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Negative Conversion of Antimitochondrial Antibody in Primary Biliary Cirrhosis : A Case of Autoimmune Cholangitis

Autoimmune cholangitis is a clinical constellation of chronic cholestasis, histological changes of chronic nonsuppurative cholangitis and the presence of autoantibodies other than antimitochondrial antibody (AMA). It is uncertain whether this entity is definitely different from AMA positive primary biliary cirrhosis (PBC), though it shows some differences. We report a case of autoimmune cholangitis in a 59-year-old woman, who had been previously diagnosed as AMA-positive PBC associated with rheumatoid arthritis, has been converted to an AMA-negative and anticentromere antibody-positive PBC during follow-up. The response to ursodeoxycholic acid treatment is poor except within the first few months, but prednisolone was dropping the biochemical laboratory data.

Key Words : *Cholangitis, autoimmune; Antibodies, antimitochondrial; Liver cirrhosis, biliary; Antibodies, anticentromere*

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INTRODUCTION

Primary biliary cirrhosis (PBC) affects predominantly middle-aged and elderly woman and is characterized by clinical manifestation of chronic cholestasis, histological changes of lymphocytic destruction of the interlobular bile duct and the presence of antimitochondrial antibody (AMA).

We diagnosed a patient as AMA-positive PBC with rheumatoid arthritis with Sjögren's syndrome. Interestingly, in the disease course at follow-up, her AMA-score were converted to negative. The patient expressed other various characteristics; disease courses, higher antinuclear antibody (ANA) titer, positive anticentromere antibody (ACA), a response to treatment, and an association with rheumatoid arthritis.

We report a case of autoimmune cholangitis that is AMA-negative and ACA-positive PBC with a review of the literature.

CASE REPORT

In April 1994, a 54-year-old woman presented with a chief complaint of multiple joint pain and dry eyes for 10 years. She had taken an antihypertensive drug 2 years ago and also had abnormal liver functions. She was diagnosed as seropositive rheumatoid arthritis with Sjögren's syndrome. She complained of mild itching sensations. She had no history of hepatitis, blood transfusion, or herbal medications. Biochemical data on admission showed alkaline phosphatase 1,167 U/L (normal value < 110 U/L), ALT 294 IU/L, AST 372 IU/L, total bilirubin 2.5 mg/dL, γ-Glutamyltranspeptidase (GGT) 825 U/L (normal value < 65 U/L), cholesterol 310 mg/dL, and triglyceride 192 mg/dL. Antimitochondrial antibody was positive (1:640 titer) by indirect immunofluorescent method and fluorescent antinuclear antibody (FANA) was positive (1:640 titer). Anti-smooth muscle antibody and anti-DNA antibody were negative. Quantitative immunoglobulins (Ig) revealed an IgG of 1,430 mg/dL (normal 700-1500), IgM of 392 mg/dL (normal 60-300), and IgA of 181 mg/dL (60-400). Viral markers showed negative HBs Ag, negative HBs Ab, positive HBcAb, and negative HCV Ab. Other general blood tests were normal. Abdominal ultrasonography showed normal echogenicity of liver parenchyme without evidence of biliary obstruction. Endoscopic retrograde cholangiopancreatography (ERCP) showed normal intra- and extrahepatic bile ducts and a normal pancreas. The liver biopsy showed a mild portal widening by moderate degree of fibrosis and mild lymphocytic inflammatory infiltration around the bile duct. The lobules were relatively preserved (Fig. 1). Based on the above results, this case was diagnosed as PBC associated with rheumatoid arthritis and Sjögren's syndrome. Divided doses of ursodeoxycholic acid (UDCA) therapy (750 mg/day) was started. She responded to the therapy with an improve-

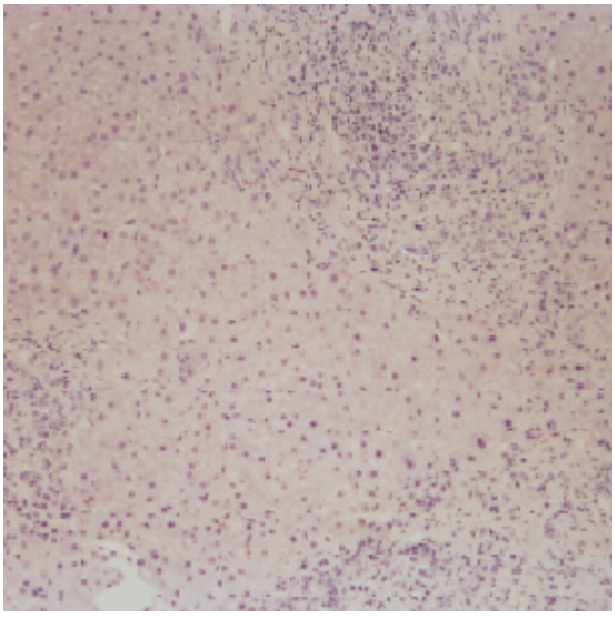

Fig. 1. Microphotography of initial liver biopsy: mild portal widening by moderate degree of fibrosis and mild lymphocytic infiltration around the bile ducts (H&E, ×100).

