A Case of IgG4-related Sclerosing Cholangitis Overlapped with Primary Biliary Cirrhosis

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Abstract

IgG4-related sclerosing cholangitis (IgG4-SC) and primary biliary cirrhosis (PBC) can both cause liver dysfunction. While IgG4-SC is associated with IgG4-related diseases such as autoimmune pancreatitis, PBC is associated with various autoimmune diseases. However, there is only one case report of an association between IgG4-SC and PBC, and this association has not been elucidated further. The treatments for these two diseases are different, i.e., corticosteroid treatment is performed for IgG4-SC and ursodeoxycholic acid is given for PBC. We report a case of IgG4-SC overlapping with PBC in a 45-year-old man who was successfully treated by combination therapy with prednisolone and ursodeoxycholic acid.

Key words: autoimmune pancreatitis, IgG4-related sclerosing cholangitis, primary biliary cirrhosis, steroid, ursodeoxycholic acid


Introduction

IgG4-related sclerosing cholangitis (IgG4-SC) is often associated with other IgG4-related diseases (1, 2). Most IgG4-SC cases are associated with AIP. However, some cases are not. Patients with IgG4-SC show liver dysfunction or jaundice due to the involvement of the extrahepatic and intrahepatic large bile ducts. Therefore, it is necessary to differentiate primary sclerosing cholangitis (PSC) and cholangiocarcinoma from IgG4-SC (2). IgG4-SC usually shows a better response to steroid therapy than other biliary diseases (1, 2).

Primary biliary cirrhosis (PBC) is a chronic and progressive cholestatic liver disease of unknown cause that usually affects middle-aged women (3-5). Associations between PBC and other autoimmune diseases such as Sjögren’s syndrome; scleroderma; and calcinosis cutis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome have been reported. Ursodeoxycholic acid (UDCA) is considered to be the preferred therapeutic agent for PBC.

While both IgG4-SC and PBC are associated with various diseases, the association between IgG4-SC and PBC has not yet been clarified, and only one case report has indicated an association between AIP and PBC (6). Herein, we report a case of IgG4-SC overlapping with PBC that was successfully treated by combination therapy with UDCA and prednisolone (PSL).

Case Report

A 45-year-old man with suspected AIP was admitted to our hospital in 2009 for further examination. He was diagnosed with idiopathic thrombocytopenic purpura (ITP) in 2006 and had received PSL treatment (initial PSL dose, 60 mg). The dose was gradually reduced and tapered off over a period of two years. The serum levels of γ-glutamyl transpeptidase (γ-GTP) and alanine aminotransferase (ALT) had increased and fluctuated for three years. The laboratory data obtained during follow-up examinations for ITP in July
2009 showed that the serum levels of aspartate transaminase (AST), ALT, alkaline phosphatase (ALP), and γ-GTP had increased to 74 U/L (normal range, 13-33 U/L), 62 U/L (normal range, 6-30 U/L), 755 U/L (normal range, 115-359 U/L), and 329 U/L (normal range, 10-47 U/L), respectively. The serum IgG, IgM, and IgA levels were 3,129 mg/dL (normal range, 870-1,700 mg/dL), 179 mg/dL (normal range, 110-410 mg/dL), and 88 mg/dL (normal range, 35-220 mg/dL), respectively. The test for antinuclear antibody (ANA) showed positive results, with a titer of 1:40, and the antimitochondrial antibody (AMA) level (enzyme-linked immunosorbent assay [ELISA]) was 133 (normal range, <7).

