A Case of Sclerosing Cholangitis without Pancreatic Involvement Thought to be Associated with Autoimmunity

Hiroaki Sawai¹, Hiroyuki Matsubayashi¹, Keiko Sasaki², Masaki Tanaka¹, Naomi Kakushima¹, Kohei Takizawa¹, Yuichiro Yamaguchi¹ and Hiroyuki Ono¹

Abstract

Sclerosing cholangitis (SC) is one of the lesions frequently seen in IgG4-related systemic diseases, causing biliary stricture and mimicking bile duct carcinoma and primary sclerosing cholangitis (PSC). Although it often accompanies autoimmune pancreatitis (AIP), autoimmune-related SC without a pancreatic lesion is very rare. A 79-year-old woman was referred to our institution with suspected diagnosis of bile duct carcinoma in the previous hospital. The patient was not icteric and fever free, but with an elevated level of serum biliary enzyme, which lead us to detect this disease. Clinical images including computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP) and intraductal ultrasonography (IDUS) demonstrated multiple strictures at the intrahepatic bile duct and enhanced wall thickness at the upper common bile duct, however her pancreas was normal. Repeated endoscopic procedures with multiple biopsies from the biliary strictures demonstrated fibrous ductal tissues with lymph-plasma cell infiltration (>10 IgG4(+) cells/HPF). By positron emission tomography using ¹⁸F-fluorodeoxyglucose (FDG-PET), the uptake of FDG was not remarkable in areas other than the biliary lesions. Additional laboratory tests showed elevated levels of serum IgG (2,571 mg/dL), and γ-globulin (29%), and positive autoantibodies, but normal IgG4 (53.2 mg/dL). Together with clinical images, laboratory and histological findings, we diagnosed this patient as sclerosing cholangitis which was thought to be associated with autoimmunity. After one year of follow-up without steroid therapy, idiopathic thrombocytopenic purpura (ITP) developed with an increased level of serological markers. We encountered a rare case of sclerosing cholangitis expected to be associated with autoimmunity, which showed biliary strictures mimicking bile duct carcinoma and needed careful diagnosis. Unlike the typical AIP, the current case demonstrated distinct serological findings and no other organ involvement. Further study is needed to clarify the characteristics of sclerosing cholangitis associated with autoimmunity with a large number of cases.

Key words: autoimmune cholangitis, sclerosing cholangitis, biliary carcinoma, IgG4, IgG, autoantibody

(DOI: 10.2169/internalmedicine.50.4471)

Introduction

Autoimmune- or IgG4-related sclerosing cholangitis (SC) is the most frequently recognized extrapancreatic lesion (74-84%) in cases with autoimmune pancreatitis (AIP) (1, 2). This type of SC is often diagnosed simultaneously with AIP or sometimes in the period following AIP (3). Recently, the chances of a misdiagnosis became rare as clinicians are acutely aware of this concept. Unique characteristics of AIP, such as age and gender deviations, pancreatic image, serum data and other organ involvement, are all known diagnostic clues of this disease (4). However, when without pancreatic involvement, the differential diagnosis needs caution, especially for the exclusion of biliary carcinoma.