ment in all biochemical parameters of cholestasis (Fig. 2). One month later after taking UDCA, her liver enzymes and alkaline phosphatase were decreased. Three months after the initial medication, ALT and AST were normalized, alkaline phosphatase decreased to 441 U/L and GGT decreased to 512 U/L. She has continued to take daily UDCA 15 mg/kg, d-penicillamine 250-500 mg, and triamcinolone 4 mg for symptomatic management of rheumatoid arthritis. Steroid was discontinued according to the improvement of arthralgia, whereas UDCA was still continued during asypmtomatic period.

From January 1996, further AMA was converted to negative, ANA showed very high titer more than 1:2,560 with discrete speckled pattern of ACA (Fig. 3). Biochemical tests kept fluctuating in spite of continuous UDCA medication.

Biochemical laboratory data in April 1997 revealed that AMA was negative, ANA positive (>1:2,560), rheumatoid factor 83 units (normal<20), anti-smooth muscle antibody negative, ANCA negative and antithyroglobulin antibody negative. The liver function tests at the time she took UDCA showed alkaline phosphatase 541 U/L, ALT 88 IU/L, AST 60 IU/L, GGT 648 U/L, cholesterol 237 mg/dL and prothrombin time 1.03 INR. Abdominal ultrasonography showed coarse echogenicity on liver parenchyme. A second liver biopsy was performed. In comparison with previous biopsy findings, the portal tracts were more widened by heavy lymphocytic infiltration and fibrosis. The lobules were relatively preserved. The inflammatory reaction was mainly centered on bile ducts with epithelial sloughing, destruction and bile ductular proliferation. Histologic features were compatible to chronic nonsuppurative destructive cholangitis (Fig. 4). Liver function tests were fluctuated in spite of UDCA treatment. Her laboratory data were dependent on steroid medication, so we restarted treatment with prednisolone (Fig. 2). Therefore, we reported a case of autoimmune cholangitis that AMA-positive PBC was con-

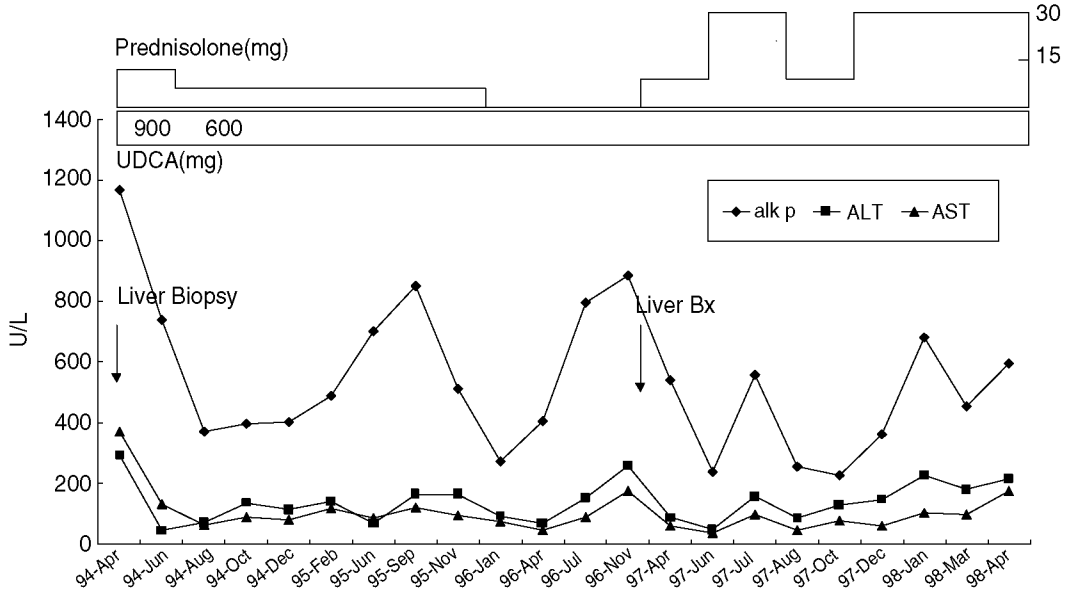

Fig. 2. Clinical courses and responses to treatment of the patient.

