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【 CASE REPORT 】

Primary Sclerosing Cholangitis and Autoimmune Hepatitis Overlapping Syndrome Complicated by Ulcerative Colitis

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Abstract:
The case of a 28-year-old man who had primary sclerosing cholangitis and autoimmune hepatitis overlapping syndrome (PSC-AIH OS) complicated by ulcerative colitis (UC) is reported. First, he was diagnosed with PSC complicated by UC and initially treated with ursodeoxycholic acid and mesalazine. Twenty-four months later, liver damage reappeared, and we performed a liver biopsy, which showed the features of AIH. We eventually diagnosed him with PSC-AIH OS complicated by UC. If liver damage worsens in PSC patients, PSC-AIH OS should be considered. The optimum management approach for PSC-AIH OS should be established.

Key words: autoimmune hepatitis, primary sclerosing cholangitis, ulcerative colitis

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Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease. It is characterized by elevated serum aminotransferases, increased total immunoglobulin G (IgG), and positive antinuclear antibody findings. Liver biopsies often show interface hepatitis and portal mononuclear cell infiltration (1). Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease, characterized by diffuse chronic inflammation and fibrosis of the biliary tree, and often is diagnosed by cholangiography techniques, such as endoscopic retrograde cholangiopancreatography (ERC) and magnetic resonance cholangiopancreatography (MRCP). The etiology and pathogenesis of PSC are not well understood, although PSC is highly associated with inflammatory bowel disease (IBD) (2). PSC-AIH overlap syndrome (PSC-AIH OS) is a rare disease characterized by the biochemical and histological features of AIH and the cholangiography abnormalities found in PSC. However, there have been few reports of AIH-PSC OS in Japan (3, 4). We herein report a case of PSC-AIH OS complicated by ulcerative colitis (UC).

Case Report

A 28-year-old man had abdominal pain and visited another hospital in March 2019. He had the symptom of bloody stool, and a blood test showed moderate liver damage, so he was introduced to our hospital. He had no history of alcohol abuse, drug addiction, blood transfusion, or toxic medication. His laboratory tests showed moderately high levels of aspartate aminotransferase (AST: 133 U/L), alanine aminotransferase (ALT: 204 U/L), and alkaline phosphatase (ALP: 409 U/L). The serum IgG level was considerably high (3,073 mg/dL), but its subclass of IgG4 level was not elevated (30.2 mg/dL). Serological testing excluded viral hepatitis. Computed tomography (CT) showed multiple dilation of the intrahepatic bile ducts and wall thickening of the extrahepatic bile duct. MRCP and ERC showed band-like strictures, beaded appearances of intrahepatic bile ducts, and a shaggy appearance of the extrahepatic bile duct. Intraductal ultrasound (IDUS) demonstrated circular-asymmetric wall thickening, irregular inner margin, and disappearance of three layers (Fig. 1). Lymphoplasmacytic infiltration without

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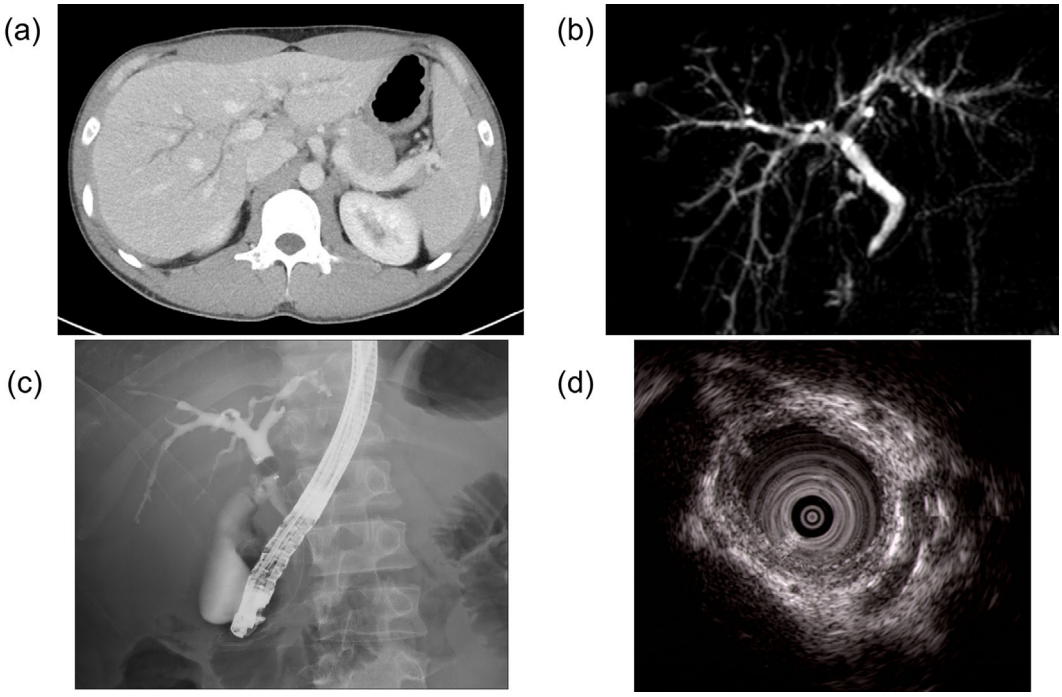

