Autoimmune Hepatitis Overlapping with Primary Sclerosing Cholangitis

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Abstract

A case of autoimmune hepatitis (AIH) complicated by primary sclerosing cholangitis (PSC) in a 36-year-old woman is reported. AIH overlapping with PSC has been rarely reported, and to the best of our knowledge, there have been no reports in Japan. Based on the criteria for diagnosis of AIH and on typical endoscopic retrograde cholangiograph (ERC) findings, the patient was diagnosed as having AIH overlapping with PSC. Her transaminase levels normalized within 1 month after administration of prednisone, azathioprine and ursodeoxycholic acid, but her cholestatic enzyme level remained elevated. The effect of treatment on the cholestatic features is thought to be an important factor for predicting the prognosis of AIH overlapping with PSC.

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Key words: AIH, PSC, endoscopic retrograde cholangiograph, prednisone, azathioprine, ursodeoxycholic acid

Introduction

Autoimmune hepatitis (AIH) is a chronic necro-inflammatory disorder of unknown etiology. The diagnosis is based on criteria that include clinical symptoms, hypergammaglobulinemia with an absence of cirrhosis, and circulating autoantibodies (1). Primary sclerosing cholangitis (PSC) is a cholestatic disease of unknown etiology characterized by diffuse inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts (2). A syndrome in which AIH and primary biliary cirrhosis (PBC) overlap is often seen (3), but there have only been a few reports of an overlap between AIH and PSC (4–13). We describe here a case of AIH associated with PSC in a female patient who fulfilled criteria for definite AIH (14) and had characteristic cholangiographic features in the biliary tracts.

Case Report

In June 1993, a 36-year-old woman was admitted to another hospital because of low-grade fever. She had no history of blood transfusion or drug allergy, and she did not drink alcohol. Laboratory data on admission are shown in Table 1. Moderate increases in aspartate aminotransferase (AST: 381 IU/l), alanine aminotransferase (ALT: 264 IU/l) and alkaline phosphatase (ALP: 28.8 KAU) were noted. Serum IgG was elevated to 3,210 mg/dl, 1.7-times more than the upper limit of the normal range. Antinuclear antibody (ANA: 1: 1,280) was positive. Histology of a liver biopsy sample revealed findings of chronic active hepatitis without cholangitis, as shown in Fig. 1. On the basis of these findings, she was diagnosed as having autoimmune hepatitis and was treated with prednisone at a dose of 30 mg/day and ursodeoxycholic acid (UDCA) at a dose of 600 mg/day. Since the ALT level decreased gradually after the start of treatment, the administration of prednisone was stopped on her own will in December 1993. However, marked increases in ALT and ALP were noted in February 1994. She was then treated with prednisone (50 mg/day) and azathioprine (100 mg/day), and the ALT level decreased. Since a moderate increase in ALP continued, she was referred to our department, and she was admitted in April 1994. Her status on admission was as follows: height, 152.0 cm; body weight, 48.2 kg; blood pressure, 120/80 mmHg; and pulse, regular at 84 beats/min. No goiter or enlargement of the cervical lymph nodes was noted. No remarkable abnormalities in the heart or lungs were noted. The liver edge was palpable three fingerbreadths under the right costal edge without tenderness. Laboratory data on admission are shown in Table 1. Moderate increases in ALP (893 IU/l) and γ -glutamyl transpeptidase (γ -GTP: 373 IU/l) were noted. The serum immunoglobulin level was not elevated. Anti-mitochondrial antibody (AMA) and anti-smooth muscle antibody (aSMA) were not detected by indirect immunofluorescence. She was positive for ANA (1: 1,280) and perinuclear anti-neutrophil cytoplasmic antibody (pANCA). The results of tests for hepatitis B virus surface (HBs)-antigen, hepatitis B virus

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Table 1. Laboratory Data in Our Patient

	Jun-93	Apr-94
WBC	5,300/ μ l	4,700/ μ l
RBC	351×10^4 / μ l	361×10^4 / μ l
PLT	ND	24.3×10^4 / μ l
AST	381 IU/l	99 IU/l
ALT	264 IU/l	65 IU/l
LDH	460 IU/l	280 IU/l
ALP	28.8 KU (normal range 2.2–10)	893 IU/l (normal range 125–335)
γ GTP	349 IU/l	373 IU/l
TB	1.41 mg/dl	0.7 mg/dl
DB	0.86 mg/dl	0.3 mg/dl
TP	8.6 mg/dl	7.6 mg/dl
Alb	3.8 mg/dl	4 mg/dl
TTT	27.7 KU	27.3 KU
ZTT	31.9 KU	14.3 KU
IgG	3,210 mg/dl	1,850 mg/dl
IgA	213 mg/dl	230 mg/dl
IgM	404 mg/dl	332 mg/dl
ANA	$\times 1,280$ (ho)	$\times 1,280$ (ho, sp)
AMA	(–) (M2)	(–)
p-ANCA	ND	$\times 1,280$
CH50	69.2 U/ml	56.2 U/ml

ND: not done.

