

## A Case of Cholestatic Autoimmune Hepatitis and Acute Liver Failure: an Unusual Hepatic Manifestation of Mixed Connective Tissue Disease and Sjögren's Syndrome

Although hepatomegaly is reported to occur occasionally in patients with mixed connective tissue disease (MCTD) or Sjögren's syndrome (SS), autoimmune liver diseases such as primary biliary cirrhosis, sclerosing cholangitis, and autoimmune hepatitis in association with MCTD or SS have rarely been described. We report a case of severe cholestatic autoimmune hepatitis presenting with acute liver failure in a 40-yr-old female patient suffering from MCTD and SS. The diagnosis of MCTD and SS was made at the age of 38. The patient presented severe jaundice and elevation of conjugated bilirubin. The patient denied alcohol and drug use and had no evidence of viral hepatitis. On the 8th day of her hospitalization, the patient developed grade III hepatic encephalopathy. She was diagnosed as autoimmune hepatitis presenting with acute liver failure based on clinical features, positive FANA and anti-smooth muscle antibodies, negative anti-mitochondrial antibodies, high titers of serum globulin, liver biopsy findings, and a good response to corticosteroid therapy. The patient was managed with prednisolone and the clinical symptoms, liver function test results, and liver biopsy findings showed much improvement after steroid therapy.

**Key Words :** Hepatitis; Mixed Connective Tissue Disease; Sjögren's Syndrome

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### INTRODUCTION

Autoimmune hepatitis (AIH) is characterized by chronic necro-inflammation of the liver of unknown cause, in which immune reactions against host antigens are found to be the major pathologic mechanism. Autoimmune hepatitis can be associated with a number of other autoimmune diseases (1). Liver involvement, except hepatomegaly, is rare in patients with mixed connective tissue disease (MCTD) or Sjögren's syndrome (SS). Only two cases of AIH associated with MCTD and SS have been reported in the literature (2, 3). The clinical features of autoimmune hepatitis vary from asymptomatic, in which the disease is discovered when abnormal serum enzyme levels are detected during a screening examination, to a severe, acute, and even fulminant hepatitis (4). Cholestatic liver dysfunction is a rare clinical manifestation of AIH. Unlike primary biliary cirrhosis and sclerosing cholangitis, AIH responds favorably to steroid therapy (5).

We describe a patient with MCTD and SS presenting with severe cholestatic AIH and acute liver failure, whose liver function abnormalities resolved after steroid therapy.

### CASE REPORT

A 40-yr-old woman was admitted to the hospital because of progressive jaundice over two months. Two years before admission, the patient was diagnosed to have an overlap syndrome of MCTD and SS. The diagnosis of MCTD was made by the presence of high titer of anti-ribonucleoprotein antibodies, edema of both hands, synovitis, Raynaud's phenomenon, and acrosclerosis. Sjögren's syndrome was diagnosed by the presence of dry mouth, dry eyes, rheumatoid factor, anti-Ro antibodies, positive results of a Schirmer's test, salivary scintigraphy, and labial salivary gland biopsy. She had been intermittently treated with prednisolone (10 mg/day), but had not taken any medications during the previous three months. She denied ethanol ingestion and recent use of hepatotoxic drugs.

On physical examination, the patient appeared acutely ill. Her temperature was 37°C, pulse rate 108/min, respiration rate 26/min and blood pressure was 110/70 mmHg. Anemic conjunctiva and icteric sclera were observed. Auscultation of the heart and both lungs were normal. The abdomen was soft with normal bowel sounds. The edge of the liver

descended 2.5 cm below the right costal margin.

Her initial laboratory findings were as follows: hematocrit 25.1%, leukocyte count 18,400/ $\mu$ L (33.7% neutrophils, 57.2% lymphocytes, 5.9% monocytes, 3.1% basophils), platelet count 151,000/ $\mu$ L, glucose 125 mg/dL, urea nitrogen 14.0 mg/dL, creatinine 1.5 mg/dL, total serum protein 8.1 g/dL, albumin 2.3 g/dL, aspartate aminotransferase 383 IU/L, alanine aminotransferase 149 IU/L, total bilirubin 26 mg/dL, conjugated bilirubin 25.3 mg/dL, alkaline phosphatase 164 U/L, LDH 1,316 IU/L,  $\gamma$ -GTP 63.0 U/L, total cholesterol 61.0 mg/dL, calcium 7.8 mg/dL, phosphorus 2.6 mg/dL, and haptoglobin 20.7 mg/dL. Test results for sodium, potassium, chloride, magnesium, and triglyceride were all within normal limits. International normalized ratio for prothrombin time was 1.25, and the activated partial thromboplastin time was 46.4 sec. The patient's reticulocyte count was 4.4%. Direct Coombs test was positive, while an indirect Coombs test was negative.