Figure 1. **(a) CT showing dilation of the intrahepatic bile duct. (b) MRCP showing multiple focal areas of strictures of the intrahepatic bile ducts, with associated dilation. (c) ERC showing diffuse structuring and dilation of the intrahepatic bile duct. (d) IDUS showing circular-asymmetric wall thickness, heterogeneous internal echo, and an unclear outer margin.**

IgG4-positive plasma cells and no malignant cells were observed by a transpapillary bile duct biopsy. He was diagnosed with definitive PSC according to the 2016 diagnostic criteria of PSC (5). Screening colonoscopy showed erythema and a decreased vascular pattern, so he was diagnosed with UC, categorized as pancolitis, Mayo Endoscopic Subscore (MES) of 1 (6). Conclusively, he was diagnosed with PSC complicated by UC and initially treated with ursodeoxycholic acid (UDCA, 600 mg/day) and mesalazine (3,000 mg/day). One month later, he had diarrhea 15 times/day. Mesalazine was withdrawn, as we considered him to have intolerance of mesalazine, and his diarrhea improved. In April 2020, 10 months after the withdrawal of mesalazine, he had abdominal pain and more than 5 bloody stools per day. Colonoscopy showed marked erythema, an absent vascular pattern, and erosions, resulting in an MES of 2. We diagnosed him with UC flare-up and added an initial dose of prednisone (PSL) at 40 mg/day. Thereafter, clinical remission was induced, and we decreased the dose of PSL gradually.

However, in June 2020, when he was treated with PSL 5 mg/day, his symptoms worsened again with more than 10 instances of diarrhea per day, so we diagnosed him with steroid-dependent UC and increased the dose of PSL to 15 mg/day. In September 2020, his liver damage had worsened. MRCP was carried out again, showing no remarkable changes. Three weeks later, his liver damage had improved without additional medication, so we suspected that this liver damage was due to transient worsening of PSC.

In November 2020, we added vedolizumab, monoclonal antibody against $\alpha_4\beta_7$ integrin to help stabilize his UC and decrease the doses of PSL. In March 2021, the number of defecations had increased, so the dose of prednisone was increased to 15 mg, vedolizumab was withdrawn, and ustekinumab, a monoclonal antibody against IL-12 and IL-23, was introduced. In May 2021, his liver damage had worsened (Fig. 2). Laboratory data at this time are shown (Table). The aggravation of cholangiographic findings was not observed on MRCP. We performed a liver biopsy which showed massive infiltration of lymphocytes and prominent interface hepatitis (Fig. 3). We assessed him as having provable AIH, according to the International Autoimmune Hepatitis Group Scoring system (7). Thus, we diagnosed him with PSC-AIH OS complicated by UC and planned to add azathioprine (AZA).

The variant of NUDT15 codon139 was Arg/Cys, which was more likely to be associated with the appearance of side effects such as thiopurine-induced leukopenia and hair loss (8). Therefore, we started to prescribe a low dose of AZA, 25 mg every other day, in addition to UDCA 600 mg/day, prednisone 10 mg/day, and ustekinumab 90 mg every 12 weeks, and he had only upper abdominal discomfort as a side effect. Thereafter, his liver damage was normalized by maintaining PSL at 10 mg/day and using AZA at the initial dose. Two months after introducing AZA, we decreased the dose of PSL to 5 mg/day and increased the dose of AZA to 25 mg/day, after which his liver function remained stable.

