Mod Rheumatol (2004) 14:169–173
DOI 10.1007/s10165-004-0286-5
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CASE REPORT

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Autoimmune hepatitis in a patient with systemic lupus erythematosus: a case report

Received: February 6, 2003 / Accepted: August 29, 2003

Abstract A 48-year-old woman was admitted to our hospital because of ascites. Laboratory data indicated the presence of systemic lupus erythematosus (SLE) with nephrotic syndrome and elevated hepatic enzymes. Treatment with prednisolone resulted in a marked clinical improvement in renal and liver dysfunction. Histopathologic analysis of renal and liver tissues showed lupus nephritis and liver cirrhosis, respectively. According to the autoimmune hepatitis scoring system, the patient had both SLE and autoimmune hepatitis.

Key words Autoimmune hepatitis · Scoring system · Systemic lupus erythematosus (SLE)

Introduction

Liver function test abnormalities are often found in patients with systemic lupus erythematosus (SLE).[1] The pathogenesis seems to vary greatly, and many factors such as hepatic congestion, vasculitis, cholestasis, viral hepatitis, fatty liver, drug-induced hepatitis, and autoimmune hepatitis (AIH) are involved in the process.[2] Indeed, a report from Japan revealed that 78 (40.4%) of 193 patients with SLE had liver function test abnormalities and that causes of the liver disease were identified in 35 (45%) of the 78 patients, including only 2 patients with AIH.[2]

Since Mackay et al. documented the presence of AIH, referred to as "lupoid hepatitis," during the 1950s,[3,4] AIH has been found to be characterized by chronic liver disease associated with positive autoimmune disease markers such as lupus erythematosus (LE) cells and antinuclear antibodies (ANAs).[3,4] Accordingly, clinical manifestations of AIH are, in part, similar to those of SLE; autoantibodies are positive in both diseases, and women are much more susceptible to the two diseases than men.[5] However, a specific immune reaction against hepatocytes in patients with AIH, which is independent of SLE, has been suggested by several investigators.[6]

Here, we report a patient who had liver cirrhosis probably caused by AIH during the clinical course of SLE. We also show the usefulness of the provisional scoring system for diagnosing AIH that was revised by the International Autoimmune Hepatitis Group in 1999.[7]

Case report

In 1993, a 48-year-old woman was diagnosed with discoid lupus erythematosus (DLE) based on the presence of immunoglobulin M (IgM) and complement depositions in erythematous areas of her face, neck, back, and hands. At that time, liver dysfunction was already present: aspartate aminotransferase (AST) 102 IU/l, alanine aminotransferase (ALT) 86 IU/l, alkaline phosphatase (ALP) 268 IU/l, γ-glutamyltransferase (GGT) 151 U/l. The skin lesions changed to scar or pigmentation without any medications when she was admitted to our hospital because of massive ascites in December 1998.

On physical examination, the patient appeared pale and edematous. Her temperature was 36.8°C, and the pulse was 68/min. Her blood pressure was 168/86 mmHg. Chest auscultation revealed normal vesicular breath sounds and heart sounds. The abdomen was soft and generally prominent, without tenderness or mass lesions. Hepatosplenomegaly

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could not be found. Both legs were edematous. Erythematous skin lesions or joint swelling could not be found.

A laboratory examination at admission (Table 1) showed anemia (hemoglobin 7.3 g/dl) and leukocytopenia (2250 cells/μl). The C-reactive protein was slightly increased to 1.23 mg/ml. Renal impairment was manifested by the elevated levels of blood urea nitrogen (BUN) 30 mg/ml and creatinine 1.8 mg/dl. Creatinine clearance was markedly decreased to 27.6 ml/min. Liver dysfunction was revealed as AST 112 IU/l and ALT 48 IU/l. The ALP activity was 471 IU/l. The serum levels of total protein and albumin were 6.0 g/dl and 1.7 g/dl, respectively. Coagulation parameters were normal except for slightly elevated levels of fibrinogen (377 mg/dl) and thrombomodulin (17.8 FU/ml). The serum levels of complement 3 (C3) and complement 4 (C4) were reduced to 30 mg/dl and 12.1 mg/dl, respectively, whereas the level of immune complexes was elevated to C1q 4.1 μg/ml. Serum levels of immunoglobulins were also increased with a polyclonal pattern (IgG 2853 mg/dl, IgM 383 mg/dl, IgA 734 mg/dl). With respect to autoantibodies, the patient was positive for ANA and anti-dsDNA. Tests for hepatitis virus markers such as hepatitis B virus surface antigen (HBsAg) and anti-hepatitis C virus (anti-HCV) as well as HBV-DNA and HCV-RNA determined by the polymerase chain reaction (PCR) and reverse transcription (RT)-PCR, respectively, were negative.