¹Division of Endoscopy, Shizuoka Cancer Center, Japan and ²Division of Pathology, Shizuoka Cancer Center, Japan
Received for publication September 2, 2010; Accepted for publication November 12, 2010
Correspondence to Dr. Hiroyuki Matsubayashi, h.matsubayashi@scchr.jp
A 79-year-old woman was referred to our institution for further examination of the biliary stricture, suspected as bile duct carcinoma in the previous hospital. She did not drink or smoke and her physical findings were not remarkable. Her disease history was not remarkable, but her father had a history of rheumatoid arthritis. The initial chance to detect this disease was abnormal laboratory data showing elevated levels of hepatobiliary enzymes and a tumor maker, i.e., AST 52 IU/L (normal: 10-40 IU/L), ALT 65 IU/L (5-40 IU/L), ALP 2,158 IU/L (115-359 IU/L), g-GTP 839 IU/L (10-40 IU/L), and CA19-9 49 IU/mL (<40 IU/mL). Serum bilirubin (0.6 mg/dL) was within the normal range (0.2-1.0 mg/dL). Enhanced computed tomography (CT) demonstrated dilatations of the intrahepatic bile ducts (Fig. 1A) and a mass-like, circular wall thickness at the upper common bile duct (Fig. 1B). These lesions were enhanced in the late phase. In spite of such a wall thickness, the biliary lumen was still open, suggesting soft tissue proliferation rather than tight stricture due to cancer invasion. Hepatic hilar lymph nodes were swollen (1.5 cm in diameter), but the pancreas was normal. By positron emission tomography with $^{18}$F-fluorodeoxyglucose (FDG-PET), strong uptake of FDG was recognized at the intrahepatic and hilar bile ducts (SU-Vmax.: 7.24) but otherwise not remarkable. The finding of colonoscopy was normal and did not suggest existence of inflammatory bowel disease. Endoscopic retrograde cholangiography (ERC) revealed a narrowing of the upper common bile duct, 25 mm in length (Fig. 2A), and diffuse dilatation of the intrahepatic bile ducts. Multiple segmental strictures were also recognized in the intrahepatic bile ducts, at proximal sites of B5 and B8 (Fig. 2B). Meanwhile, endoscopic retrograde pancreatography (ERP) showed a normal pancreatogram (Fig. 2C). Papilla of the Vater was macroscopically normal and abnormal arrangement of pancreobiliary duct was not recognized. Transpapillary intraductal ultrasonography (IDUS) revealed homogeneously low-echoic, circular-symmetric, smooth wall thickness at the upper common bile duct (Fig. 3). Cytology of the aspirated bile and brushing sample from the narrowing bile duct did not demonstrate malignancy. Forceps biopsy was performed from seven sites including strictures and dilated ducts and histology of these samples showed lymph-plasma cells’ infiltration with abundant fibrosis (Fig. 4A). On IgG4 immunostaining, tissues from the biliary stricture (Fig. 4B), but not from the papilla demonstrated >10 IgG4 positive plasma cells in the high-power field (HPF)(5 cells/HPF at papilla). To confirm these results, ERCP, forceps biopsy and bile cytology using nasobiliary drainage were repeated on the following day, and all showed negative results for malignancy. On additional laboratory tests, serum levels of IgG and γ-globulin were elevated to 2,571 mg/dL (870-1,700 mg/dL) and 29% (10.6-20.5%), respectively. Serum level of IgG4 (53.2 mg/dL) was within normal range (4.8-105 mg/dL), but IgG1 was extremely high (1,440 mg/dL, normal: 320-748 mg/dL). Serum antinuclear antibody (ANA) and anti-DNA antibody were strongly positive at $\times1,280$ and $\times320$ dilution, respectively, but other autoantibodies, such as rheumatoid arthritis particle agglutination (RAPA), antimitochondrial antibody (AMA), Sjögren syndrome-A (SS-A) antibody, Sjögren syndrome-B (SS-B) antibody, proteinase-3 (PR-3) anti-neutrophil cytoplasmic autoantibody (C-ANCA) and myeloperoxidase (MPO) ANCA (P-ANCA) were negative. Referring to the Japanese criteria of AIP (2006) (4), we diagnosed as autoimmune cholangitis (AIC) according to the following conditions, 1) smooth, circular-symmetric wall thickness of the bile duct detected by clinical images, 2) positive for serum autoantibody, 3) pathology with >10 IgG4(+) plasma cells’ infiltration in the high-power field, and 4) negative for biliary malignancies by repeated multiple biopsies.

The patient refused steroid therapy and was closely followed up with intake of ursodeoxycholic acid as an outpatient. Every three months, she underwent blood tests and image examinations such abdominal US, MRI and trunk CT, however image findings were stable. One year after the in-
Initial diagnosis, suddenly her platelet number dropped to 94,000, in contrast to the increasing level of serum IgG (3,249 mg/dL) and IgG1 (1,970 mg/dL). A diagnosis of idiopathic thrombocytopenic purpura (ITP) was made with positive serum platelet-associated IgG (PAIgG)(230 ng/10^7 cells, normal: <46 ng/10^7 cells) and negative work-up for blood malignancies by bone marrow aspiration. At present, the platelet number is smoldering around 100,000 without steroid therapy during the two months since the diagnosis of ITP.

