

Two Cases of Primary Sclerosing Cholangitis Overlapping with Autoimmune Hepatitis in Adults

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Abstract

Overlap syndrome between primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) is extremely rare in Japan. We herein report two adult patients with PSC-AIH overlap syndrome. They were diagnosed with PSC-AIH overlap syndrome based on the findings of endoscopic retrograde cholangiography and liver biopsy, and using the International Autoimmune Hepatitis Group scoring system. In both cases, PSC preceded AIH, and combination therapy with steroid and ursodeoxycholic acid was effective. Because there are few reported cases in Japan, it is important to study more cases to shed light on the clinical and pathological features of PSC-AIH overlap syndrome.

Key words: primary sclerosing cholangitis, autoimmune hepatitis, immunosuppression, ursodeoxycholic acid, International Autoimmune Hepatitis Group scoring system

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Introduction

Primary sclerosing cholangitis (PSC), a progressive cholestatic liver disease characterized by diffuse chronic inflammation and fibrosis of the biliary tree, affects primarily young to middle-aged men (1). In contrast, autoimmune hepatitis (AIH) is a chronic hepatitis characterized by auto-immunologic features with a female preponderance (2). These two diseases have well-defined clinical, morphological, and serological profiles. A variant form, so-called overlap syndrome, in which patients present with features of both PSC and AIH, was first described about 20 years ago (3, 4). However, reports of PSC-AIH overlap syndrome in adults are very rare in Japan (5, 6). We herein describe two cases of adult patients with PSC complicated with AIH.

Case Reports

Patient 1

A 19-year-old man was found to have a biochemical liver function abnormality in a checkup in April 2011. He had no history of alcohol abuse, drug addiction, blood transfusion, or toxic medication, and his family history was not contributory. Serological testing excluded viral hepatitis and autoimmune or metabolic liver diseases, but endoscopic retrograde cholangiography (ERC) showed diffuse stricturing and dilatation of the intrahepatic bile duct (Fig. 1). Therefore, he was referred to our hospital for further investigation and management in September 2011. His serum immunoglobulin G4 (IgG4) level was within the normal range. Liver biopsy specimens revealed marked inflammation and slight fibrosis in the portal tract, as well as piecemeal necrosis; damage to the biliary epithelial cells and IgG4-positive cells were absent (Fig. 2). We excluded secondary sclerosing cholangitis. Therefore, we diagnosed him with PSC and prescribed ur-

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Figure 1. ERC showed diffuse stricture and dilatation of the intrahepatic bile duct.

sodeoxycholic acid (UDCA) (600 mg/day).

Three months later, however, he was admitted to our hospital due to exacerbation of liver function tests reflecting generalized damage to hepatocytes as follows: aspartate aminotransferase (AST), 700 IU/L; alanine aminotransferase (ALT), 1,308 IU/L; alkaline phosphatase (ALP), 358 IU/L (reference range: 115-359); total bilirubin (T.Bil), 3.7 mg/dL; antinuclear antibody (ANA) titers, 1:40; and serum IgG, 2,144 mg/dL. There were no findings indicative of drug-induced liver injury, and markers of hepatitis viruses were negative.

We performed re-biopsy, and the biopsy specimens showed massive infiltration of lymphocytes and plasma cells, and fibrotic expansion in the portal tract compared with the first liver biopsy specimens. In addition, prominent interface hepatitis and intralobular focal necrosis were noted (Fig. 3). He was assessed to have probable AIH using the International Autoimmune Hepatitis Group (IAIHG) scoring system (7). His liver pathologic condition was considered to be PSC-AIH overlap syndrome (Table 1). Therefore, prednisone was started using an initial dose of 50 mg/day with UDCA (600 mg/day). The treatment reduced the serum aminotransferase and IgG levels immediately. Thus, prednisone was gradually tapered by 5 mg every 2 weeks depending on the serum aminotransferase levels. Six weeks after starting treatment, he was discharged with amelioration of biochemical parameters, and he has been followed up with 5 mg of prednisone with normal liver biochemistry by his general practitioner (Fig. 4).