The concentrations of IgG, IgA, and IgM were 4,630 mg/dL, 397 mg/dL, and 311 mg/dL, respectively. Serum electrophoresis showed polyclonal gammopathy. The serum circulating immune complex was 1.39  $\mu$ g/mL (normal <1.23  $\mu$ g/mL), C3 26 mg/dL (normal 50-90), and C4 10 mg/dL (normal 10-40). A test for anti-nuclear antibodies was positive, at a titer of 1:2,560, with a speckled pattern of staining. Tests for the rheumatoid factor, anti-RNP, anti-SSA, and anti-smooth muscle antibodies were all positive. Tests for antibodies to ds DNA, Sm, SSB, mitochondria, liver-kidney microsome, platelets, cardiolipin antibodies, and lupus anticoagulant were all negative. A test for hepatitis A IgG antibodies was positive. Tests for hepatitis A IgM antibodies, hepatitis B surface antigen and antibody, hepatitis C IgG antibodies and cytomegalovirus antibodies were all negative. Tests for antibodies to the Epstein-Barr nuclear antigen and viral capsid antigen (IgG) were both positive. Urinalysis was normal, except for positive results for uro-

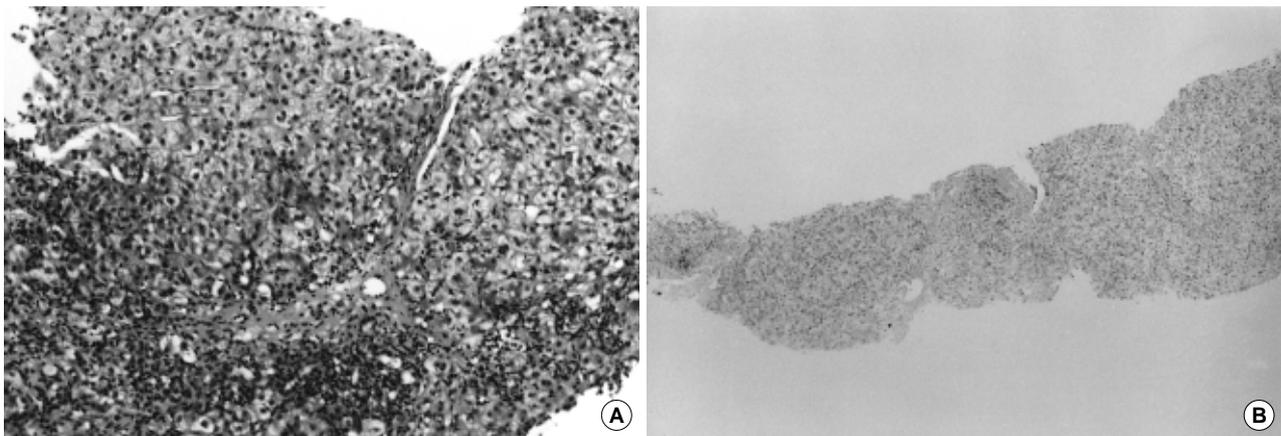


Fig. 1. The initial needle aspirated biopsy specimen of the liver on the 19th hospital day show: (A) piecemeal necrosis, bridging necrosis, hepatocellular necrosis, cholestasis in the hepatocyte with bile ductule proliferation and moderate infiltration of chronic inflammatory cells in the portal area and (B) bridging fibrosis (A: H&E,  $\times$  100; B: Masson-Trichrome,  $\times$  40).