Urinalysis showed 4+ proteinuria and 3+ occult blood. The amount of proteinuria was approximately 5.2 g/day, and the urine sediment contained 10–20 erythrocytes and 5–10 leukocytes per high-power field without cellular casts.

The abdominal echogram and computed tomography (CT) scan showed enlargement of the left lobe of the liver, mild splenomegaly, and marked ascitic fluid retention; and the aspirated fluid was a transudate containing a few noninflammatory cells. These findings suggested that the patient had SLE with nephrotic syndrome in an active stage. In addition, according to the scoring system revised by the International Autoimmune Hepatitis Group in 1999,[7] she had definite AIH with a pretreatment score of 16 (Table 2).

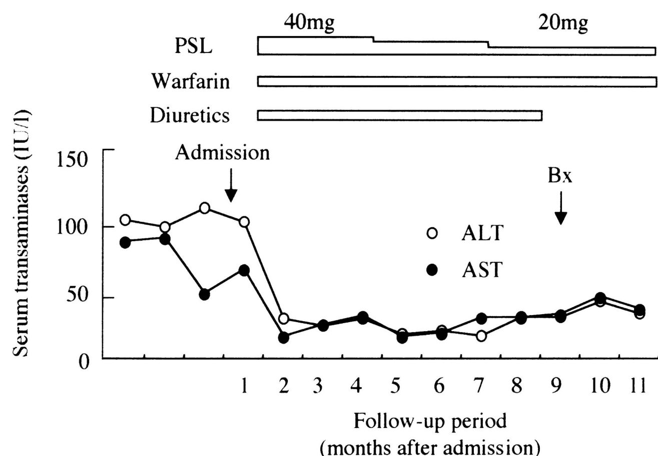
Treatment with predonisolone (PSL) 40 mg/day and warfarin 2 mg/day was started. The increased serum levels of BUN and creatinine as well as the elevated hepatic enzyme levels at admission promptly returned to normal after the treatment. Creatinine clearance was restored to 84.6 ml/min, and the amount of proteinuria was decreased to less than 1 g/day. Consistent with these results, the leg edema and ascites gradually diminished, and both had disappeared completely 9 months after the start of PSL treatment (Fig. 1).

We then performed ultrasonography-guided renal biopsy and peritoneoscopy-guided liver biopsy. The renal biopsy specimen showed apparent membrane thickening (Fig. 2A) with marked deposition of IgG, IgM, C3, and C1q on the glomerular basement membrane (Fig. 2B), which was classified as lupus nephritis type Va using the World Health Organization (WHO) classification. Peritoneoscopy indicated macronodular cirrhosis (Fig. 3A). Histopathological examination showed bridging necrosis with regenerative nodule and rosetting of liver cells (Fig. 3B). When the AIH

