

Autoimmune Hepatitis-systemic Lupus Erythematosus Overlap Syndrome Diagnosed after Tapering Immunosuppressive Therapy

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The differential diagnosis of systemic lupus erythematosus (SLE) and autoimmune hepatitis (AIH) is difficult due to the resemblance of these two disorders. However, the accurate diagnosis is important for prognosis and treatment that are different from each other. We report a case of AIH-SLE overlap syndrome which tapering of prednisone and azathioprine therapy deteriorated the condition of a patient due to flare up of SLE. The patient was a 28-year-old woman diagnosed as AIH. After administrations of prednisone and azathioprine, her condition was improved. During dose reduction, she was admitted to our hospital as fever and dyspnea. She diagnosed as lupus nephritis. After high dose treatment with corticosteroids and azathioprine, she recovered. Once the diagnosis of autoimmune disease such as SLE or AIH has been made, clinicians should also be fully aware of concomitant other autoimmune disease.

Key Words: Autoimmune hepatitis, Overlap syndrome, Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a typical systemically-infiltrating autoimmune disease that is characterized by formation of autoantibodies. SLE has a multitude of clinical manifestations in the skin, joint, kidney, lung, hematopoietic organs, as well as the neurologic and the cardiovascular system. SLE may show various clinical phases and disease progressions unique to each patient, and that the SLE diagnosis can be difficult in the early stage of pathogenesis [1]. Autoimmune hepatitis (AIH) is an autoimmune disease that causes inflammation of the

liver. AIH may develop at all ages, but young females with an age of 15 to 25 years and menopausal women with an age of 45 to 60 years are frequently afflicted with this disease [2]. AIH shows auto-antibodies in the blood, causes hyperglobulinemia, and characteristically displays inflammation in the vicinities of the hepatoportal system and tissue necrosis. Abnormal liver function is reported in about 25% to 50% of SLE patients, but hepatic involvement in the way of SLE is not common. Generally, viral hepatitis, drug induced liver injuries, hepatic congestion or vasculitis are known to cause abnormalities of the liver in SLE patients. Accordingly, the differential diagnosis of SLE hepatitis and AIH is difficult due to the resemblance of these two disorders. Nevertheless, accurate diagnosis is important for prognosis and treatment that are different from each other [3]. Therefore, we report a case of ALH-SLE overlap syndrome, showed improvement after immunosuppressant treatment following the diagnosis of AIH, which flares up as the doses of immunosuppressant are tapered off.

Case Report

A 28-year-old female patient was admitted to this hospital due to increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels for the health examination. The patient suffered from fatigue for the last two months. She did not have any remarkable finding in her past medical history and family history, and did not administer any drug, drink alcohol, or smoke cigarettes. She showed an ill-looking appearance. Her vital signs showed a blood pressure of 110/70 mmHg, a heart rate of 72 beats/min, a respiratory rate of 20 breaths/min, and a temperature of 37°C. There were non-specific findings on physical examination. She had neither hepatomegaly nor splenomegaly. Other than that,

laboratory test showed white blood cell (WBC) count of 2,500/ μ L, hemoglobin 13.9 g/dL, platelet 159,000/ μ L, prothrombin time 13.9 seconds (92%, international normalized ratio 1.05), AST 352 IU/L, ALT 382 IU/L, alkaline phosphatase 1,430 IU/L, gamma-glutamyl transferase 314 IU/L, total bilirubin 0.60 mg/L, direct bilirubin 0.25 mg/L and blood urea nitrogen/creatinine 20/0.41 mg/dL. Results for viral markers including hepatitis B surface antigen, anti-hepatitis C virus, hepatitis A virus immunoglobulin M antibody were negative, hepatitis B virus surface antibody was positive. Urinalysis showed no evidences of proteinuria and hematuria.

The ceruloplasmin and 24-hour urine copper levels and the Kayser-Fleischer ring, which were carried out in order to rule out Wilson's disease, were negative. A serologic test showed the levels of immunoglobulin G 2,765 mg/dL, immunoglobulin A 581 mg/dL and immunoglobulin M 37.16 mg/dL. It also showed positive antinuclear antibodies (1:640, homogenous type), positive anti-smooth muscle antibody, negative anti-liver/kidney microsomes antibody, and negative anti-mitochondrial antibodies. Human leukocyte antigen type was DR4.