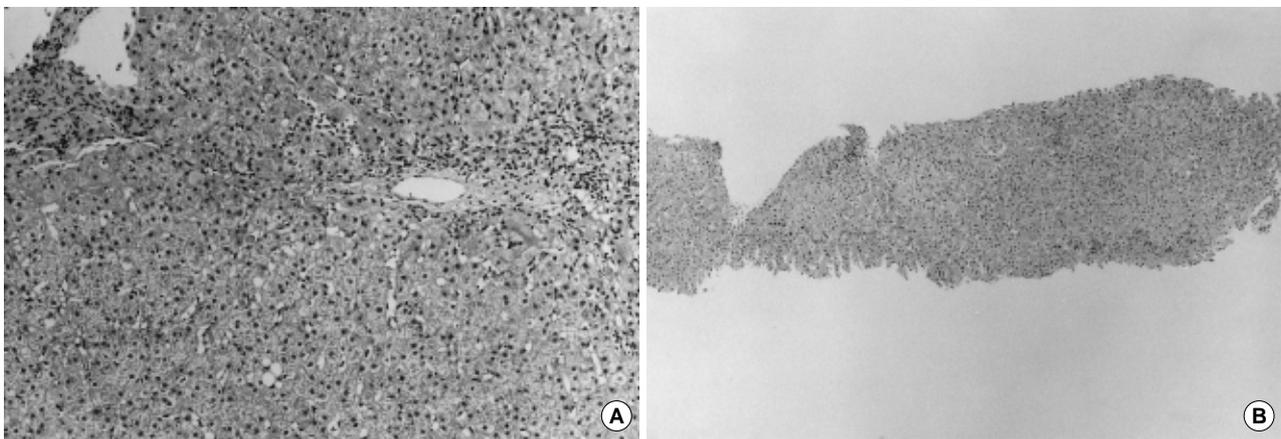


Fig. 2. The follow-up liver biopsy after treatment with steroids for seven months revealed improved histologic findings (A: H&E,  $\times$  100; B: Masson-Trichrome,  $\times$  40).

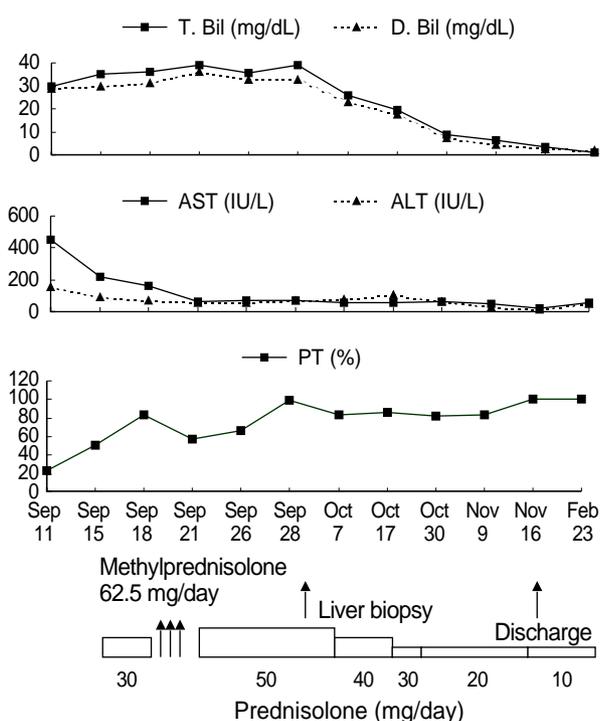


Fig. 3. Clinical course and follow-up laboratory findings.

bilinogen and bilirubin.

A radiography of the abdomen demonstrated an ileus on the periumbilical area. An abdominal ultrasonographic examination showed mild hepatosplenomegaly, small amounts of ascites, no dilatation of the bile ducts, and no masses. A liver scan disclosed a very inhomogeneous and lobulated contour of the liver and splenomegaly with high splenic activity. Endoscopic retrograde cholangiopancreatography performed on the fourth hospital day demonstrated no abnormalities of the bile ducts. Prednisolone (30 mg/day) was administered beginning on the fifth hospital day, on the presumptive diagnosis of AIH.