Figure 1. A, B. Histological findings in a liver biopsy specimen taken on June 5, 1993. A portal tract is infiltrated with an increased number of lymphocytes and shows piecemeal necrosis. A widened portal area with extensive fibrosis and partly bridging fibrosis is also noted. Focal necrosis is seen in the parenchyma. However, there are no findings such as periductal fibrosis, bile duct damage or loss of bile ducts (HE stain, A: $\times 10$, B: $\times 200$).

core (HBc)-antibody and hepatitis C virus (HCV)-antibody were all negative. Her human leukocyte antigen (HLA) typing was positive for A24, A31, B35, B61, Cw4 and DR4.

Endoscopic retrograde cholangiography (ERC) revealed shortening and irregularities of intra- and extrahepatic bile ducts compatible with PSC (Fig. 2). There was no evidence of inflammatory bowel disease on colonoscopic examination. A liver

biopsy performed again in May 1994 showed significant amelioration of hepatitis with mild residual inflammatory infiltrate in the portal tracts but no evidence of cholangitic changes (Fig. 3). Based on the criteria for diagnosis of AIH and on the ERC findings, she was diagnosed as having AIH overlapping with PSC. One year later, her ALT and IgG levels had normalized but ALP and γ -GTP levels remain elevated. She has since been

Figure 2. Endoscopic retrograde cholangiography reveals a mixture of narrowing and dilatation of both intra- and extrahepatic bile ducts. A diverticula finding (arrow) is observed at the common bile duct.

treated with prednisone (7.5 mg/day) and azathioprine (100 mg/day).

Discussion

The initial diagnosis of AIH seems quite sound in this case. According to the revised criteria for diagnosis proposed by the International Autoimmune Hepatitis Group (14), the AIH score was calculated to be 18, defined as 'definite' AIH. Histologically, the liver biopsy specimen showed interface hepatitis that was compatible with AIH. On the other hand, the diagnosis of PSC in this case was made on the basis of typical cholangiographic findings in the setting of cholestatic liver enzyme elevations, although the liver biopsy specimen showed no cholangitic findings or periductal fibrosis. Currently, the diagnostic criteria for PSC are based on characteristic cholangiographic findings, and a liver biopsy is not generally required to establish a diagnosis of PSC (15). In fact, the frequency of the fibrous-obliterative cholangitis in liver biopsy specimens is only about 10–50% in patients with PSC (16–18). Therefore, she was diagnosed as having AIH overlapping with PSC. After the diagnosis, the AIH score was recalculated to be 23, defined as 'definite' AIH.

AIH overlapping with PSC has rarely been reported; to the best of our knowledge, only 27 cases have been reported (see Table 2). There appear to have been no reports in Japan. In the 27 documented cases of AIH overlapping with PSC, PSC was diagnosed before the onset of AIH in 3 cases, at the same time as the onset of AIH in 6 cases, and after the onset of AIH in 18 cases. These overlapping cases have been observed more frequently in young men (15/27), although AIH occurs most frequently in women between the ages of 10 and 30 years or in late middle age (19). An association of inflammatory bowel diseases was reported in 19 of the 27 cases. Although ulcerative colitis is complicated by AIH without PSC, the presence

A

B

Figure 3. A, B. Histological findings in a liver biopsy specimen taken on April 1, 1994. A portal tract is infiltrated with lymphocytes but to a lesser degree than that observed in the previous liver biopsy specimen (Fig. 1A). There are no findings such as periductal fibrosis, bile duct damage or loss of bile ducts (HE stain, A: $\times 40$, B: $\times 400$).

Table 2. Clinical and Laboratory Characteristics of Published Cases with AIH/PSC Overlap Syndrome