Table 1. Laboratory results

Peripheral blood	
WBC count	2250/μl
Neutrophils	47%
Lymphocytes	42%
Monocytes	11%
RBC count	256×10^4/μl
Hemoglobin	7.3 g/dl
Hematocrit	25.8%
Platelets	6.9×10^4/μl
Biochemistry	
Total protein	6.0 g/dl
Albumin	1.7 g/dl
Total bilirubin	0.4 mg/dl
AST	112 IU/l
ALT	48 IU/l
LDH	419 IU/l
ALP	471 IU/l
GGT	52 IU/l
Total cholesterol	150 mg/dl
Blood urea nitrogen	30 mg/dl
Creatinine	1.8 mg/dl
Sodium	142 mEq/l
Chloride	115 mEq/l
Potassium	4.2 mEq/l
Glucose	92 mg/dl
Coagulation studies	
PT	0.98 INR
APTT	25.9 s
Protein C	78%
Protein S	84%
Antithrombin III	63%
Lupus anticoagulant	41.5 sec
Anti-phospholipid Ab	48 U/ml
Anti-β2 GP1 Ab	–
Urinalysis	
Gravity	1.010
Protein	4+
Occult blood	3+
Glucose	–
Urobilinogen	–
Cell casts	
Creatinine clearance	27.6 ml/min
Serology	
C-reactive protein	1.23 mg/dl
Hepatitis B surface antigen	–
Anti-Hepatitis C Ab	–
Hepatitis C virus RNA	–
Hepatitis B virus DNA	–
IgG	2853 mg/dl
IgA	734 mg/dl
IgM	383 mg/dl
ANA	×640
Anti-dsDNA Ab	196.0 IU/ml
Anti-ssDNA Ab	315.0 AU/ml
C3	30 mg/dl
C4	12.1 mg/dl
C1q	4.1 μg/ml
Anti-smooth muscle Ab	–
Anti-liver kidney microsome Ab	–
ESR	32 mm/h

Ab, antibody; APL, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APTT, activated partial thromboplastin time; ESR, erythrocyte sedimentation rate; GGT, γ-glutamyltransferase; Ig, immunoglobulin; LDH, lactate dehydrogenase; PT, prothrombin time; RBCs, red blood cells; WBCs, white blood cells



Ccr (ml/min)	27.6	46.8	91.2	84.6
Proteinuria (g /day)	5.2	4.2	3.7	0.9
Alb (g /dl)	1.7	2.2	3.1	3.7
C3	30	59	87.7	128
C4	12.1	13.8	12.6	17.3
Anti-dsDNA	196	29.0	11.3	3.9

Fig. 1. Clinical course of the patient. *Alb*, albumin; *ALT*, alanine transaminase; *AST*, aspartate transaminase; *Bx*, biopsy; *C3*, *C4*, complements 3 and 4; *Ccr*, creatinine clearance; *PSL*, prednisolone

Table 2. Diagnosis of autoimmune hepatitis in our patient according to a scoring system by the International Autoimmune Hepatitis Group[7]

Parameters/features	
Female	+2
ALP/AST (or ALT) ratio	1.5–3.0 ± 0
Serum globulins or IgG >2.0	+3
ANA, SMA, or LKM-1 >1:80	+3
Hepatitis viral markers negative	+3
Drug history negative	+1
Average alcohol intake < 25 g/day	+2
Liver histology	+5
Other autoimmune diseases	+2
Response to therapy: complete	+2
Aggregate score	
Before treatment	16 (>15; definite AIH)
After treatment	23 (>17; definite AIH)

score was reevaluated after PSL treatment, the score was increased to 23 owing to the positive liver histology and response to therapy (Table 2).

Discussion

Elevated serum aminotransferases are frequently found in patients with SLE during the clinical course of the disease, although the elevations are usually mild and transient, as they are related to disease activity. They probably are due to subclinical liver disease with an almost total absence of severe liver involvement in these patients.[1,2] In contrast, several studies have shown the presence of chronic active hepatitis with a poorly defined pathogenesis in some patients with SLE.[1,2,6]