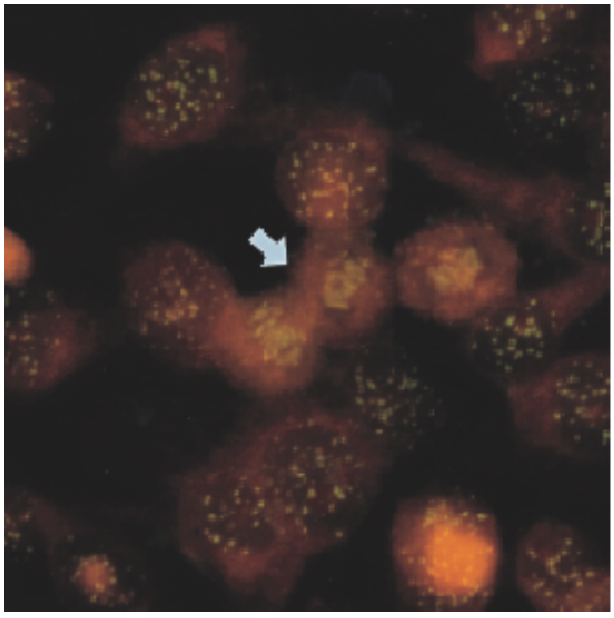

Fig. 3. FANA finding: typical discrete speckled immunofluorescent staining comparable to anticentromere antibodies in both interphase nuclei and metaphase chromatin (arrow) (×1000).

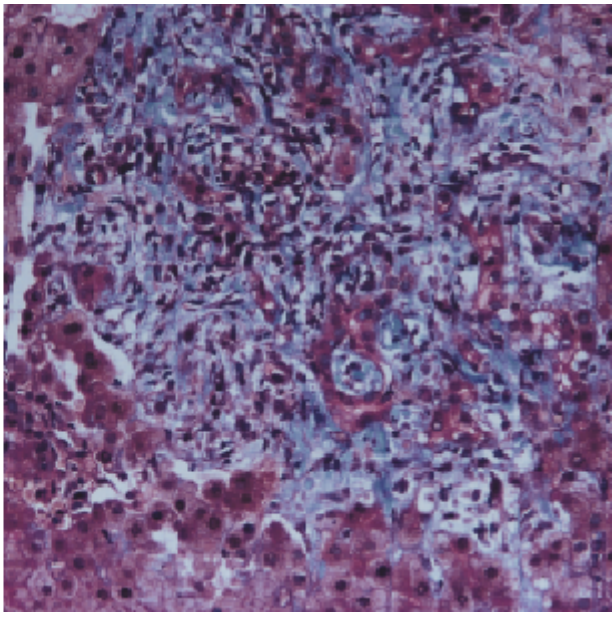

Fig. 4. Microphotography of follow-up liver biopsy, three years later: the inflammatory reaction was mainly centered on bile ducts with epithelial sloughing, destruction and bile ductular proliferation. Compared with the previous biopsy, portal tracts were more fibratic and infiltrated more heavily with lymphocytes (Masson-Trichrome, ×200).

verted to AMA-negative PBC with a positive ACA.

DISCUSSION

Autoimmune cholangitis is a clinical constellation of chronic cholestasis, histological changes of chronic nonsuppurative cholangitis and the presence of autoantibodies other than antimitochondrial antibody (AMA). It was introduced by Brunner et al. (1) to describe a chronic liver disease which clinically, biochemically, and histologically seemed to be typical of PBC, except that the antimitochondrial antibody test was negative. He reported three female cases as autoimmune cholangitis and treated them with prednisolone and azathiopurine. It is uncertain if this entity is definitely different from AMA positive primary biliary cirrhosis, but it showed some differences in the clinical spectrum.

Serum AMA determination is the most useful test to diagnose PBC, since it is positive in 90-95% of cases. But, 5-8% of PBC patients have been reported AMA-negative (2, 3). The inciting antigen for AMA are located on the inner part of the mitochondrial membrane; the specific antigen has been defined as being the 74 kDa E2 subunit of the pyruvate dehydrogenase complex. AMA is defined by an indirect immunofluorescence test and immunoblotting techniques or enzyme linked immunosorbent assay (ELISA) (2, 4). Although this autoantibody has an important diagnostic role and it seems to appear before MHC II expression on biliary epithelium in PBC, its contribution in mediating bile duct and hepatic injury is uncertain.