The laboratory data obtained on admission showed elevated serum levels of AST, ALT, ALP, and γ-GTP (54 U/L, 42 U/L, 876 U/L, and 231 U/L, respectively). The levels of these liver enzymes decreased gradually after UDCA administration. The serum IgG level was 3,785 mg/dL and IgG 4 level was 968 mg/dL (normal range, 4.8-105 mg/dL). The serum levels of CEA and CA19-9 were 0.7 U/mL (normal range, <5 ng/mL) and 5.7 U/mL (normal range, <37 U/mL), respectively. Endoscopic retrograde pancreatography (ERP) showed focal irregular narrowing of the main pancreatic duct in the head and segmental narrowing in the body and tail; these narrowings were separated (Fig. 2A). Endoscopic retrograde cholangiography (ERC) revealed diffusely distributed stenosis of the intrahepatic bile ducts without prestenotic dilation and bile duct branches (Fig. 2B). The cholangiogram was classified as Type 2b according to our cholangiographic classification (7). Biliary intraductal ultrasonography (IDUS) revealed that the continuous wall from the intra-pancreatic bile duct to the upper bile duct, which had appeared normal in the cholangiogram, was thickened (Fig. 2C). IDUS for the bile duct revealed a circular and symmetric smooth outer margin, smooth inner margin, and homogeneous internal echo pattern. The wall thickness of the bile duct was 1.2 mm. These IDUS findings were typical for IgG4-SC according to our previous report (8).

We performed percutaneous liver biopsy for histopathological evaluation of the liver. Liver biopsy revealed moderate lymphoplasmacytic infiltration in the portal area and lymphocyte infiltration into the bile duct (Fig. 3A, B). These findings were consistent with those of chronic nonsuppurative destructive cholangitis. Abundant IgG4+ plasma cell infiltration was observed, and the number of IgG4+ plasma cells, calculated as the average count of positive plasma cells in three high power fields (HPFs), was 14/HPF (Fig. 3C). These findings were classified as having small duct involvement of IgG4-SC in accordance with our previous report (9).

The patient was diagnosed with AIP according to both the Japanese diagnostic criteria of AIP, 2006 (10) and the International consensus diagnostic criteria (ICDC) (11). Thus, the patient had both PBC and AIP. On the basis of the ERC, IDUS, and liver biopsy findings, we considered that the patient had IgG4-SC. In addition, we considered the possibility that liver dysfunction was caused by IgG4-SC in addition to PBC, and hence, steroid therapy was administered. The initial PSL dose was 30 mg.

The serum levels of AST, ALT, ALP, and γ-GTP at the time of steroid therapy initiation were 30, 23, 685, and 136 U/L, respectively. Two weeks after the start of PSL administration, the serum levels of AST, ALT, ALP, and γ-GTP decreased to 21, 23, 410, and 94 U/L, respectively. CT showed
improvement of the enlargement of the pancreas, and ERP revealed improvement of the narrowing of the main pancreatic duct. ERC also showed slight improvement of diffusely distributed stenosis of the intrahepatic bile ducts.

On the basis of the CT and ERCP findings, we considered that the response to steroid therapy was good, and hence, we gradually decreased the PSL dose. The patient was discharged and followed up. The liver enzyme levels improved one month after the initiation of steroid therapy. We assumed that the improvement was mainly attributable to PSL and decided to discontinue the administration of UDCA. Two months after we stopped UDCA and decreased the PSL dose to 8 mg, the liver enzyme levels increased gradually. Six months after the initiation of PSL administration, the serum levels of AST, ALT, ALP, and γ-GTP increased to 57, 64, 307, and 268 U/L, respectively. We considered that the increase was mainly due to the discontinuation of UDCA. Therefore, we resumed the administration of UDCA (900 mg); the dose of PSL remained the same (8 mg). Subsequently, the laboratory values decreased gradually. The clinical course is shown in Fig. 4. We examined the AMA (ELISA) levels six times during the clinical course. The maximum and minimum levels of AMA (ELISA) were 179 and 133, respectively. The high levels have been maintained since the diagnosis of PBC. Combination maintenance therapy with UDCA (900 mg) and PSL (8 mg) was continued until January 2012.