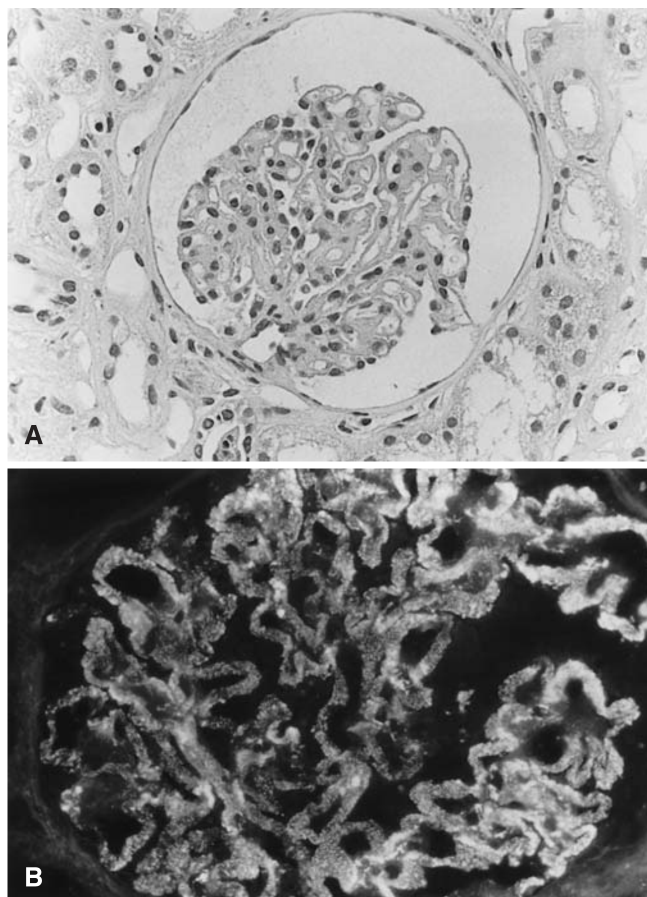


Fig. 2. Histopathologic findings of renal biopsy specimen. **A** Membrane thickening in the glomerulus. Similar lesions were detected in almost all glomeruli on the specimen, indicating that the patient had lupus nephritis WHO type Va. H&E. **B** Direct immunofluorescence microscopy showing marked staining for immunoglobulin (IgG). Similar staining for IgA, IgM, C3, and C1q is observed

It has been reported that liver dysfunction is found in 21%–55% of SLE patients.[2,8,9] In 15%–42% of these cases it was associated with the SLE itself. Suzuki et al.[2] analyzed liver diseases in 193 patients with SLE and found abnormal aminotransferase levels in 78 (40.4%). Among them were 12 patients in whom no cause could be found other than the SLE. In 23 patients the liver diseases were identified as follows: AIH in 2 cases, primary biliary cirrhosis (PBC) in one case, virus infection in 6 cases, drug allergy in 2 cases, fatty liver in 9 cases, gallstones or cholecystitis (or both) in 3 cases.[2] Matsumoto et al. performed an autopsy study involving 73 Japanese patients with SLE.[10] They revealed that hepatic arteritis occurred in 15.1%, periportal (chronic active) hepatitis (probably AIH) or cirrhosis in 2%, PBC in 2.7%, and nodular regenerative hyperplasia (NRH) in 6.8%, in association with SLE. Virus hepatitis or cirrhosis occurred in 4.1%, drug-induced hepatitis or cholangitis (or both) in 2.7%, hepatic congestion in 71.2%, and fatty liver in 72.6%. The causes of liver abnormalities in SLE patients were summarized as follows: (1) SLE itself, (2) liver abnormalities associated with SLE (AIH, PBC, NRH), (3) thrombotic events regardless of whether associated with the lupus

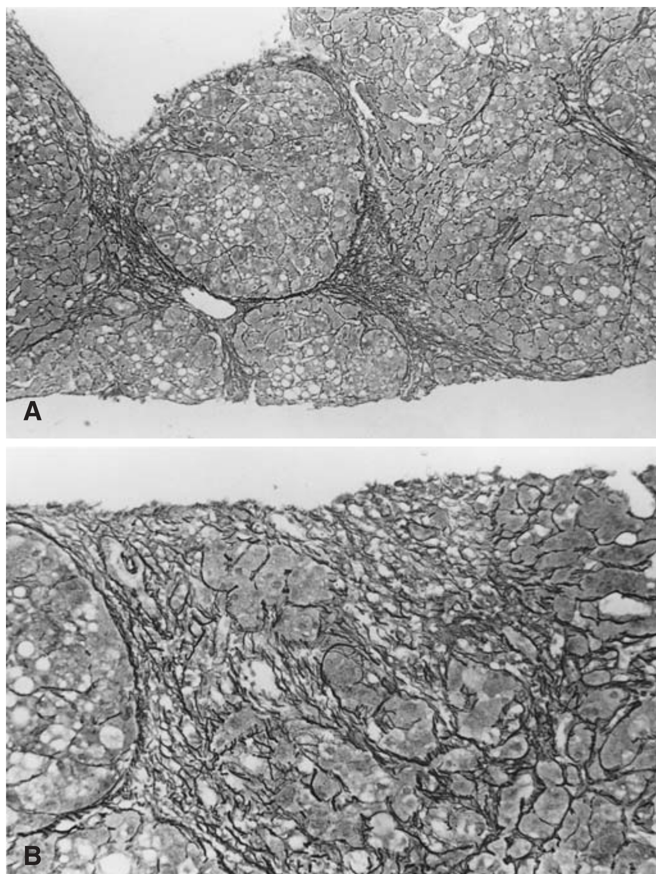


Fig. 3. Histopathologic findings of liver biopsy specimen. Note the bridging necrosis (**A**) and rosette formation (**B**) of the hepatocytes. Silver stain