Abdominal ultrasound showed no evidence of biliary obstruction, but showed heterogeneities of the liver, as well as hepatomegaly and splenomegaly. The liver biopsy revealed interface hepatitis and periportal fibrosis, in which there are lymphocytes and plasmacytes which infiltrate periportal area, porto-central bridging necrosis, and intralobular inflammation (Fig. 1). In consideration of such histopathologic and hematologic findings, the AIH score for this patient in accordance with the revised diagnostic criteria of the International Autoimmune Hepatitis Group was 19 points, corresponding to a definitive AIH diagnosis. This patient was administered with 1 mg/kg prednisolone and 50 mg azathioprine daily. Her symptom of fatigue improved after the treatment. On the seventh day of treatment,

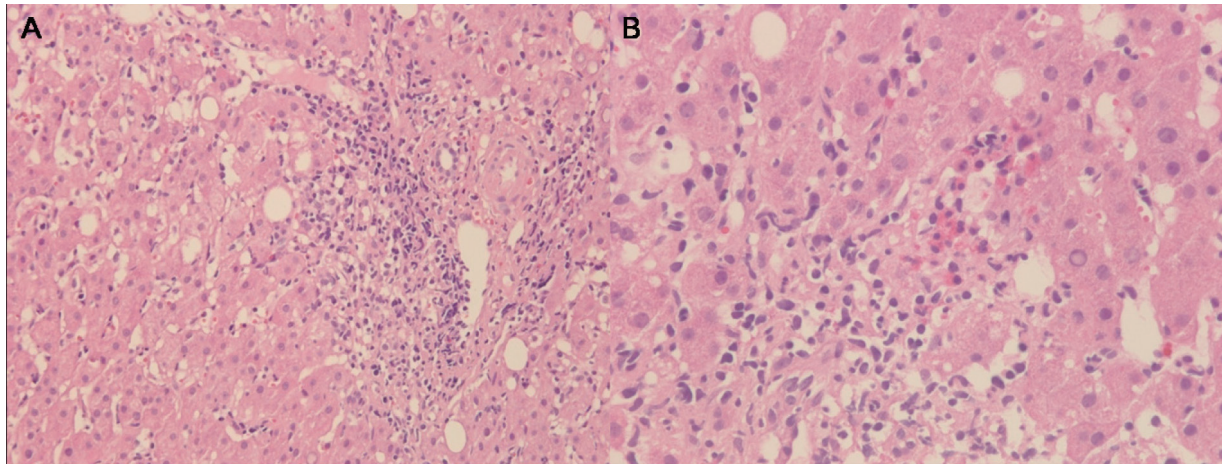


Fig. 1. Microscopic findings of liver biopsy. (A) Marked porto-periportal activity is shown (H&E stain × 200). (B) Focal foci eosinophilic infiltration is noted (H&E stain × 400).

her laboratory test showed improvement with liver function test showing AST 99 IU/L and ALT 124 IU/L. Thus, the drug dosages were carefully tapered and maintenance dosages were reduced to 20 mg prednisolone and 25 mg azathioprine daily in outpatient department. However, the patient was suddenly admitted to the emergency department with chief complaints of mildly-laborious breathing difficulty and fever after one month. The physical examination showed jaundice, hepatomegaly, and bilateral edema of wrists. Her vital signs were a blood pressure of 120/80 mmHg, a heart rate of 100 beats/min, a respiratory rate of 20 breaths/min, and a temperature of 38.3°C. The blood test revealed WBC 2,100/ μ L, hemoglobin 7.1 g/dL and platelet 116,000/ μ L. Peripheral blood smear, decreased haptoglobin, and positive direct Coombs' test showed findings that concur with the diagnosis of hemolytic anemia. The laboratory test showed AST 246 IU/L, ALT 138 IU/L, alkaline phosphatase 1,265 IU/L, gamma-glutamyl transferase 2,259 IU/L, total bilirubin 18.9 mg/L, direct bilirubin 6.6 mg/L, total protein 6.3 g/dL, albumin 2.5 g/dL, prothrombin time 15.5 seconds (international normalized ratio 1.21).