Patient 2

A 61-year-old man was referred and admitted to our hospital for evaluation of an abnormal biliary tree with cholestatic liver function test in March 2015. The patient's history included an appendectomy in his youth and a left nephrectomy for left renal cell carcinoma with stent placement and vena cava filter insertion for deep vein thrombosis that de-

veloped during the nephrectomy at 48 years of age. The serology for viral hepatitis and AIH was negative. The serum IgG level was 1,333 mg/dL, and the IgG4 level was 133 mg/dL (reference range: 4-108 mg/dL). Contrast-enhanced computed tomography (CECT) revealed dilatation of the intrahepatic bile duct and bile duct stricture from the hilar hepatic lesion to the extrahepatic bile duct with wall thickening (Fig. 5). CECT showed no recurrence or metastasis of the renal cell carcinoma. ERC showed diffuse multiple stricturing of the hilar and intra- and extrahepatic bile ducts accompanied by dilatation of the distal bile ducts (Fig. 6). Intraductal ultrasound (IDUS) revealed circular-asymmetric wall thickness, heterogeneous internal echo, and an unclear outer margin (Fig. 7). Brushing cytology of the bile duct was negative. A liver biopsy specimen showed mild interface hepatitis with portal inflammation and interlobular focal necrosis. Biliary fibrosis, neoplastic lesion, and IgG4-positive cells were not observed (Fig. 8). We excluded secondary sclerosing cholangitis. Based on our investigations, we diagnosed him to have PSC and started UDCA (600 mg/day).

Two months after discharge, however, his liver function test findings were exacerbated again as follows: AST, 771 IU/L; ALT, 810 IU/L; ALP, 659 IU/L; T. Bil, 4.1 mg/dL; ANA titers, <1:40; and serum IgG, 1,344 mg/dL. There was no episode that would suggest drug-induced liver injury, and markers of hepatitis viruses were negative. We performed re-biopsy of the liver, and liver specimens showed prominent necroinflammatory features with severe interface hepatitis and multiple interlobular focal necroses, as well as periportal fibrosis. A characteristic periductal 'onion-skin' fibrosis was not observed (Fig. 9). He was assessed as having probable AIH using the IAIHG scoring system (7). Under the diagnosis of PSC-AIH overlap syndrome (Table 2), he was treated with pulsed methylprednisolone (500 mg/day for 3 days) followed by 60 mg/day of oral prednisone added to UDCA. The prednisone was tapered to 20 mg daily 6 weeks later, and he was discharged. Magnetic resonance cholangiopancreatography (MRCP) showed no marked changes in the biliary lesions in 6 weeks (Fig. 10). Colonoscopy with multiple biopsies revealed no inflammatory bowel disease. The prednisone was tapered to 15 mg 8 months later at the outpatient clinic with very slight elevation in his liver biochemistry findings (Fig. 11).

Discussion

Rabinovitz et al. first reported overlap syndrome between PSC and AIH in 1992 (3). It has been reported that PSC-AIH overlap syndrome occurs in less than 6% of patients with PSC (8-12). This syndrome is extremely rare in Japan (3, 4), possibly because the prevalence of PSC is lower in Japan than in Europe or North America (13). However, the true prevalence of PSC-AIH overlap syndrome is unknown, as the diagnostic criteria for PSC-AIH overlap syndrome remain controversial (14). PSC-AIH overlap syn-