anticoagulant, (4) viral hepatitis or liver cirrhosis, (5) drug-induced hepatitis, (6) other liver diseases (e.g., hepatic congestion, fatty liver).[1,2]

In the present case, the patient satisfied the criteria for SLE set forth by the American Rheumatism Association (discoid rash, pancytopenia, proteinuria, positive anti-double-stranded DNA antibody, and positive ANA). She developed active SLE during the course of DLE. At the onset of DLE, she already had moderately elevated serum aminotransferase levels. She was negative for HBV and HCV even using PCR and RT-PCR, respectively. She had no history of alcohol or hepatotoxic drug intake. She also had a moderately elevated serum IgG level and was positive for autoantibodies. Antibodies to smooth muscle and mitochondria were negative. The abdominal echogram and CT scan showed a liver cirrhosis pattern and massive ascitic fluid retention, although there was no evidence of particular changes in her liver. According to the clinical data mentioned above, it was suggested that her liver dysfunction was associated with either AIH or the SLE itself. Moreover, it occurred before the SLE.

It is sometimes difficult to clarify whether AIH occurs in patients with SLE. Indeed, this patient had SLE in an active stage. Both conditions are associated with features of autoimmunity such as polyarthralgia, hypergammaglobulinemia, and a positive ANA. Both usually show a favorable response to corticosteroid therapy.[11] However, periportal piecemeal necrosis variably associated with lobular activity, rosetting of liver cells, and dense lymphoid infiltrates are prominent in AIH. In contrast, in SLE the inflammation is usually lobular and occasionally periportal with a paucity of lymphoid infiltrates. Antibodies to smooth muscle (anti-actin) are found in 60%–80% of AIH patients but also in 30% of SLE patients. Other autoantibodies such as anti-liver-specific protein or, more specifically, antibody to its main constituent, the asialoglycoprotein receptor, are often present in patients with AIH.[12,13] The complications and therapy of AIH are different from those of SLE. Ulcerative colitis is frequently complicated with AIH but not as frequently with SLE. In addition, the activity of AIH in patients with SLE is likely to be underestimated when the two conditions coexist.

The International Autoimmune Hepatitis Group proposed a scoring system for the diagnosis of AIH in 1993.[14] Following its appearance, both the descriptive criteria and the scoring system have been widely used by many investigators, although the pathogenesis of AIH remains to be determined.[6,15] In 1999, the revised form was described by the same group.[7] The revised criteria and scoring system included serum biochemistry (any abnormality in serum aminotransferases), serum immunoglobulins, serum autoantibodies, viral markers, liver histology, other etiological factors (e.g., alcohol or hepatotoxic drugs), and response to therapy.

According to the scoring system described in 1999,[7] our patient's pretreatment score was 16 (>15 indicates definite AIH), indicating that she had definite AIH. At that point, almost all etiologies of liver abnormalities were excluded. After PSL treatment, elevated levels of hepatic enzymes promptly returned to normal levels. In addition, histopathological examination of the liver tissue revealed the presence of liver cirrhosis with rosette formation of liver cells. Thus, her posttreatment AIH score was increased to 23, where a score of >17 indicates definite AIH. These results suggest that the patient had both SLE and AIH.

Conclusions

Histopathological analysis of the liver tissue is important for clarifying the pathogenesis of liver function test abnormalities and completing the scores using AIH criteria in patients with SLE. The proposed criteria were applied to our patient with SLE in the presence of periportal (chronic, active) hepatitis in the liver biopsy. The signs of interfacing hepatitis – predominantly lymphoplasmacytic infiltrate and rosetting of liver cells – are positive parameters that might be needed. Therefore, we suggest that the scoring system for diagnosis of AIH is useful even in a patient with SLE.

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