A Case of Autoimmune Hepatitis with Antimitochondrial Antibody and No Detectable Antinuclear Antibody

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(Received for Publication: February 13, 2004)

Abstract

In Japan, antinuclear antibody (ANA) and/or smooth muscle antibody (SMA) can be detected in almost all patients with autoimmune hepatitis (AIH). Antimitochondrial antibody (AMA) is usually found in patients with primary biliary cirrhosis (PBC), which is characterized by histologic evidence of inflammatory destruction of interlobular bile ducts, and is considered to be a diagnostic hallmark of the disease. We report here a 63-year-old female who exhibited the clinical and histological features of AIH without detectable ANA and SMA, but who had AMA. She developed severe hepatitis with marked transaminase elevation and responded well to corticosteroid treatment, and remission occurred with maintenance therapy. Pretreatment liver biopsy revealed severe parenchymal damage accompanied by other characteristics of AIH, but no bile duct lesions suggestive of PBC were seen. Although the autoantibody pattern was unusual, we diagnosed this case as AIH. Although few cases of AMA-positive AIH have been reported, as with typical AIH, immunosuppressive therapy is recommended.

Key Words:

antinuclear antibody, antimitochondrial antibody, autoimmune hepatitis, primary biliary cirrhosis

[Introduction]

Autoimmune hepatitis (AIH) is an unresolved inflammation of the liver of unknown etiology 1). It is characterized by elevated serum 中介-globulins and the presence of circulating organ-non-specific autoantibodies, and histologic findings of liver cell damage with interface hepatitis 2). In Japan, 98% of AIH patients have the antinuclear antibody (ANA) or smooth muscle antibody (SMA), and some of the rest have the type 1 liver-kidney microsomal antibody (anti-LKM-1) 3). Antimitochondrial antibody (AMA), another autoantibody, is detected in almost all patients with primary biliary cirrhosis (PBC) and is considered to be a diagnostic hallmark of the disease 4).
PBC is a cholestatic liver disease that is histologically characterized by destruction of the intrahepatic bile ducts (predominantly interlobular bile ducts). It has been reported that 8% of patients with AIH are positive for AMA and such patients are diagnosed as having PBC/AIH overlap syndrome, which has the clinical and histological features of both PBC and AIH. We report here a case of chronic active hepatitis with marked hyper-globulinemia in which serum AMA was present while serum ANA and SMA were not detected. The clinical course and histological findings strongly suggested that this patient had AIH.

**[Case Report]**

**Clinical course**

A previously healthy 63-year-old female with a 2-month history of polyarthralgia (fingers and bilateral knee joints) and 2-week fever of more than 38 °C was referred to our hospital in August 2002. Her mother had suffered from rheumatoid arthritis. Laboratory tests revealed mildly abnormal liver enzymes with aspartate aminotransferase (AST) at 65 IU/l (normal <32), alanine aminotransferase (ALT) at 103 IU/l (normal <37), and ALP at 513 IU/l (normal <360), and the tests also revealed marked hyper-globulinemia (3.1g/dl; normal <1.5). She was treated with 5 mg/day of prednisolone (PSL) and the fever disappeared. However, the arthralgia persisted and the patient was admitted for further examination in October 2002. Although her liver function tests on admission were almost normal with AST 43 at IU/l, ALT at 51 IU/l and ALP at 484 IU/l, they rapidly worsened within 2 weeks from the admission: total bilirubin 3.7 mg/dl (normal <1.2), AST 1347 IU/l, ALT 1295 IU/l, and ALP 1608 IU/l (Table). The patient had no history of alcohol consumption or medication, except PSL administration. Viral serologies were negative for hepatitis A, B, and C. Immunologically, ANA, SMA, and anti-LKM-1 were not detected, but both AMA and anti-M2 were confirmed. From these findings, we considered that the patient had PBC basically and an immunological disorder would be responsible for exacerbation, and we increased the dose of PSL to 40 mg/day and added 600 mg/day of ursodeoxycholic acid (UDCA). After one week, jaundice developed and total bilirubin was 11.5 mg/dl, although liver enzyme levels began to improve, and the dose of PSL was increased to 60 mg/day. Liver function tests indicated improvement and arthralgia disappeared (Fig. 1). The dose of PSL was tapered and all liver function test levels were normalized in December 2002. We reduced PSL to 7.5 mg/day in January 2003, but the patient developed high
fever and arthralgia within two weeks of this reduction. The dose of PSL was again increased to 30 mg/day, and fever disappeared. However, serum levels of AST and ALT gradually increased and laboratory data revealed AST 104 IU/l, ALT 407 IU/l, ALP 409 IU/l in March 2003, and thus PSL was increased to a dose of 50 mg/day. After this increase in PSL, enzyme levels were normalized, and PSL was reduced very gradually. Although arthralgia persisted and required treatment with non-steroidal anti-inflammatory drugs, all the liver enzyme level have remained normal for more than 10 months with 10 mg/day of PSL.

Liver pathology

Liver biopsy was performed just prior to administration of high-dose PSL. Histological findings showed moderate fibrous expansion in the portal area with some portal-portal bridging necrosis, although the lobular architecture was essentially preserved (Fig. 2). Moderate inflammatory cell infiltration of predominantly mononuclear cells with some plasma cells was seen in portal areas, and limiting plates were distorted with marked piecemeal necrosis (Figs. 3, 4). Severe hepatocellular damage was seen with some central zonal necrosis (Fig. 5), focal necrosis, and numerous acidophilic bodies. There were no findings suggestive of PBC, such as chronic nonsuppurative destructive cholangitis, loss of bile ducts or granuloma. These histological findings suggested active chronic hepatitis and were compatible with autoimmune hepatitis.

