Autoimmune Hepatitis Accompanied by Systemic Lupus Erythematosus

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Abstract

We report a series of five patients with autoimmune hepatitis (AIH) accompanied by systemic lupus erythematosus (SLE) (AIH-SLE overlap). Serologic tests showed that all patients were positive for antinuclear antibody and double-stranded DNA antibody. Histological examination of the liver showed that three of the patients had chronic hepatitis with severe activity. One of the other two had acute and severe hepatitis with submassive necrosis in both portal and lobular areas. The last patient already had liver cirrhosis. All patients had a mild form of SLE and showed a rapid response to corticosteroid. There was no serious involvement of organs other than the liver in any of the patients, and the prognoses were comparatively good in all patients.
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Key words: lupoid hepatitis, lupus hepatitis, anti-dsDNA antibodies, corticosteroid

Introduction

Autoimmune hepatitis (AIH) (lupoid hepatitis) is an autoimmune liver disease caused by the presence of autoantibodies, including antinuclear antibodies (ANA), and hypergammaglobulinemia. The pathohistological features of AIH in the liver are plasma cell and lymphocyte infiltration, and piecemeal necrosis in the portal tracts (1). Patients with AIH occasionally suffer from other autoimmune diseases.

Similarly, systemic lupus erythematosus (SLE) is an autoimmune disorder affecting multiple organs and complicated by other autoimmune diseases. In patients with SLE, increased serum levels of liver enzymes are common. Hepatotoxic drugs, viral hepatitis, and fatty liver are thought to be the main causes of hepatic lesions in patients with SLE (2–4). However, liver damage not due to any of the above factors has been seen in some patients with SLE. It is not clear whether such damage is caused by a primary liver disease such as AIH or a hepatic manifestation of SLE (5–7). Here, we describe five female patients who had histologically proven AIH accompanied by clinically diagnosed SLE.

Case Reports

Case 1

A 36-year-old woman presented in 1983 with Raynaud's phenomenon, arthralgia, butterfly-type facial erythema, dry mouth, and positive ANA. She was diagnosed as having SLE associated with Sjögren's syndrome and treated with prednisolone (PSL). Seven years later, at the age of 43 years, laboratory data showed severe liver dysfunction with elevated levels of aspartate aminotransferase (AST) (504 IU/*l*), alanine aminotransferase (ALT) (400 IU/*l*), γ globulin (4.29 g/dl) and IgG (4,491 mg/dl). The titer of ANA was 1 : 640, and its pattern was speckled. Anti-double-stranded DNA (anti-dsDNA) antibodies were also present. Histological examination of a liver biopsy sample revealed extensive necrosis of hepatocytes with severe infiltration of lymphocytes and plasma cells in the portal tracts (Fig. 1), findings compatible with submassive necrosis and severe activity frequently found in patients with AIH. Based on these clinical and pathological findings, she was diagnosed as having SLE-AIH overlap. Treatment with PSL (60 mg/day) and azathioprine (50 mg/day) was started. Liver functions were normalized within one month. The patient has been in remission for eight years since the diagnosis.

Case 2

A 21-year-old woman presented in 1986 with jaundice, edema, ascites, pleural effusion, hyperglobulinemia, and

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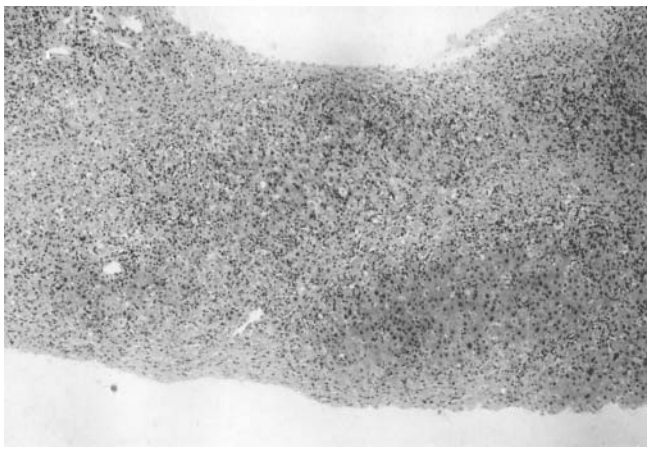

Figure 1. Pathohistological examination of a liver biopsy sample in case 1 showed submassive necrosis. Extensive necrosis of hepatocytes with severe infiltration of lymphocytes and plasma cells was noted in the portal areas.