Autoimmune cholangitis can not be classified under either rubric because cholestatic findings associated with it preclude the diagnosis of autoimmune hepatitis and its lack of antimitochondrial antibodies restrict its categorization as PBC (5). The differences of AMA-negative PBC compared with AMA positive PBC have been noted by various reports. First, AMA-negative PBC is associated with higher ANA titier (71-95%) than AMA-positive PBC (31-56%). Also, 37-95% of the AMA-negative cases were anti-smooth muscle antibody positive compared with the AMA-positive cases (9-56%). (3, 6). Second, IgM and γ-globulin levels were lower in AMA-negative PBC (2, 3). Serum immunoglobulin and transaminase level in AMA-negative PBC were more decreased than AMA-positive PBC (7).

In addition, antibody to carbonic anhydrase which is an enzyme found in epithelial cells including the bile ducts and may promote cholestasis, was found in higher levels in AMA-negative patients compared to AMA-positive patients (8). AMA-negative group had a significantly higher incidence of asthenia, and a higher and earlier incidence of liver failure than AMA-positive group (9). There were no significant differences in the other laboratory tests, gender, hepatic histology, and clinical features (3, 6, 7, 9, 10). It is still controversial whether autoimmune cholangitis is an independent

entity or simply PBC without serum antimitochondrial antibody. AMA in our patient converted to negative and ANA titer was remarkably high during follow-up but other autoantibodies were not detected. There was a case report that AMA was converted to negative PBC and that case also showed signs of typical steroid dependent autoimmune hepatitis. In that case, patient showed typical PBC pictures initially and then AMA was lost and high titer of ANA was appeared during follow-up. That patient showed hepatitis-features with elevation of serum aspartate aminotransferase and piecemeal and bridging necrosis at last (11). Like that case, our case show negative conversion of AMA and flare-up of ANA titer simultaneously. Our patient did not show hepatitis features but responded to steroid medication. However, there was also a report that autoimmune chronic hepatitis highly responsive to immunosuppressive therapy has been followed by the development of a characteristic picture of PBC (12).

The interesting finding in this case was the positive ACA (Fig. 3). There was a discrete speckled pattern of ANA at high titer, however, the patient did not complain about any symptom and sign of CREST syndrome. ACA was identified by the appearance of typical discrete speckled staining in both interphase nuclei and metaphase chromatin (13). ACA is a specific marker for the CREST variant of systemic sclerosis (55-98%). ACA can occasionally be found in patients with primary biliary cirrhosis (17-30%), SLE, localized scleroderma and Raynaud's phenomenon (29.6%), and is hardly found in any of the patients with chronic autoimmune hepatitis (13-15).

There are two effective modalities for treating PBC. UDCA improves liver biochemistry and delays time of death or liver transplantation in patients with less advanced disease. UDCA leads to a rapid fall in all biochemical markers of cholestasis and improves histologic features except fibrosis (16-17). Orthotopic liver transplantation not only prolongs survival but also improves the quality of life in patients with decompensated hepatic failure. The recommended treatment for autoimmune cholangitis is also UDCA. Kim et al. (18) reported that the beneficial biochemical effect of UDCA therapy was comparable to that of AMA-positive PBC. Effect of administration of prednisolone or azathioprine is still controversial; prednisolone treatment results in decreased serum transaminase levels and there is evidence of less inflammatory activity on histologic examination of liver biopsy specimens (1, 19). GGT does not reach normal levels because of irreversible bile duct damage (19). But, Taylor et al. (20) noted that no patient reacted favorably to this therapeutic protocol. Orthotopic liver transplantation resulted in similar outcomes to those found in AMA-positive patients. Therefore, the treatment of autoimmune cholangitis is still controversial.

The natural history of autoimmune cholangitis is likely to parallel the chronic progression of PBC (2, 18, 20, 21). There is no report of AMA-negative PBC during long term follow-up. There was one report about follow up of the patients with either symptomatic or asymptomatic PBC for up to 19 years (mean, 6.9 years). Their multivariate analysis of clinical features presented that age, hepatomegaly, and elevated levels of serum bilirubin at the onset of disease indicated a poor prognosis (22).

In reviewing this case, we emphasize the following points : (1) AMA was converted to be negative with a discrete speckled pattern of FANA, which is called, ACA-positive at high titer in the course of follow-up, (2) in our case, glucocorticoid was more effective than UDCA, especially, during the AMA-negative period, and (3) our case was associated with rheumatoid arthritis and Sjögren's syndrome. In PBC, it is known to be associated with a variety of disorders presumed to be autoimmune in nature, such as rheumatoid arthritis, CREST syndrome, scleroderma, Sjögren's syndrome, autoimmune thyroiditis, pernicious anemia and renal tubular acidosis (23-24).

In summary, we reported a case of autoimmune cholangitis that AMA-positive PBC was converted to AMA-negative PBC with a positive ACA. Its histologic finding was chronic nonsuppurative destructive cholangitis.

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