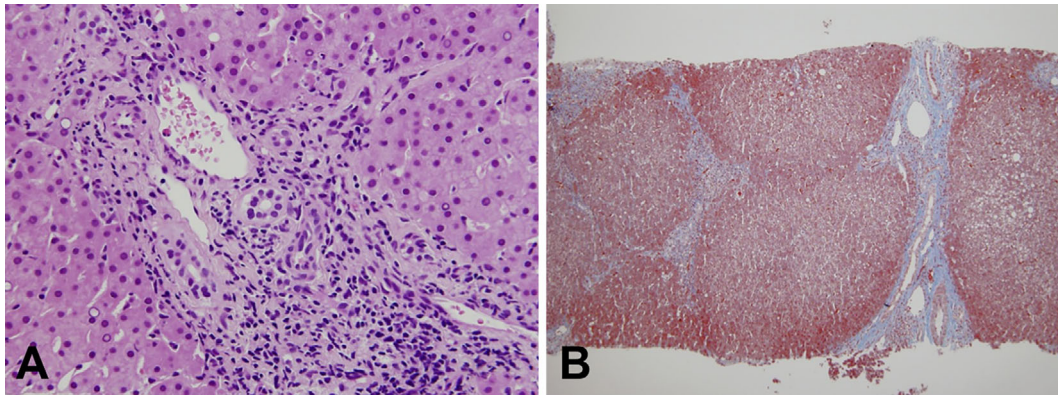


Figure 2. The histological findings in a liver biopsy specimen taken in October 2011. (A) Hematoxylin and Eosin staining showed interface hepatitis with marked portal lymphocytic infiltration (original magnification $\times 400$). (B) Masson trichrome staining showed slight portal fibrosis (original magnification $\times 100$). There were no findings of periductal fibrosis and cholangiopathy.

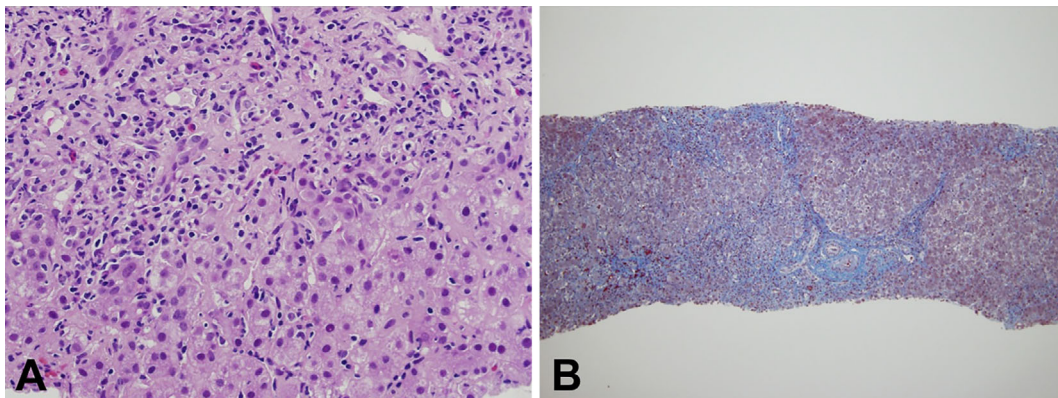


Figure 3. The histological findings in a liver biopsy specimen taken in February 2012. (A) Hematoxylin and Eosin staining showed massive infiltration of lymphocytes and plasma cells (original magnification $\times 400$). (B) Masson trichrome staining showed fibrotic expansion in the portal tract (original magnification $\times 100$). These histopathological findings were much worse than the previous histopathological findings.

Table 1. Laboratory Findings of Patient 1.

	At diagnosis of PSC	At diagnosis of AIH
White blood cell count (3,500-8,500 / μ L)	5,060	4,830
Hemoglobin (13.5-17.0 g/dL)	16.9	15.7
Platelet count (15.0-35.0 $\times 10^4$ / μ L)	16.9 $\times 10^4$	16.5 $\times 10^4$
Total protein (6.7-8.3 g/dL)	8.0	7.7
Albumin (3.5-5.5 g/dL)	4.9	4.2
Aspartate aminotransferase (13-33 U/L)	41	700
Alanine aminotransferase (8-42 U/L)	62	1,308
Alkaline phosphatase (115-359 U/L)	404	358
Lactate dehydrogenase (119-229 U/L)	164	320
Total bilirubin (0.3-1.2 mg/dL)	1.1	3.7
Gamma-glutamyltranspeptidase (10-47 U/L)	145	117
Immunoglobulin G (870-1,700 mg/dL)	1,572	2,144
Immunoglobulin G4 (4-108 mg/dL)	ND	22.4
Immunoglobulin A (110-410 mg/dL)	206	270
Immunoglobulin M (33-190 mg/dL)	103	98
Anti-nuclear antibody	$\times 40$	$\times 40$
Anti-mitochondrial antibody	(-)	(-)
IAIHG scoring system	13 (probable)	14 (probable)