Urinalysis revealed hematuria (++) and proteinuria (++) , while erythrocyte sedimentation rate and C-reactive protein increased with levels showing 38 mm/hr, and 24.5 mg/L, respectively. The laboratory test showed positive antinuclear antibody (1:640, homogenous type), positive anti-double strand DNA antibody, negative lupus anticoagulant, negative anti-cardiolipin antibody, and normal levels of C3 and C4 quantitative test. Proteinuria was evident with the level of 24-hour urine protein of 904.64 mg/day. The histologic test of the kidney led to the diagnosis of Class 1 lupus kidney disease by WHO Classification (Fig. 2). Among eleven components of the American College of Rheumatology (ACR) criteria for SLE diagnosis, she had components of 1) histologically-confirmed lupus nephritis, 2) leukopenia, 3) abnormal hematologic finding of hemolytic anemia, 4) positive anti-nuclear antibodies, and 5) positive anti-dsDNA antibodies, confirming the diagnosis of SLE. The patient was started with 1 mg/kg methyl prednisolone and 400 mg hydroxychloroquine daily. As the dose of methyl prednisolone was reduced, azathioprine 1 mg/kg per day was added. Then, her clinical symptoms improved, as well as her laboratory test,

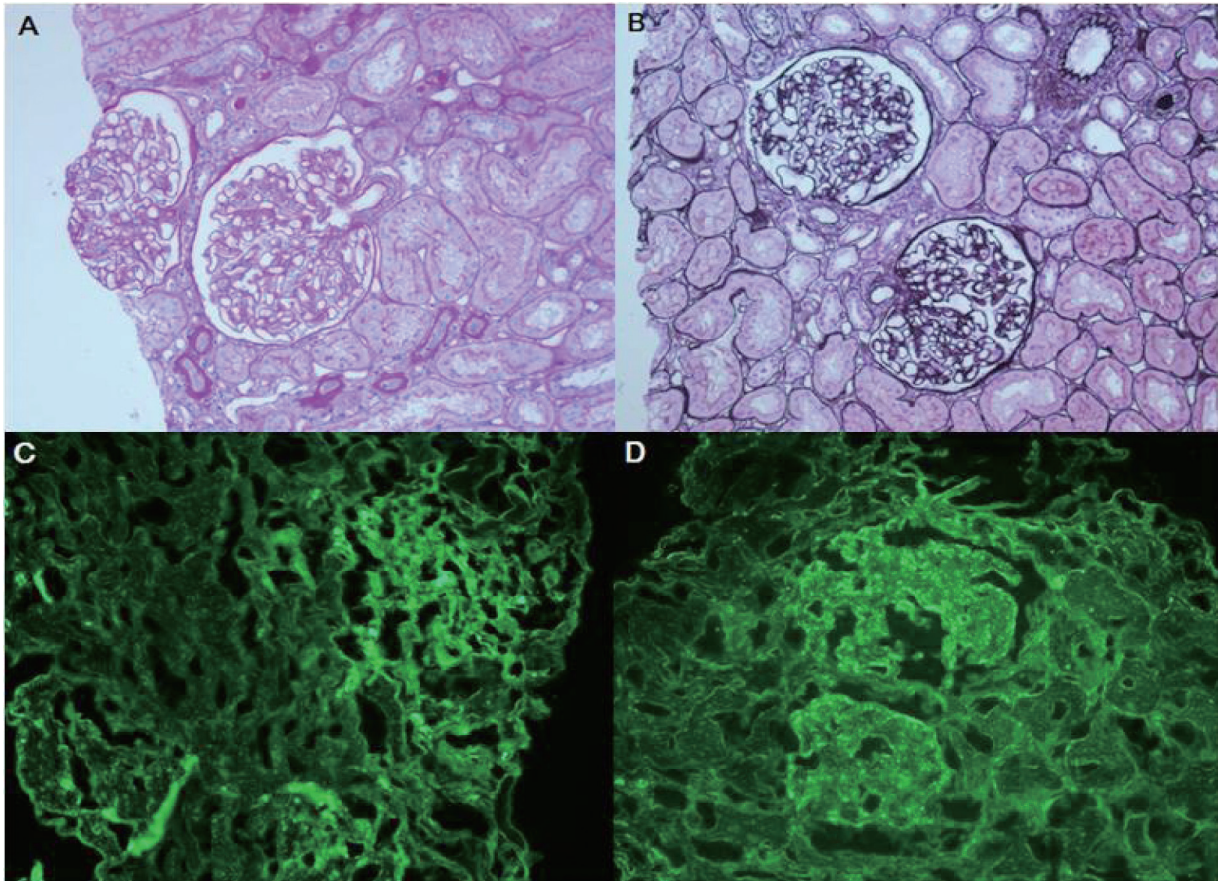


Fig. 2. Microscopic findings of kidney biopsy. (A) Slightly enlarged glomeruli are seen (PAS stain, $\times 200$). (B) Thin capillary wall is noted (Silver stain $\times 200$). (C) C3 deposit is noted (IF stain $\times 200$). (D) IgG deposit is noted (IF stain $\times 200$).

including proteinuria, also improved. She was discharged from the hospital and has been followed up on an out-patient department.