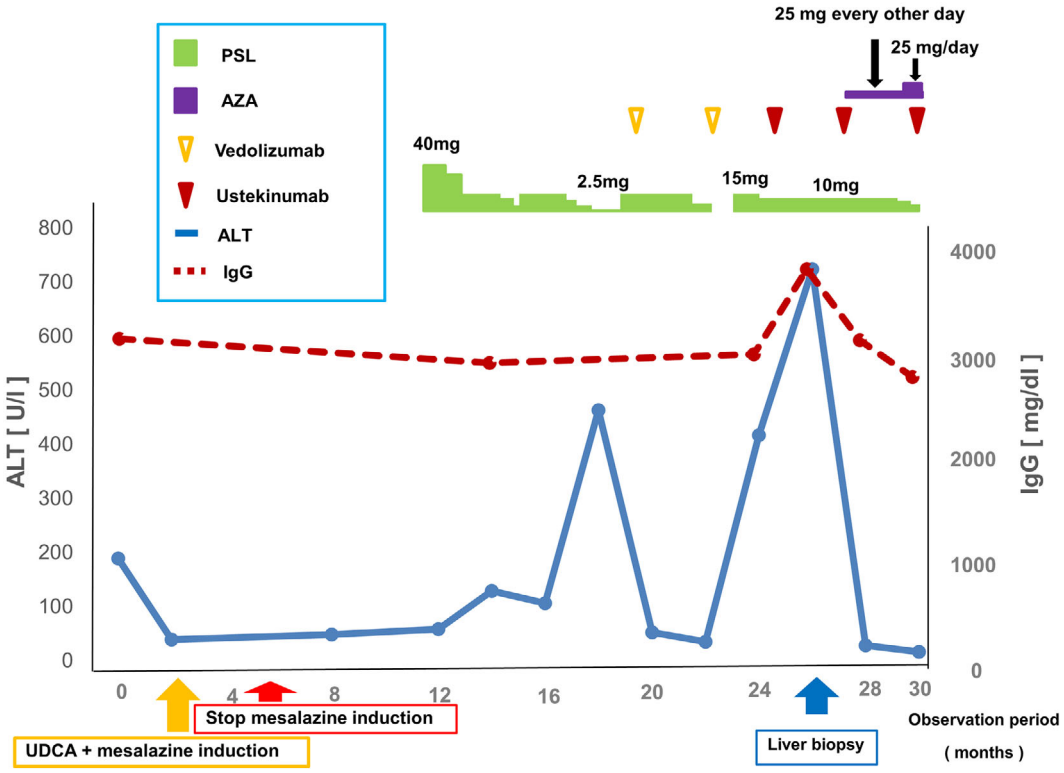

Figure 2. **Changes in the levels of serum markers during the clinical course. ALT: alanine aminotransferase, IgG: immunoglobulin G, UDCA: ursodeoxycholic acid**

Table. **Laboratory Data on Admission.**

Blood count		Biochemistry		LDL	77 mg/dL
WBC	9,100 μL	TP	8.9 g/dL	Fe	22 μg/dL
Neut	26.1 %	Alb	3.7 g/dL		
Lymph	50.7 %	AST	351 U/L	Virus marker	
RBC	4.67×10^6 /μL	ALT	708 U/L	HBsAg (CLEIA)	0.0 (-) C.O.I.
Hb	11.7 g/dL	LDH	288 U/L	anti-HCV (CLEIA)	0.0 (-) C.O.I.
Plt	46.3×10^4 /μL	ALP	137 U/L		
		T. Bil	1.1 mg/dL	Other	
Coagulation		CK	64 U/L	ANA	40×
PT	81.8 %	BUN	11.1 mg/dL	AMA-M2	<1.5 Index
PT-INR	1.12	Cre	0.85 mg/dL	Anti-smooth muscle antibody	40×
APTT	34.9 s	Glu	83 mg/dL	Anti-LKM antibody	<5 Index
		NH3	72 μmol/L	TSH	0.876 uIU/mL
IgG	3,821 mg/dL	Na	139 mEq/L	FT3	3.05 pg/mL
IgA	165 mg/dL	K	4.9 mEq/L	FT4	1.03 ng/dL
IgM	139 mg/dL	Cl	105 mEq/L	FIB-4	0.83 Index
		T-CHO	154 mg/dL	CEA	0.9 ng/mL
NUDT allele	Arg/Cys	TG	105 mg/dL	CA19-9	9.6 U/mL

Discussion

The diagnosis of PSC-AIH OS in adults requires the coexistence AIH and cholangiographic or histologic features of PSC, and approximately 1.4-17% PSC patients are diagnosed with PSC-AIH OS (9). PSC-AIH OS is more common in children; up to 50% of children with AIH have cholangiographic features of PSC (10). Another report showed that comorbid IBD was present in 44% of PSC-AIH OS patients (11). The long-term prognosis of PSC-AIH OS remains controversial. Several studies showed that PSC-AIH OS has a good prognosis (12, 13), but other studies showed that PSC-AIH OS has a poor prognosis and shorter time to liver transplantation than patients with AIH alone (14, 15).