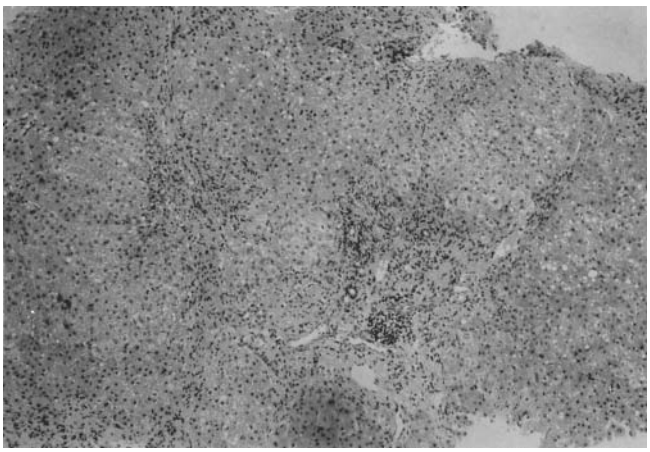

Figure 2. Pathohistological examination of a liver biopsy sample in case 2 showed piecemeal necrosis with severe infiltration of lymphocytes and plasma cells in the portal areas. Bridging fibrosis was also noted between portal areas.

positive ANA. The laboratory data revealed abnormal liver biochemistry: AST, 374 IU/*l*; ALT, 874 IU/*l*; total bilirubin, 4.2 mg/dl; and γ globulin, 4.1 g/dl. She was diagnosed as having SLE and treated with PSL (40 mg/day). Following an improvement in the symptoms, the dose of PSL was gradually reduced to 5 mg/day. Ten years later, at the age of 31 years, she presented with fever, arthralgia, and pleural effusion. Laboratory data were as follows: AST, 28 IU/*l*; ALT, 26 IU/*l*; cholinesterase, 93 IU/*l*; albumin, 3.0 g/dl; and γ globulin, 2.6 g/dl. The titer of ANA was 1 : 2,560, and its pattern was speckled. Both anti-dsDNA and anti-Sm antibodies were present. Thrombocytopenia and hypocomplementemia were also found. Histologically, the liver biopsy sample taken in 1986 showed piecemeal necrosis with severe infiltration of lymphocytes and plasma cells in some portal tracts and bridging fibrosis linking these portal tracts to others (Fig. 2). The one obtained ten years later showed cirrhosis with a macronodular pattern. These clinical and histological findings suggested that she had AIH-SLE overlap. She was treated with an increased dose of PSL (30 mg/day). Symptoms improved, and she has been in remission for eight years.

Case 3

A 28-year-old woman presented in 1977 with Raynaud's phenomenon. Twenty-eight years later, at the age of 56 years, she presented with leg edema and struma. Further examination revealed pericardial effusion and esophageal varices. Laboratory data were as follows: AST, 32 IU/*l*; ALT, 17 IU/*l*; cholinesterase, 146 IU/*l*; albumin, 3.4 g/dl; and γ globulin, 1.99 g/dl. The titer of ANA was 1 : 1,280, and its pattern was speckled. Antibodies to dsDNA, Sm, U1RNP, thyroglobulin and microsome were present. Pancytopenia and hypocomplementemia were also found. Histological examination of a liver biopsy sample showed severe fibrous extension in the portal tracts with portal-to-portal and portal-to-central vein bridging fibrosis, but no infiltration of inflammatory cells or piecemeal necrosis. These findings suggested that she had AIH-SLE overlap and Hashimoto's disease. She was treated with PSL at a dosage of 30 mg/day. The pericardial effusion and hypocomplementemia subsided rapidly. The patient has been in remission for three years.

Case 4

A 43-year-old woman presented in 1985 with facial erythema, arthralgia, and skin ulcer. She was diagnosed as having SLE and treated with PSL (20 mg/day) at another hospital. Three years later, at the age of 46 years, she presented with jaundice and general fatigue. Laboratory data were as follows: AST, 1,195 IU/*l*; ALT, 1,031 IU/*l*; total bilirubin, 6.2 mg/dl; and γ globulin, 1.99 g/dl. The titer of ANA was 1 : 1,280, and its pattern was speckled. Anti-dsDNA antibodies were present. Histological examination of a liver biopsy sample showed piecemeal necrosis with severe infiltration of lymphocytes and plasma cells in the portal tracts and also fibrous extension of the portal tracts. These findings suggested that she had AIH-SLE overlap. She was treated with PSL at a dosage of 40 mg/day, and liver function tests showed improvement. The patient has been in remission for twelve years.