AST: aspartate aminotransferase, IAIHG: International Autoimmune Hepatitis Group, ND: not done

drome has been reported more often in children than adults, even though PSC is less common in children (15). Indeed, patients with PSC-AIH overlap syndrome are significantly younger and have higher levels of ALT and IgG than patients with PSC alone (16). Most reported cases have been diagnosed based on the IAIHG scoring system, as well as cholangiography and liver biopsy findings. However, the IAIHG recently recommended that patients with suspected overlap syndrome be classified on the basis of their primary disease as AIH, PSC, or primary biliary cirrhosis (PBC) and advocated that the IAIHG scoring system not be used to diagnose overlap syndrome (14). Therefore, the IAIHG suggested that the coexistence of cholestatic liver diseases (PSC or PBC) and AIH should be classified as "PSC with features of AIH" or "PBC with features of AIH", respectively (14). Despite the fact that precise diagnostic criteria have not been established yet, physicians are urged to perform a diagnostic evaluation in clinical practice. We therefore diagnosed both of the present cases with PSC-AIH overlap syndrome,

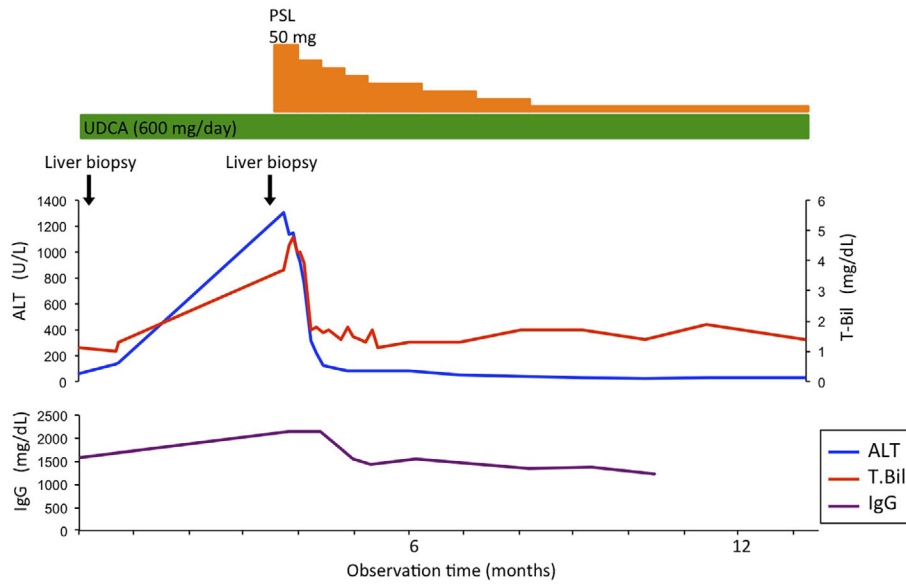


Figure 4. Changes in the levels of serum markers during the clinical course. The levels of ALT, T.Bil, and IgG decreased after the administration of PSL. ALT: alanine aminotransferase, T.Bil: total bilirubin, IgG: immunoglobulin G, PSL: prednisone

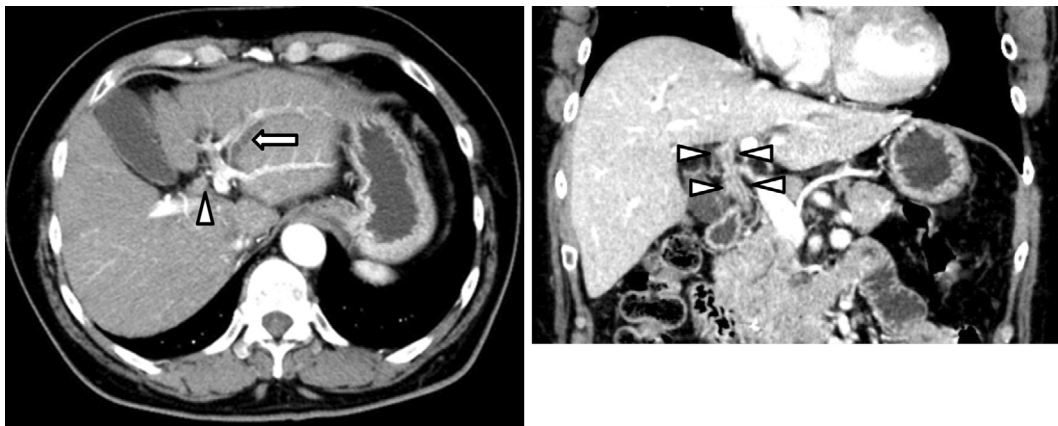


Figure 5. CECT showed dilatation of the intrahepatic bile duct (arrow) and bile duct stricture from the hepatic hilar lesion to the extrahepatic bile duct with wall thickness (arrow head).