Regarding the treatment for PSC-AIH OS, the EASL 2015 AIH guidelines recommend that addition of UDCA to immune-suppression be considered. However, very few re-

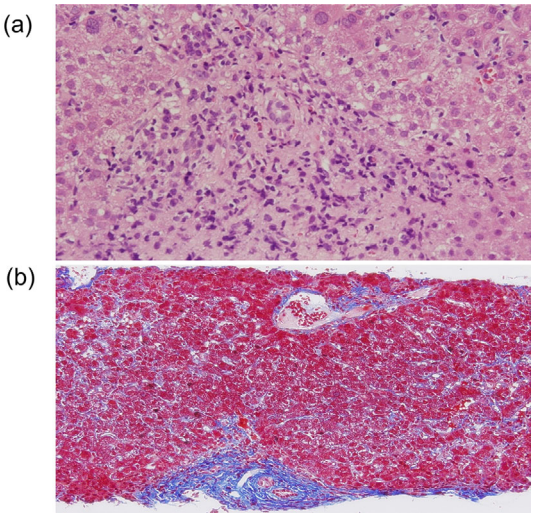

Figure 3. The histological findings by a liver biopsy. (a) Hematoxylin and Eosin staining showing massive infiltration of lymphocytes and plasma cells (original magnification ×200). (b) Azan staining showing fibrotic expansion in the portal tract (original magnification ×100). These histopathological findings suggested autoimmune hepatitis.

ports have described the features of PSC-AIH OS, including its treatment, because the condition is so rare (16, 17). Therefore, it is difficult to draw any firm conclusion regarding the optimal treatment for PSC-AIH OS (10).

Thus far, there have been very few reports of PSC-AIH OS, especially in Japanese adults (18), so we report the first case of PSC-AIH complicated by UC in an adult (Supplementary material). Igarashi et al. reported a Japanese case of PSC-AIH OS in a 61-year-old man who was diagnosed with PSC first and then treated with UDCA. His liver damage was improved by UDCA at first but reappeared a few months later. Therefore, a liver biopsy was performed, and he was diagnosed with PSC-AIH OS (4). In our case, the patient was diagnosed with PSC-AIH OS 24 months after the initial diagnosis of PSC and UC. If liver damage worsens in patients with AIH or PSC, PSC-AIH OS should be considered, and an investigation by a liver biopsy should be performed. Although the recent diagnostic criteria allow us to diagnose PSC without a liver biopsy (5), we feel that a pathological examination is essential for the diagnosis of PSC-AIH OS.

Although UC is treated with mesalazine in general, our case had severe diarrhea after the introduction of mesalazine, and we considered him to be mesalazine-intolerant. The mechanism underlying mesalazine intolerance is unknown, although the metabolism of mesalazine has been studied. The frequency of mesalazine intolerance is about 7% in Japan, and the main adverse reactions are exanthema, a fever, nausea and vomiting, angioedema, and liver damage (19). Our case was treated with steroids because of mesalazine intolerance, and this was also effective for AIH. This may be the reason why the diagnosis of AIH was delayed until 24 months after the initial diagnosis of PSC and UC.

For the treatment of AIH, combination therapy of AZA and steroid is effective in patients who do not improve with steroid monotherapy (20). Among the side effects of AZA, severe acute leukopenia and total hair loss are associated with variants of NUDT15 codon139. It has been reported that the frequency of Cys/Cys homozygotes is 1%, and Arg/Cys and Cys/His heterozygotes constitute about 20% of NUDT15 gene polymorphisms (8). Our patient had the variant of Arg/Cys, which is a risk factor for side effects, such as thiopurine-induced leukopenia. Therefore, we started the administration of AZA quite carefully.

In conclusion, when liver damage worsens in patients with AIH or PSC, we should consider the possibility of PSC-AIH OS and perform a liver biopsy. Further investigations are needed to establish the management of PSC-AIH OS.

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

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