A) The pathology of the resected bile duct revealed a dense transmural lymphoplasmacytic infiltration and fibrosis (H&E stain, 100X), (B) The higher power view showed typical sclerosing fibrosis pattern, dense fibroblast and inflammatory cells surrounded the glands (H&E stain, 200X), (C) With immunohistochemical staining for IgG showed diffuse IgG positive cells. (D) With immunohistochemical staining for IgG4, the IgG4-positive plasma cells account for 80 – 100 per high-power field and IgG4/IgG ratio is about 70 percent.

showed nearly normal liver functions with AST 17 U/L, ALT 24 U/L, total bilirubin 1.2 mg/dl and mild elevated alkaline phosphatase 329 U/L (65 – 272). The serum IgG and IgG4 were checked after surgery and both were within the normal limits, IgG was 665 mg/dL (650~1600) and IgG4 was 87.5 mg/dL (3~200). He was discharged with full recovery 12 days after surgery.

Discussion

The IAC is one of the IgG4 associated sclerosing disease. In fact, the IgG4 associated sclerosing disease had been reported to involve many organs, causing IgG4 associated sclerosing pancreatitis, cholangitis, retroperitoneal fibrosis, sialadenitis, lymphadenopathy, thyroiditis, nephritis, pneumonia, prostatitis, and some inflammatory pseudotumors[11]. Overlapping of these IgG4 associated sclerosing diseases is common. They are characterized by an elevated serum IgG4, extensive IgG4-positive plasma cells and T-lymphocyte infiltration in the involved organs and well responded to steroid therapy. The pathogenesis of IgG4-associated sclerosing disease remains undetermined.

Diagnosis of IAC requires a high index of suspicion. The differential diagnoses include primary sclerosing cholangitis (PSC), cholangiocarcinoma, pancreatic cancer and benign traumatic

biliary stricture. The cholangiographic appearance of IAC is not specific. The stricture of bile duct in IAC might be in lower end of common bile duct when combined with AIP. Some were multiple and may be in the intrahepatic or the hilar hepatic bile duct and very similar to that of PSC[12-14]. When the stricture is solitary and had no other combined pancreatic disease, it will be difficult to differentiate from carcinoma. Our case had a solitary stricture in hilar hepatic duct and normal pancreas which led to misdiagnosis of cholangiocarcinoma preoperatively. The elevated serum IgG4 is a hallmark of IAC, but it is not diagnostic for the disease. Not all IAC cases have high serum IgG4[12,15]. On the contrary, some cases of PSC and other diseases might have high serum IgG4. It is difficult to differentiate cholangiocarcinoma from IAC by present imaging studies[16]. Use of IgG4 immunostaining on cytology specimens is not recommended because the density of IgG4-positive cells in the tissue cannot be determined from these specimens. Mild tissue IgG4 immunostaining can occur in other diseases[17]. Therefore, endoscopic brush cytology could not help to make a diagnosis of IAC, but a malignant result of cytology could exclude IAC. It was our mistake, not performing brush cytology during ERCP. Preoperative diagnosis is sometimes difficult, especially when serum IgG4 is not high. Histological examination of the surgical specimen is needed to make a final diagnosis in some rare cases like our patient.

The optimal steroid treatment regimen of IAC is not defined. Most patients respond initially to steroids but relapse is not uncommon[17]. In patients with IAC, careful observation for relapse of cholangitis or other possible IgG4 associated sclerosing diseases is mandatory both during and after withdrawal of the steroid therapy. Though surgery is not indicated in patients with IAC, surgery had been performed in a great proportion of patients for the difficulty in making a precise diagnosis preoperatively before[17].

Because of the steroid-responsive nature, it is important to differentiate IAC from primary or other secondary sclerosing cholangitis. Nonetheless, use of steroid treatment must be very cautious to avoid the risks imposed by delaying the diagnosis and treatment of a malignant biliary stricture.

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酷似膽管癌的免疫球蛋白G4相關性膽管炎：一病例報告

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摘 要

免疫球蛋白G4相關性膽管炎(IgG4-associated cholangitis)在臨床病理上是一個新興的疾病。先前認爲它是屬於自體免疫性胰臟炎(autoimmune pancreatitis)的胰臟外合併症之一。目前則將它重新歸類爲免疫球蛋白G4相關性硬化疾病(IgG4-associated sclerosing disease)之一。這類疾病的特點是血清中有高濃度的免疫球蛋白G4與被侵犯的器官中有廣泛的帶免疫球蛋白G4之漿細胞的浸潤。我們報告一個臨床上酷似膽管癌的阻塞性黃疸患者，於手術後證實爲免疫球蛋白G4相關性膽管炎的病例。