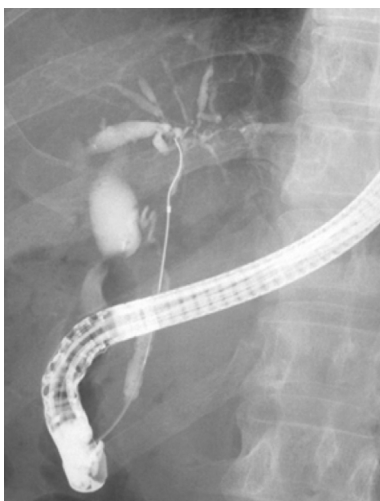


Figure 6. ERC showed dilatation of the distal intrahepatic bile duct and diffuse multiple stricturing of the hilar and intra- and extrahepatic bile ducts.

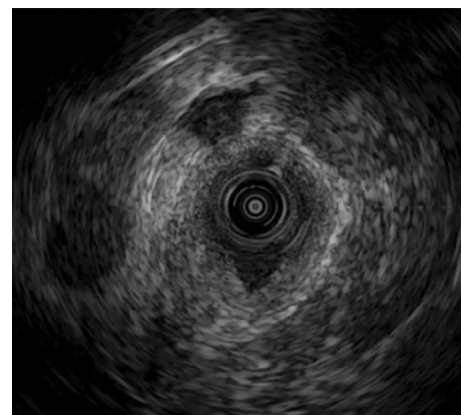


Figure 7. IDUS showed circular-asymmetric wall thickness, heterogeneous internal echo, and an unclear outer margin.

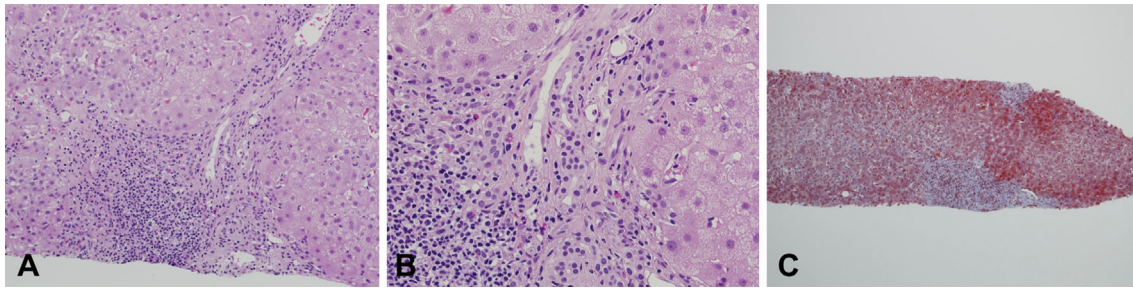


Figure 8. The histological findings in a liver biopsy specimen taken in March 2015. Hematoxylin and Eosin staining showed mild interface hepatitis with portal inflammation and focal intralobular necrosis (original magnification A: $\times 200$, B: $\times 400$). (C) Masson trichrome staining showed no findings of biliary fibrosis (original magnification $\times 100$).