On 8th day of her hospitalization, the patient developed grade III hepatic encephalopathy. She was treated with intravenous methylprednisolone (62.5 mg/day) for three days. Her encephalopathy improved with intravenous steroid administration along with conservative management for hepatic encephalopathy. Intravenous steroid injections were changed to oral prednisolone 50 mg (1 mg/kg/day), and then slowly tapered. A needle aspirated liver biopsy was undertaken on the 19th hospital day. Histology showed moderate piecemeal necrosis, bridging necrosis, moderate hepatocellular necrosis, mild cholestasis in the hepatocytes with mild bile duct proliferation in the portal area, moderate infiltration of chronic inflammatory cells in the portal area and bridging fibrosis (Fig. 1). Follow-up needle aspirated liver biopsy at seven months of steroid therapy demonstrated improved histologic findings with focal hepatocellular necrosis, mild infiltration of chronic

inflammatory cells in the portal area and fibrous portal expansion (Fig. 2). The patient's elevated bilirubin level began to decline after the administration of steroids for 20 days (Fig. 3), and eventually normalized in five months. She is now managed with prednisolone 5 mg/day.

## DISCUSSION

We described a patient with overlap syndrome of MCTD and SS presenting with severe cholestatic autoimmune hepatitis and acute liver failure, whose jaundice and abnormal liver function test results resolved following steroid therapy. Mixed connective tissue disease is an overlap syndrome combining features of systemic lupus erythematosus, systemic sclerosis and polymyositis, together with the presence of antibodies to U1 RNP. SS is an autoimmune exocrinopathy in which the exocrine tissues are invaded by immune cells. The differential diagnosis of cholestatic liver disease includes various etiologies (6). In our patient, there was no evidence of extrahepatic obstruction or biliary tract stricture on imaging studies, and no drug history that may cause cholestasis. These initial findings led us to consider autoimmune liver diseases including primary biliary cirrhosis (PBC), sclerosing cholangitis, AIH and autoimmune cholangitis to explain the liver problems in our patient. The final diagnosis of AIH was made on the basis of positive FANA and anti-smooth muscle antibody testing, high titers of serum globulin, no evidence of current hepatitis virus infection, histologic findings, and a good response to corticosteroid therapy, all of which met the diagnostic criteria for AIH proposed by the International Autoimmune Hepatitis Group (7). Generally, the elevations in serum aminotransferase levels are more striking than the elevations of bilirubin or alkaline phosphatase, but the profound cholestatic liver dysfunction in our patient was an unusual manifestation of AIH. There are two conditions in which the features of both AIH and PBC, which usually shows the clinical manifestations of cholestatic liver disease, occur; overlap syndrome and autoimmune cholangitis (1). In overlap syndrome, the histologic findings of AIH are accompanied by the presence of the antimitochondrial antibody that is a characteristic serologic findings of PBC. In autoimmune cholangitis, the histologic features of both AIH and PBC may be present. These two conditions can be excluded through liver biopsy and by the absence of antimitochondrial antibodies. It is important to distinguish AIH from viral hepatitis, especially hepatitis C. Hepatitis C often has similar clinicolaboratory and pathologic findings with AIH (8). Negative results of repeated tests for anti-HCV antibody and a good response to steroid therapy excluded the possibility of HCV infection in our patient.

Although hepatomegaly is sometimes observed in MCTD patients, a few cases of AIH associated with MCTD

have been reported (2, 3, 9-13). HLA-DR4 has been reported to be related to AIH and MCTD (13). However, HLA typing was not performed in our patient.

Liver involvement in SS patients is rare and subclinical with histological features predominantly of stage I PBC (14). The association of AIH with MCTD and SS is extremely rare. Only two cases of AIH, MCTD and SS have previously been described (2, 3).

AIH can be categorized into three subtypes based on immunoserologic findings (1). In this case, positive antinuclear antibodies, anti-smooth muscle antibodies, negative anti-mitochondrial antibodies and anti-LKM antibodies suggested that the patient had type I AIH. In addition to cholestatic manifestations, acute liver failure was also an unusual initial presentation of AIH in this case. Acute liver failure has seldom been reported in a patient with AIH type I (15).

The laboratory findings of a positive direct Coombs test, increased levels of reticulocyte counts, serum LDH, and serum unconjugated bilirubin, increased urine urobilinogen, and a decreased serum haptoglobin level in our patient were all compatible with the features in autoimmune hemolytic anemia. And, autoimmune hemolytic anemia has been considered to be one of the disorders associated with AIH (1).