Case 5

A 28-year-old woman presented in 1976 with jaundice, fatigue, fever, and hypergammaglobulinemia. Results of liver function tests were as follows: AST, 366 IU/*l*; ALT, 485 IU/*l*; total bilirubin, 5.9 mg/dl; and γ globulin, 4.8 g/dl. ANA was positive. The liver biopsy sample histologically

Table 1. Clinical Features of Patients with AIH Accompanied by SLE

Variables	Case No.				
	1	2	3	4	5
Age (yr)	43	21	56	46	28
Sex	F	F	F	F	F
ALT (IU/*l*)	400	874	17	1,031	485
TB (mg/dl)	1.4	4.2	0.6	15.8	5.9
WBC (/μl)	4,200	3,900	2,000	10,000	4,500
PLT ($\times 10^4$/μl)	24.1	7.4	12.4	25.3	11.1
ANA (1:)	640	2,560	1,280	160	640
aDS-DNAab	+	+	+	+	+
LE cell	–	+	–	–	+
aSmab	–	+	+	–	–
aSMAab	–	–	–	–	+
γ globulin (g/dl)	4.3	4.18	1.99	1.59	4.8
IgG (mg/dl)	3,997	4,500	2,225	2,059	4,900
CH50 (U/ml)	40	<10	20.5	33.4	22.6
HLA-DR	4, 8	2, 8	8, 9	nt	2, 4
Proteinuria	–	–	+	–	–
Fever	+	+	–	+	+
Liver histology	portal and lobular hepatitis, submassive necrosis	CAH→LC	LC	CAH	CAH
Therapy	PSL 30 mg + AZP 50 mg	PSL 30 mg	PSL 20 mg	PSL 40 mg	PSL 30 mg + AZP 100 mg
Outcome	remission	remission	remission	remission	remission

ALT: alanine aminotransferase, TB: total bilirubin, WBC: white blood cell, PLT: platelet, ANA: anti-nuclear antibody, aDS-DNAab: anti-double-strand DNA antibody, aSm: anti-Sm antibody, aSMA: anti-smooth muscle antibody, HLA: human leukocyte antigen, CAH: chronic active hepatitis, LC: liver cirrhosis, PSL: prednisolone, AZP: azathioprine.

showed piecemeal necrosis with moderate infiltration of lymphocytes and plasma cells in the portal tracts with fibrous extension of the portal tracts. She was diagnosed as having "lupoid hepatitis" and was treated with both PSL (60 mg/day) and azathioprine (50 mg/day). The dose of PSL was gradually reduced to 5 mg/day, and azathioprine was discontinued following clinical improvement. Four years later, at the age of 32 years, she presented with severe fatigue, fever, arthralgia, pleural effusion, facial erythema, sunburn and hematuria. Laboratory data were as follows: AST, 177 IU/*l*; ALT, 166 IU/*l*; and γ globulin, 2.6 g/dl. The titer of ANA was 1 : 640, and its pattern was speckled. Antibodies to dsDNA and smooth muscle were present. Thrombocytopenia and hypocomplementemia were also found. These findings suggested that she had AIH-SLE overlap. Lupus cystitis was also diagnosed on the basis of findings from a biopsy of urinary bladder mucosa. She was treated with PSL at a dosage of 30 mg/day, and the symptoms improved. She has been in remission for twenty years.

Clinical features of these five patients with AIH-SLE overlap are summarized in Tables 1 and 2.

Table 2. Clinical Features of Patients with AIH Accompanied by SLE Satisfying Criteria of SLE

Criterion	Case No.				
	1	2	3	4	5
Malar rash	+	+	–	+	+
Discoid rash	–	–	–	–	–
Photosensitivity	–	–	–	–	–
Oral ulcer	–	–	–	–	–
Arthritis	+	+	+	+	+
Serositis	+	+	+	–	+
Renal disorder	–	–	+	–	–
Neurogenic disorder	–	+	–	–	–
Hematologic disorder	–	+	+	–	–
Immunologic disorder	+	+	+	+	+
ANA	+	+	+	+	+

Discussion

All five patients described here showed the presence of ANA with a speckled pattern and of anti-dsDNA antibodies. Symptoms and laboratory data of all five patients fulfilled

the American College of Rheumatology (ACR) (formerly, the American Rheumatism Association) criteria for SLE (8). AIH was also diagnosed in all five patients on the basis of histological findings in liver biopsy samples of chronic active hepatitis, the presence of ANA and hypergammaglobulinemia. It was confirmed that the cause of the hepatic lesions in these patients was not viral infection, hepatotoxic drugs, or metabolic liver disease. Relatively high scores for AIH (14–17) based on the criteria of the International Autoimmune Hepatitis Group (9) were obtained in all patients. These high scores might have been due to the fact that all patients were women and had low alcohol consumption, and that none of them had a history of recent hepatotoxic drug usage or parenteral exposure to blood products. In addition to the high scores, histological findings and good response to treatment contributed to the definite diagnosis of AIH in the five patients.