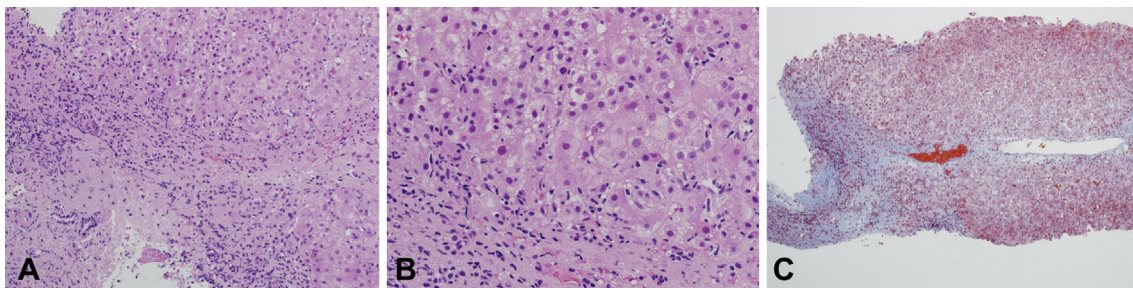


Figure 9. The histological findings in a liver biopsy specimen taken in June 2015. Hematoxylin and Eosin staining showed prominent necroinflammatory features with severe interface hepatitis and multiple interlobular focal necroses, as well as periportal fibrosis. (C) Masson trichrome staining showed no characteristic periductal onion-skin fibrosis (original magnification $\times 100$).

Table 2. Laboratory Findings of Patient 2.

	At diagnosis of PSC	At diagnosis of AIH
White blood cell count (3,500-8,500 / μ L)	5,780	4,510
Hemoglobin (13.5-17.0 g/dL)	15.3	14.1
Platelet count (15.0-35.0 $\times 10^4$ / μ L)	17.3 $\times 10^4$	12.6 $\times 10^4$
Total protein (6.7-8.3 g/dL)	6.7	6.3
Albumin (3.5-5.5 g/dL)	4.0	3.2
Aspartate aminotransferase (13-33 U/L)	349	771
Alanine aminotransferase (8-42 U/L)	486	810
Alkaline phosphatase (115-359 U/L)	564	659
Lactate dehydrogenase (119-229 U/L)	229	359
Total bilirubin (0.3-1.2 mg/dL)	2.1	4.1
Gamma-glutamyltranspeptidase (10-47 U/L)	646	532
Immunoglobulin G (870-1,700 mg/dL)	1,333	1,344
Immunoglobulin G4 (4-108 mg/dL)	133	106
Immunoglobulin A (110-410 mg/dL)	155	176
Immunoglobulin M (33-190 mg/dL)	49	69
Anti-nuclear antibody	<40	<40
Anti-mitochondrial antibody	(-)	(-)
IAIHG scoring system	12 (probable)	15 (probable)

AST: aspartate aminotransferase, IAIHG: International Autoimmune Hepatitis Group, ND: not done

as other case reports have done, using the IAIHG scoring system.

For diagnosing PSC, we excluded secondary sclerosing cholangitis based on a lack of such factors as acquired immune deficiency syndrome cholangiopathy, biliary duct neoplasm and surgery, choledocholithiasis, congenital abnor-

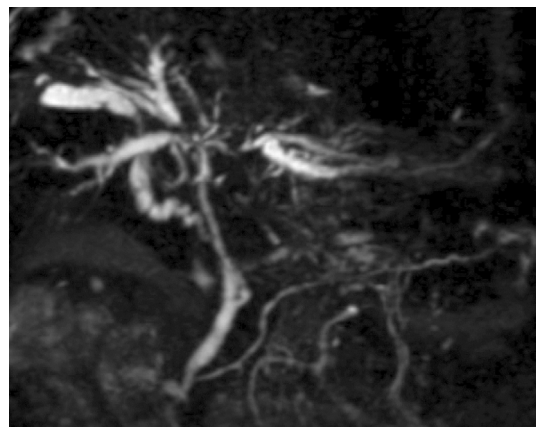


Figure 10. Follow-up MRCP did not show any changes in the biliary lesions 6 weeks after the start of steroid treatment.

malities, caustic sclerosing cholangitis, ischemia, IgG4-related sclerosing cholangitis, or floxuridine infusion. Consequently, we diagnosed both of the present patients with PSC. For diagnosing AIH, however, the liver function tests indicated cholestatic liver biochemistries at the first referral, and the first liver biopsies showed very subtle inflammation in both patients. Therefore, we could not diagnose either patient with AIH at the first referral. We diagnosed PSC-AIH overlap syndrome a few months after the diagnosis of PSC,