Glucocorticoid therapy remains the mainstay of therapy for AIH. Combining this treatment with azathioprine is sometimes preferred by physicians because it is associated with fewer side effects than higher dose prednisolone alone (5). Generally, a biochemical response occurs within one to three months after the initiation of treatment, although remission has been reported in a very small percentage of patients even after years of treatment. In our case, serum bilirubin level began to decline after 20 days of steroid therapy, and to be normalized in five months. In patients with AIH who experience spontaneous or pharmacologically induced remission, the histologic findings may revert to inflammation confined to the portal areas or to inactive cirrhosis, if cirrhosis has already been established (1). In our patient, the initial liver biopsy on the 19th hospital day showed moderate hepatocellular necrosis and bridging fibrosis. The follow-up liver biopsy in the state of remission revealed an improvement of the disease activity with focal hepatocellular necrosis and fibrous portal expansion. To our knowledge, this is the first case report of MCTD and SS associated with cholestatic AIH and acute liver failure, in which clinical remission and histological improvement were observed with steroid therapy.

In summary, cholestatic AIH can be associated with MCTD and SS, and usually responds well to steroid therapy. However, other cholestatic disorders with immunologic

features, such as PBC and sclerosing cholangitis, are resistant to steroid treatment. Therefore, it is important to include AIH in the differential diagnosis of patients with MCTD and SS who also exhibit cholestatic hepatopathy.

## REFERENCES

1. Krawitt EL. Autoimmune hepatitis. *N Engl J Med* 1996; 334: 897-903.
2. Wada T, Motoo Y, Ohmizo R, Terada T, Nakanuma Y. Association of mixed connective tissue disease, Sjögren's syndrome and autoimmune hepatitis: report of a case. *Jpn J Med* 1991; 30: 278-80.
3. Ohta M, Takami S, Hoppo K, Hayashi K, Sobajima J, Okuda M, Mochi T, Shimamoto K, Kagawa K, Okanoue T, Kashima K. A case of autoimmune hepatitis associated with mixed connective tissue disease and Sjögren's syndrome. *Acta Hepatol Jap* 1990; 31: 4548.
4. Czaja AJ. Diagnosis and therapy of autoimmune liver disease. *Med Clin North Am* 1996; 80: 973-94.
5. Czaja AJ. Treatment of autoimmune hepatitis. In: Nishioka M, Toda G, Zemya. eds. *Autoimmune hepatitis*. Amsterdam: Elsevier, 1994; 1994: 283-304.
6. Pasha TM, Lindor KD. Diagnosis and therapy of cholestatic liver disease. *Med Clin North Am* 1996; 80: 995-1019.
7. Johnson PJ, McFarlane IG. Meeting report: International Autoimmune Hepatitis Group. *Hepatology* 1993; 18: 998-1005.
8. Czaja AJ, Magrin S, Fabiano C, Fiorentino G, Diquattro O, Craxi A, Pagliaro L. Hepatitis C virus infection as a determinant of behavior in type I autoimmune hepatitis. *Dig Dis Sci* 1995; 40: 33-40.
9. Marshall JB, Ravendhran N, Sharp GC. Liver disease in mixed connective tissue disease. *Arch Intern Med* 1983; 143: 1817-8.
10. Rolny P, Goobar J, Zettergren L. HBs Ag-negative chronic active hepatitis and mixed connective tissue disease syndrome. An unusual association observed in two patients. *Acta Med Scand* 1984; 215: 391-5.
11. Maeda M, Kanayama M, Hasumura Y, Takeuchi J, Uchida T. Case of mixed connective tissue disease associated with autoimmune hepatitis. *Dig Dis Sci* 1988; 33: 1487-90.
12. Iwamoto H, Tsuji H, Fukui N, Watanabe H, Nunoi K, Murai K, Akagi K, Fujishima M, Yamada T. A case of mixed connective tissue disease associated with chronic active hepatitis. *Nippon Shokakibyo Gakkai Zasshi* 1989; 86: 1331-4.
13. Inoue K, Okajima T, Tanake E, Ando B, Takeshita M, Masuda A, Yamamoto M, Sakai K. Mixed connective tissue disease associated with autoimmune hepatitis and thyroiditis. *Endocr J* 1999; 46: 173-7.
14. Skopouli FN, Barbatis C, Moutsopoulos HM. Liver involvement in primary Sjögren's syndrome. *Br J Rheumatol* 1994; 33: 745-8.
15. Herzog D, Rasquin-Weber AM, Debray D, Alvarez F. Subfulminant hepatic failure in autoimmune hepatitis type I: an unusual form of presentation. *J Hepatol* 1997; 27: 578-82.