Discussion

IgG4-SC has been recently recognized as one of the IgG4-related diseases. AIP was recognized worldwide as one of the IgG4-related diseases. ICDC for AIP were recently proposed to promote the worldwide recognition of this disease (11). Sclerosing sialadenitis, retroperitoneal fibrosis, and renal involvement are regarded as IgG4-related diseases (12). Similar immunohistopathological features such as lymphoplasmacytic infiltration and abundant IgG4-positive plasma cells are also observed in patients with IgG4-related diseases. However, thus far, PBC has not been recognized as an IgG4-related disease on the basis of clinical and pathological findings.

PBC is a chronic and slowly progressive cholestatic disease that is associated with other autoimmune diseases such as Sjögren’s syndrome, scleroderma, and CREST syndrome (5). ITP is associated with PBC; however, an association between IgG4-related diseases and PBC has not been reported. Some cases of thrombocytopenia associated with
AIP have been reported (13-16), which indicates an association between thrombocytopenia with IgG4-related diseases. In the present case, the patient had a 3-year history of ITP, and ITP was the clinical sign for the diagnosis of PBC.

The association between IgG4-SC and PBC has not yet been clarified. Further, there has been only one case report on the coexistence of AIP and PBC (6). In that case, PBC was diagnosed on the basis of the AMA (ELISA) and liver biopsy findings. AIP was diagnosed on the basis of pancreatic biopsy findings. AIP was not definitely diagnosed in that case because the serum IgG4 level was normal and IgG4 immunostaining for pancreatic biopsy specimen was not performed. However, ERC revealed bilateral intrahepatic and proximal common bile duct stenoses. The findings on the cholangiogram were typical for type 4 IgG4-SC according to our classification (7) and classified as level 1 other organ involvement according to the ICDC (11). Therefore, we considered that case to be diagnosed as definitive AIP according to the ICDC.

The characteristic histological finding of PBC is the asymmetric destruction of the intralobular bile ducts within portal triads. Several histological staging systems have been proposed according to the degree of cholestasis, inflammation, and fibrosis. Whether liver biopsy is mandatory to confirm the diagnosis of PBC is still controversial. However, histological evidence of nonsuppurative destructive cholangitis and destruction of small- or medium-sized bile ducts is recommended as one of the three diagnostic criteria for PBC (3). Furthermore, liver biopsy for IgG4-SC by using IgG4 immunostaining is useful for its differential diagnosis from PSC (17, 18). We recently reported that small bile duct involvement in IgG4-SC, defined as the presence of bile duct damage associated with ≥10 IgG4+ plasma cells per HPF, was observed in 26% of patients with IgG4-SC (9). Patients with small bile duct involvement more commonly showed strictures of the intrahepatic bile ducts on cholangiography, and liver biopsy was especially useful for patients with intrahepatic biliary strictures on cholangiography, similar to the findings in patients with PSC. In the present study, nonsuppurative destructive cholangitis and bile duct damage associated with ≥10 IgG4+ plasma cells per HPF was observed. These findings were typical for PBC and small bile duct involvement in IgG4-SC. The cholangiogram of the present case showed an intrahepatic stricture. A similar correlation as that reported in our previous study (9) was found between the cholangiogram and liver biopsy findings.

Patients with IgG4-related disease usually show a good response to steroid therapy. ICDC incorporated response to steroid therapy into the diagnostic criterion. Furthermore, UDCA administration is considered as the preferred treatment for PBC because it significantly improves the serum levels of liver enzymes. However, whether there is a survival benefit for the treatment of PBC with UDCA still remains controversial. Usually, we do not use UDCA for treating IgG4-SC, and the effectiveness of UDCA for IgG4-SC has not been clarified. However, UDCA has beneficial effects on liver biomarkers of patients with PSC. Therefore, steroid therapy might be effective for IgG4-SC patients with small duct involvement.

In the present case, the serum ALP levels fluctuated depending on the treatment regimen. Because this patient showed features of both PBC and IgG4-SC, we considered that combination therapy with UDCA and PSL is necessary. In the previous report on the coexistence of AIP and PBC, only UDCA was administrated and steroid therapy was not performed (6).

In summary, the present report is the first case report indicating that combination therapy with UDCA and PSL is...
effective for IgG4-SC overlapping with PBC.

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

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