Fig. 1. Clinical course of the patient with antimitochondrial antibody positive autoimmune hepatitis. Alanine aminotransferase (ALT), normal <37 IU/L; total bilirubin (T. Bil) normal <1.2 mg/dL; PSL, prednisolone; UDCA, ursodeoxycholic acid.
In Japan, nearly all patients with AIH have ANA and/or SMA. We report here a case with chronic active hepatitis of unknown etiology. Her clinical course strongly suggested AIH, although she had no detectable ANA or SMA. She developed high fever and arthralgia concurrently with hepatitis and had marked hyper-globulinemia. These are characteristic findings of AIH and histological evidence such as periportal inflammation and piecemeal necrosis (interface hepatitis) is also suggestive of AIH. However, she had no detectable autoantibodies related to the disease. Furthermore, she was positive for...

Fig. 2. Lobular architectures are essentially preserved with moderate fibrous expansions of portal areas (silver impregnation, x4).
lower figure: Portal-central bridging necroses are occasionally found (silver impregnation, x10). (P: portal area, C: central vein)

Fig. 3. Moderate fibrous expansion of portal area with severe piecemeal necroses is seen. No apparent bile duct damages suggesting CNSDC and epitheloid granuloma are recognized (HE, x10).

Fig. 4. Marked inflammatory cell infiltration predominantly with mononuclear cells and scattered plasma cells is seen (HE, x40).

Fig. 5. Note central zonal necroses with severe parenchymal damage (HE, x40).

[Discussion]

In Japan, nearly all patients with AIH have ANA and/or SMA. We report here a case with chronic active hepatitis of unknown etiology. Her clinical course strongly suggested AIH, although she had no detectable ANA or SMA. She developed high fever and arthralgia concurrently with hepatitis and had marked hyper-globulinemia. These are characteristic findings of AIH and histological evidence such as periportal inflammation and piecemeal necrosis (interface hepatitis) is also suggestive of AIH. However, she had no detectable autoantibodies related to the disease. Furthermore, she was positive for...
AMA, which is frequently detected in patients with PBC. AMA is classified into 9 subclasses, and of these, the M2 class (anti-M2) is highly specific for PBC and is considered a diagnostic hallmark. Serological evidence thus suggested PBC, but other clinical findings, including response to corticosteroid and histological evidence, suggested AIH. Using the international criteria the patient was diagnosed as probable AIH with an aggregate score 14 before treatment (probable AIH, 10-15; definite AIH>15), despite testing positive for AMA, which gave a score of minus 4. Czaja et al. proposed a clinical entity for variant forms of AIH and classified this into overlap syndrome and outlier syndrome. However, our case would not be included in this category because it is defined as hepatitis having autoimmune features but that does not satisfy the criteria for a definite or probable diagnosis of autoimmune hepatitis.

Although 'antimitochondrial antibody-positive AIH' might be a terminological contradiction, two cases with ANA negative and AMA positive, have been reported to date. Their hepatic damages were moderate without jaundice. And they responded to corticosteroid therapy, which is a standard treatment for AIH, and one case did not respond to UDCA, which is a standard treatment for PBC. In our case, hepatitis was relatively severe accompanied with marked jaundice, and remission was inducted by sufficient dose of corticosteroid administration. Although UDCA was administered continuously as an adjuvant of corticosteroid therapy throughout the course of illness, relapse occurred after reduction of corticosteroid, which is an important finding suggestive of AIH.

In conclusion, although it is rare, AMA-positive AIH exists and corticosteroid should be selected as an induction therapy.

References
抗ミトコンドリア抗体陽性で抗核抗体陰性の自己免疫性肝炎の1例

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抄 録

自己免疫性肝炎（AIH）は原因不明の持続性あるいは再燃性の肝炎で、高β2グロブリン血症、抗核抗体（ANA）陽性、組織学的にはpiecemeal necrosisを伴う門脈周囲および肝小葉内の肝細胞障害が特徴である。抗ミトコンドリア抗体（AMA）は小葉間胆管を病変の主座とする原発性胆汁性肝硬変（PBC）に特異性の高い自己抗体と知られ、AIHでの検出頻度は低い。われわれは著明な高β2グロブリン血症を伴うもANA陰性でAMA陽性のAIHの1例を経験した。症例は63才女性。発熱、多関節痛のため当院入院後、黄疸を伴う強い肝機能障害が出現。肝炎ウイルスマーカー陰性、ANA陰性、抗肝臓ミクロゾーム抗体陰性、抗平滑筋抗体陰性、AMA40倍陽性、抗M2抗体陽性（Index154）で、生検肝組織ではzonal necrosisおよび著明なpiecemeal necrosisを伴う高度な実質炎を認め、PBCを示唆する胆管病変には乏しかった。プレドニゾロン投与にて肝炎は改善し、維持療法にて肝機能は正常を維持している。自己抗体以外は検査所見をふくめて臨床経過はすべてAIHに合致しており、国際診断基準スコアでも治療前14点（疑診）であり、AIHと考えられた。ANA陰性でAMA陽性のAIHの報告は極めて少なく、興味深い症例と考え報告する。

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