Hepatic lesions due to the pathogenic process of SLE have been thought to be rare. However, recent studies have indicated that liver involvement in patients with SLE is of a more significant clinical importance than had been thought (6). Hepatomegaly was seen in 30 to 50% of patients with SLE (10), and elevated levels of liver enzymes was found in 19 (23.5%) of 81 patients (3). The difference between AIH and hepatic lesions in SLE has long been an indistinct issue. Oka reported that 5 (3%) of 162 patients with AIH satisfied the ACR criteria for SLE (11). Tamai et al also reported that 2 of 21 patients with AIH satisfied the criteria (12). On the other hand, hepatic lesions, whether chronic or acute, are thought to be relatively rare in patients with SLE. Runyon et al reported that only 4 (1.7%) of 238 patients with SLE had chronic active hepatitis or liver cirrhosis (6). Similarly, Matsumoto et al, who surveyed 1,468 Japanese patients with SLE, reported that only 17 (1.1%) of them had liver cirrhosis (13). In addition, there have been very few reported cases of AIH complicated with SLE. Thus, AIH and SLE overlap is a comparatively rare condition, although its exact frequency is not clear.

A prospective study revealed that about one-third of patients with SLE had elevated serum levels of transaminases not related to drugs or alcohol but associated with disease activity of SLE (14). AIH, previously called “lupoid hepatitis”, and SLE-associated hepatitis, also known as “lupus hepatitis”, have been defined as two different disease entities (15), although both are autoimmune disorders with polyarthralgia, hypergammaglobulinemia and positive ANA. Differentiation of SLE-associated hepatitis from AIH with extrahepatic manifestations is usually not easy.

Several histological and clinical features, however, have been suggested to be useful for discriminating AIH from SLE (4). Periportal piecemeal necrosis associated with lobular activity, rosetting of liver cells or dense lymphoid infiltrates is prominent in AIH, while, in SLE, inflammation is usually lobular and occasionally (peri) portal with a paucity of lymphoid infiltrates. Clinical and laboratory features of malar rash, pleural fluid, oral ulcer, leukopenia, proteinuria and hypocomplementemia are clearly indicative of SLE. However, it is difficult to distinguish SLE-associated hepatitis from AIH only by serologic tests. The five patients in the present study were all positive for anti-dsDNA antibodies which are found in both SLE and AIH and considered to be a nonspecific manifestation of inflammatory activity. The presence of anti-dsDNA antibodies is not related to histological findings, mortality or therapeutic response to glucocorticoid. As was expected, these antibodies disappeared in all five patients after steroid therapy was started. It has recently been reported that immunofluorescence for anti-dsDNA antibodies was negative in 52% to 86% of patients with AIH (16, 17) but positive in 80% to 90% of patients with active SLE. The conclusion is that AIH may be serologically different from SLE in that its frequency is low and positivity is transient.

Two of our five patients were also positive for anti-Sm antibodies, which are highly specific, though relatively insensitive, to SLE. Indeed, the presence of anti-Sm antibodies is included in the revised ACR criteria for the diagnosis of SLE, even though they are found in only about 20% to 30% of patients with SLE. Therefore, the presence of anti-Sm antibodies in patients with AIH suggests complication by SLE.

Analysis of HLA-DR with AIH demonstrated DR4 specificity (RR=14.8) in Japan (18). On the other hand, the association of HLA-DR2 with SLE is not strong (RR 2.74 for DR2 (DRB1*1501)) (19). According to this report, HLA DR4 was positive in two of the four patients tested, and HLA-DR2 was positive in 2 patients.

None of the five patients described here had severe symptoms of nephropathy or encephalopathy, which are characteristic of SLE, and all patients responded well to corticosteroid therapy and achieved complete recovery from both lupus symptoms and liver dysfunction. These results suggest that SLE and AIH lesions in patients with both diseases might be sensitive to corticosteroid therapy. The etiologies of AIH and SLE remain unknown, although various possible mechanisms have been proposed. To clarify them and establish diagnostic criteria, AIH complicated by SLE should be considered not as a part of the range of AIH, but rather as a category of AIH-SLE overlap.

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