Discussion

Although SLE and AIH are different kinds of diseases, they are similar aspects in female dominance, genetic disposition, multiple joint pains, hyper-gammaglobulinemia, presence of autoantibodies, effective steroidal treatment, and others [4]. However, AIH has morbidity for advanced

liver disease, while SLE has morbidity for end stage renal disease. With respect to treatment and prognosis of each disease, different issues of importance are dealt with, making it necessary to differentiate between these two diseases. AIH, which had been designated as lupoid hepatitis in the past, was hematologically defined as a type of chronic autoimmune disease with clinical manifestations of SLE. The 1993 International Autoimmune Hepatitis Group incorporated a scoring system for past medical history, laboratory findings, genetic factors, histologic test of the liver, response to treatment, and others. The International Autoimmune Hepatitis Group

suggested the diagnostic criteria with the scoring system in order to make differential diagnosis between SLE-accompanied hepatitis and AIH [5,6]. Nevertheless, it is not easy to make a differential diagnosis of AIH and lupus hepatitis with such diagnostic criteria alone.

Although ANAs are important serological markers of both AIH and SLE, ANA is not specific and includes various spectrums of autoantibodies. Anti-RNA, anti-dsDNA, anti-SSA, anti-SSB, and anti-histone antibodies were found in the early stage of SLE. Despite anti-dsDNA is specific for diagnosis of SLE, patients with AIH have 23% incidence of anti-dsDNA positivity showing lower titer [7]. Anti-SMA showed highly sensitive in AIH, but some SLE patients with liver involvement has positivity of anti-SMA. Anti-RNP antibody was present in 44% of SLE patients, however did not showed in AIH patients. Therefore, anti-RNP antibody could help the differential diagnosis between AIH and SLE hepatitis [8].

Pathologic findings are crucial in differential diagnosis between AIH and SLE hepatitis. The presence of cirrhosis or periportal hepatitis, periportal piecemeal necrosis associated variably with lobular activity, and rosette formation of hepatocytes are critical findings for the diagnosis of AIH, but do not exclude SLE. The presence of only lobular hepatitis is more compatible with SLE. In both SLE hepatitis and treated AIH, the inflammatory infiltrate consists mainly of lymphocytes, whereas in untreated AIH, these cells are mixed with plasma cells [9-11].

Our patient had interface hepatitis and periportal fibrosis, in which there are lymphocytes and plasmocytes which infiltrate periportal area, porto-central bridging necrosis, and intralobular inflammation. ANA and anti-SMA antibody were the positive serological markers; its positivity is sufficient to diagnose definite AIH as a total score of 19 points by the above criteria before initiating the treatment. Then, combination therapy of steroids and azathioprine led to

improvement in the clinical presentation and liver function tests. However, as the doses were tapering, the patient suddenly developed dyspnea. The diagnosis of SLE was confirmed by the diagnostic criteria set by the ACR [12]. Notwithstanding, the common aspects of these two diseases, the identification of lupus nephritis through pathologic examinations of the liver and kidney led to the diagnosis of an overlap syndrome of AIH and SLE. As such, there have been reports that satisfy the diagnostic criteria of both SLE and AIH simultaneously, when SLE patients show abnormal results of liver function test [13,14]. However, up to now, there has been no previous case report, in which a patient is diagnosed as having an AIH, treated with steroids and azathioprine with an improved outcome in clinical symptoms and laboratory tests, which led to tapering of the doses. During tapering of the doses, the patient was admitted due to respiratory difficulties and proteinuria, then kidney biopsy confirms the diagnosis of SLE.

Our patient did not have abnormalities of renal functions in the early diagnostic phase of AIH. However, owing to the presence of microscopic hematuria and proteinuria, the consideration of a possibility of SLE development and additional laboratory tests could avoid symptomatic exacerbation during the treatment. Therefore, once the diagnosis of autoimmune disease such as SLE or AIH has been made, clinicians should also be fully aware of concomitant other autoimmune disease.

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