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Acute Liver Failure in an Antimitochondrial Antibody-Positive 63-Year-Old Man

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Key Words
Primary biliary cirrhosis · Acute liver failure · Autoimmune hepatitis · Overlap syndrome

Abstract
Antimitochondrial antibody (AMA) is one of the representative features of primary biliary cirrhosis (PBC). PBC is a female-dominant disease usually presenting intrahepatic bile duct destruction, cholestasis and fibrosis with or without chronic nonsuppurative destructive cholangitis. We presented the case of a 63-year-old man with acute liver failure who had AMA, pronounced alanine aminotransferase elevation and high bilirubinemia. We administered corticosteroids and rescued this patient without liver transplantation. It is well known that some patients within the spectrum of autoimmune liver disease present with characteristics of both PBC and autoimmune hepatitis. Although corticosteroids may be associated with a significant worsening of adverse events in patients with PBC, if acute liver failure in AMA-positive cases is progressive, the administration of corticosteroids has to be considered, as well as the preparation of urgent liver transplantation.

Introduction

Autoimmune hepatitis (AIH) patients usually present elevated serum aminotransferase levels (3–10-fold increase), marked hypergammaglobulinemia (typically IgG), positive titers of autoantibodies, histological findings of interface hepatitis and portal plasma cell infiltration [1], although atypical cases also exist [2–4]. Typical primary biliary cirrhosis (PBC) patients are females in the age range

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of 30–65 years, presenting with biochemical signs of cholestasis and the presence of antimitochondrial antibody (AMA), and they are asymptomatic or suffer from fatigue or pruritus [5–9]. Diagnosis can be made in patients who have elevated alkaline phosphatase (ALP) levels of at least 6 months duration, in combination with the presence of AMA (≥1:40) [5]. Serum aminotransferase levels usually are only slightly elevated, whereas IgM concentration is typically increased [5].

Some patients within the spectrum of autoimmune liver disease present with characteristics of both PBC and AIH and are commonly classified as having an 'overlap syndrome' [5, 10]. In AIH patients, AMA is occasionally seen at low titers, but an AMA anti-pyruvate dehydrogenase complex-E2 (AMA-M2) pattern, which is specific to PBC, is rarely detected [5]. Muratori et al. [11] reported that only 2% of type 1 AIH patients were AMA-positive. Overlap cases are usually selected either on the basis of biochemical and serological findings or of histological features, although limitations due to biopsy size and sampling error should always be kept in mind in the assessment of a liver biopsy [5].

The acute and fulminant forms of AIH were recognized by the International Autoimmune Hepatitis Group in 1992, when it codified diagnostic criteria and waived the requirement for 6 months of disease activity to establish the diagnosis [1, 4], although it is still difficult to diagnose and treat the acute and fulminant forms of AIH [2, 4, 12]. We present a case of acute liver failure with overlap features of both PBC and AIH who was successfully treated with corticosteroids without liver transplantation.

Case Report

A 63-year-old Japanese man was referred to Chiba University Hospital at the end of April 2011 for the treatment of acute liver failure. Blood tests showed serum alanine aminotransferase (ALT) 2,415 IU/l, aspartate aminotransferase (AST) 3,253 IU/l, ALP 804 IU/l, total bilirubin 12.7 mg/dl, and prothrombin time international normalized ratio 1.65. Two weeks earlier, liver dysfunction had first been diagnosed at his regional clinic. At that time he had developed fatigue, pruritus and jaundice. Clinical data at admission to our hospital are shown in **table 1**. His medical history consisted of mild cerebral infarction 8 years before and surgery for inflammation of the right middle ear in his twenties. He had been taking medicines such as fenofibrate, allopurinol, diclofenac sodium, valsartan, nilvadipine and aspirin for hyperlipidemia, hyperuric acid, lumbar herniated disk and hypertension for more than 1 year. He occasionally drank alcohol and had no family history of liver diseases or autoimmune disorders. Physical examination on admission revealed jaundice but no consciousness disturbance. Computed tomography showed minimal ascites and mild hepatosplenomegaly with a thickened gall bladder wall (**fig. 1**). Doppler ultrasound color flow imaging showed inversion of venous flow, suggesting portal hypertension, although endoscopic findings did not reveal any esophageal or gastric varices. There were no positivities of hepatitis viral markers (table 1). Possible reactivation of herpes simplex virus and drug-induced liver injury were not completely ruled out at that time. Because of the positivity for antinuclear antibody and AMA, especially AMA-M2, we considered him to have autoimmune liver disease such as AIH or overlap syndrome with characteristics of both PBC and AIH, and so the administration of corticosteroids was initiated [2]. He was first treated with 1,000–125 mg of methylprednisolone daily for 10 days, and then with 60–5 mg prednisolone daily for approximately 110 days. He also started taking 600 mg of ursodeoxycholic acid daily for about 90 days. Total bilirubin continued to rise up to 31.2 mg/dl, but then recovered. He was released from our hospital 120 days after admission. After his discharge, he was treated daily with 5 mg of prednisolone and 600 mg of ursodeoxycholic acid.