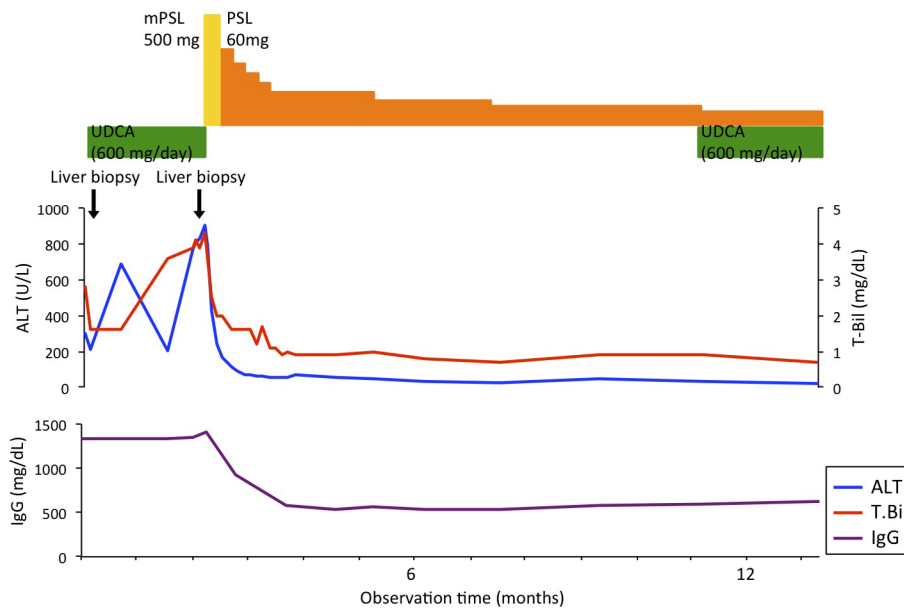


Figure 11. Changes in the levels of serum markers during the clinical course. The levels of ALT, T.Bil, and IgG decreased after the administration of mPSL and PSL. ALT: alanine aminotransferase, T.Bil: total bilirubin, IgG: immunoglobulin G, mPSL: methylprednisolone, PSL: prednisone

when the patients showed re-exacerbation of liver function tests and compatible liver histology for AIH. In this respect, we understand the difficulties associated with the diagnosis of AIH due to the clinical course of chronic cholestatic liver disease. However, re-biopsy of the liver revealed more inflammation and necrosis than the first biopsy specimens in both patients. Therefore, we confirmed that AIH overlapped with PSC.

Regarding coexisting inflammatory bowel disease (IBD), patients with PSC-AIH overlap syndrome have a high prevalence of IBD, like patients with PSC alone (17-19). However, our cases did not have IBD, presumably due to the low prevalence of IBD in patients with PSC in Japan (13).

Most patients with PSC-AIH overlap syndrome are treated with immunosuppressive therapy consisting of steroid, azathioprine, or cyclosporine in combination with UDCA (16). Indeed, immunosuppression is beneficial for the AIH component, and UDCA has a favorable effect on the PSC component; thus, it has been reported that treatment with steroids or azathioprine combined with UDCA improves the liver biochemistry in the short term in patients with PSC-AIH overlap syndrome (15, 16). In our two cases, as well, UDCA alone could not improve the liver biochemistry, but prednisone with UDCA did. Thus, we believe that although UDCA alone was not effective, a combination of prednisone and UDCA can be effective in treating the AIH aspect of PSC-AIH overlap syndrome. Regarding the long-term outcome, progression of PSC and liver fibrosis is observed in the majority of patients. However, they seem to have a better outcome than patients with classical PSC (16, 19, 20). Of note, though: it has been reported that patients with PSC-AIH overlap syndrome have a poorer prognosis and shorter time to liver transplantation than AIH-

only patients (10, 20-23).

Besides the fact that distinctive diagnostic criteria for PSC-AIH overlap syndrome have not been established, the number of reported cases of PSC-AIH overlap syndrome is too small to draw definitive conclusions. To elucidate the epidemiology, pathophysiology, treatment efficacy, and long-term outcome of PSC-AIH overlap syndrome, investigation of more cases is needed, especially in Japan.

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

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