**Discussion**

For bile duct strictures, a variety of diseases come up as candidates for the differential diagnosis, both benign and malignant. Benign candidates include PSC, IgG4-SC, scar caused by physical contact of bile duct stone, previous biliary surgery, injury, ischemic bile duct damage, change by intra-arterial chemotherapy, immune deficiency, etc. (5, 6). Malignancy includes bile duct carcinoma, invasion of carcinoma from the pancreas and gallbladder, and others. Accurate diagnosis can be made by referring to the patient’s history, laboratory data and clinical images in most of the cases. However, in the current case, several diseases were still suspected based on only the clinical information, such as IgG4-SC, PSC and bile duct carcinoma. Actually, to date, 20 cases of IgG4-related SC have been reported, and almost all cases were misdiagnosed as bile duct carcinoma and surgically resected (7-13). Literature information on the characteristics of these diseases is summarized in Table 1. The
clinical findings of the present case, including age, type of serum marker, location and appearance of biliary stricture and disease history without inflammatory bowel disease, were uncommon for PSC. In contrast, clinical images of biliary stricture showing smooth, circular-symmetric wall thickness, high titer of serum IgG and autoantibodies, and IgG4(+) plasma cell infiltration were all compatible with autoimmune-associated SC. Current IDUS findings showing circular-symmetric wall thickness, with inner and outer smooth margins were typical for IgG4-SC (14). Steroid trial was thought as another diagnostic method, which was recently applied for atypical cases of AIP after negative work up for malignancy (15), but it was not undertaken due to the patients’ refusal and non-symptomatic physical condition. The most important step in the differential diagnosis was to exclude biliary malignancies. The sensitivity of biopsy for bile duct carcinoma is reported to have a wide range 54-100% (14, 16, 17), but it increased up to 100% by obtaining multiple biopsy from the stenotic site (17). To thoroughly exclude the possibility of biliary cancer, we examined repeated endoscopic procedures with multiple biopsies from the strictures and repeated cytologies. For more than one year of follow-up, no change was recognized in serum biliary enzymes, tumor markers and clinical images, suggesting the non-neoplastic biliary stricture.

Clinically, a differential diagnosis of IgG4-SC from PSC is an important process based on their different treatment methods. However, due to the ambiguous definitions of these diseases, a clear line had not been drawn between the two diseases (18, 19). Again, the type of serum marker, site and shape of the stricture and other organ involvement are characteristically different. In general, IgG4 (80-90%), rheumatoid factor and ANA are frequently positive in IgG4-SC (4), in contrast to the high sensitivity of p-ANCA (80%) for PSC (18) (Table 1). Nakazawa et al reported that band-like strictures, beaded or pruned tree appearance and diverticulum-like formations were more frequent in PSC, and the segmental stricture, long stricture with prestenotic dilatation and stricture of the distal common bile duct were more common in IgG4-SC in the cholangiography (8). Inflammatory bowel disease (IBD) is often (70-80%) associated in patients with PSC but it is recognized in only 6% of IgG4-SC (7, 20) (Table 1). In 2006, Mendes et al (21) described that a small proportion of PSC patients (9%) had elevated level of serum IgG4, and their clinical courses were different from those of other patients. It was also reported that there are two peaks of onset of age in Japanese cases with PSC (20-30 years and 50-60 years) similar to the Western cases with PSC (22) (40 years) and Western cases with IgG4-SC (20) (65 years), respectively. These reports suggested the possibility that patients of IgG4-SC had been wrongly grouped with patients of PSC and highlighted the importance of a careful differential diagnosis between PSC and IgG4-SC.

Unlike autoimmune pancreatitis (AIP), the current case
was not accompanied with elevated serum IgG4 or other organ involvement (4, 23) despite the high level of serum IgG, IgG1, ANA and anti-DNA. In the case of AIP, the sensitivity of serum IgG4 is reported to be 90% (24) and an extra-pancreatic lesion is depicted by FDG-PET in 85% (23). It was also interesting that current case was free from pancreatic involvement during the follow-up for more than a year without steroid therapy. According to a recent report (25), the moderate level of IgG4(+) plasma cells (about 10 cells/HPF) is not thought as really specific to IgG4-related diseases. All these findings are in contrast to those of typical AIP-SC. In HISORt criteria, it is reported that most IgG4-SC is accompanied by a pancreatic lesion (7). Within reports of 20 cases of SC without a pancreatic lesion, only 3 cases reported by Hamano et al (9) provided individual data in detail and not much further information is available on this disease. As the current case did not show an elevation of serum IgG4, we could not diagnose as IgG4-SC. Although the findings of high level of serum antibodies and occurrence of ITP lead us to think that the onset of this case must be associated with autoimmunity, we did not have the criteria to diagnose this case. In order to establish the definitive concept of sclerosing cholangitis associated with autoimmunity including IgG4-SC and AIP-SC, it will be necessary to collect and investigate more cases.

We encountered a case of autoimmune-associated sclerosing cholangitis without pancreatic involvement. In the current case, spectrums of serological markers and extrachole-
docal lesions were distinct from the common cases of AIP-SC, so that further analyses are needed with larger numbers of cases. In such a case, careful differentiation is necessary in order to exclude biliary malignancies.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

Authors are grateful to Miss Megumi Yamanashi and Miss Tomomi Miyakawa for their careful support.

Institutional review board of Shizuoka Cancer Center ethically approved this case report.

References

10. Miura H, Miyachi Y. IgG4-related retroperitoneal fibrosis and sclerosing cholangitis independent of autoimmune pancreatitis. A re-

© 2011 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html