Author	Age/Sex	AST/ALP	Treatment	Complication	Onset time
Minuk	18/W		PSL	EV, UC, pancreatitis	AIH→PSC
	30/W	35/946	PSL	UC, chr.thyroiditis	PSC→AIH
Rabinovitz	30/M	385/446	PSL, AZP	UC	simultaneous
Leggett	3 patients		PSL, AZP	UC (2/3)	PSC→AIH
Lawrence	39/M	132/380	PSL, AZP, cycA	UC	AIH→PSC
Roberts	8 patients (4M, 4W)			UC (7/8)	PSC→AIH (1), simultaneous (2), AIH→PSC (5)
Wurbs	28/W	85/387	PSL, AZP	—	simultaneous
Gohlke	18/M	232/914	AZP, PSL, UDCA	—	AIH→PSC
	28/M	104/1202	PSL, AZP, UDCA	UC	AIH→PSC
	18/M	151/577	PSL, AZP, UDCA	EV	AIH→PSC
McNair	38/M	252/1245	PSL, AZP	UC, chr.cholecystitis	AIH→PSC
	20/W	320/1216	PSL, AZP, UDCA	—	simultaneous
	26/M	1750/156	PSL, AZP	—	AIH→PSC
	14/M	996/505	PSL, AZP	UC	AIH→PSC
	18/M	304/1115	UDCA, PSL, AZP	—	AIH→PSC
Koskinas	18/M	212/542	PSL, cycA, UDCA, AZP, LT	UC, pyoderma gangrenosum	AIH→PSC
Griga	24/W	240/779	UDCA, PSL	Crohn's disease	simultaneous
	28/W	300/274	UDCA, PSL	—	PSC→AIH

Author	PSC type	Treatment effect	Autoantibodies	HLA
Minuk	extra, intra	effect on ALT	ANA, aSMA	B8
	extra, intra	no effect	aSMA	ND
Rabinovitz	extra, intra	effect on ALT	ANA, aSMA	A1, B8, Bw6, DR3, DQw2, BRw52a
Leggett		effect on 2 pts	aSMA (2/3)	ND
Lawrence	intra	no effect	aSMA	ND
Roberts				
Wurbs	intra	effect on ALT, ALP	LP, aSMA	A1, A2, B8, B44, Bw4, Bw6, Cw7
Gohlke	intra	effect on ALT	ANA, aSMA, p-ANCA	A1, B8, DR3
	intra	effect on ALT	ANA, p-ANCA	A1, B8, DR3
	extra, intra	effect on ALT	ANA, aSMA, p-ANCA	A1, B8, DR3
McNair	intra	effect on ALT	ANA, aSMA, p-ANCA	B8, DR3
	extra, intra	effect on ALT	ANA, aSMA, p-ANCA	ND
	intra	effect on ALT, ALP	ANA, p-ANCA	A1, B8, DR3
	intra	effect on ALT	ANA, aSMA, p-ANCA	A1, B8, DR3
	extra, intra	effect on ALT, ALP	aSMA, p-ANCA	ND
Koskinas	intra	effect on ALT	ANA	A2, A32, B7, B21 (49), Bw4, Bw6, DR10, DR6 (13)
Griga	intra	effect on ALT, ALP	ANA, p-ANCA	ND
	extra, intra	effect on ALT	ANA, p-ANCA	B8, DR4

CsA: ciclosporin, LT: liver transplantation, EV: esophageal varices, UC: ulcerative colitis, LP: anti-liver-pomcreas antibody, ND: not done.

of PSC seems to raise the frequency of association of inflammatory bowel diseases. There was no evidence of inflammatory bowel disease in our case. One possible explanation for this is that the characteristics of PSC patients in Japan are different from those in other countries. The incidence of associated inflammatory bowel disease in Japanese patients with PSC is 21%, which is lower than that reported in other countries (20).

The nature of the relationship between AIH and PSC is not

known, although both diseases are believed to be caused by autoimmune reactions. As an abnormality of immunogenetic background, an association of HLA has been reported for both diseases. Previous studies have shown that both AIH and PSC are associated with HLA B8 and DR3 (19, 21), suggesting a common genetic basis. As shown in Table 2, B8-DR3 haplotype was observed in 77.8% of (7/9) AIH cases overlapping with PSC. Our case was positive not for B8-DR3 haplotype but for DR4, which is associated with a high degree of suscep-

tibility to disease in Japanese AIH patients (22). However, the relationship between HLA-DR4 and AIH overlapping with PSC is uncertain, because there have been no reports of AIH overlapping with PSC in Japan. In addition, autoantibodies such as ANA, aSMA and pANCA and hypergammaglobulinemia are found in both diseases. However, these markers show no disease specificity and can not explain the cause of AIH overlapping with PSC.

Immunosuppressive drugs such as prednisone, azathioprine and cyclosporine have been used for treating cases of AIH overlapping with PSC. The response of immunosuppressive therapy observed for normalization of ALT level, whereas ALP level may be amenable to UDCA (10). In our case, the ALT level normalized within 1 month after administration of prednisone, azathioprine, and UDCA, but the cholestatic enzyme level remained elevated. Since a good response to immunosuppressive therapy is observed in patients with hepatitis-like features, it is conceivable that the effect of treatment on cholestatic features is an important factor for predicting the prognosis of overlap of AIH and PSC. Diagnosis of this overlap syndrome and close monitoring are essential for determining the optimal time for liver transplantation.

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