During his hospitalization, 70 days after the start of corticosteroid treatment, transjugular liver biopsy was performed (**fig. 2**). The liver biopsy specimen showed the architecture of the liver as being preserved, indicating no cirrhosis, but revealed submassive hepatic necrosis, findings compatible with

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overlap syndrome with characteristics of both PBC and AIH. The AIH score was 16 after completion of corticosteroid treatment, pointing to AIH compatibility [1].

One year later, he was well but complained of pruritus. His liver function tests were improved (ALT 11 IU/ml, AST 22 IU/ml, total bilirubin 0.6 mg/dl, IgM 166 mg/dl, and IgG 1,176 mg/dl), but his antinuclear antibody and AMA were still positive. Doppler ultrasound color flow imaging showed no inversion of venous flow and no ascites.

Discussion

We present a 63-year-old Japanese man with acute liver failure and positivity for AMA-M2 who was successfully treated with corticosteroids. Before admission he had no symptoms, and ALP was not examined. However, ALP levels were still elevated in mid-October 2011, AMA-M2 was still positive (8 IU/ml), and he had intractable pruritus, suggesting that PBC also existed. We diagnosed him as overlap syndrome having AIH and PBC features.

PBC-AIH overlap syndrome is a clinical entity characterized by the occurrence of both conditions at the same time in the same patient [13]. We and others previously reported the consecutive occurrence of AIH and PBC [9, 13]. It is very important for patients with acute liver failure such as the present case to be treated as soon as possible. We used corticosteroid therapy and made preparations for urgent liver transplantation [14, 15].

Corticosteroids may be associated with a significant worsening of osteoporosis in patients with PBC [5–7]. We previously reported that corticosteroids are effective for AIH with acute presentation [2] and that they are also effective for overlap syndrome having AIH and PBC features with acute transaminase elevation [10]. Ichai et al. [12] indicated that there is a point beyond which AIH cannot be salvaged by drug therapy, and this point can be defined only by assessing the immediate response to corticosteroid treatment [4]. This assessment can be made over a 2-week interval, which is sufficiently short to avoid the infectious complications associated with protracted immunosuppressive therapy and liver failure [4, 12]. In our case, prothrombin time recovered relatively soon after the administration of corticosteroids. Corticosteroid therapy remains appropriate for severe, immediately life-threatening and fulminant AIH, although the treatment should be limited to 2 weeks or less [4].

We present a case of acute liver failure with overlap features with both PBC and AIH, who was successfully treated with corticosteroids without liver transplantation. In conclusion, it seems important to finely judge the corticosteroid use for atypical cases of autoimmune liver diseases with acute presentation over shorter periods. Of course, further studies are urgently needed.

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Disclosure Statement

The authors have nothing to disclose.

Table 1. Laboratory data on admission to Chiba University Hospital

White blood cells	10,300/μl	Gamma-glutamyl transpeptidase	116 IU/l
Hemoglobin	13.1 g/dl	Total bilirubin	18.0 mg/dl
Platelets	38.2 × 10^4/μl	Direct bilirubin	13.5 mg/dl
PT-INR	1.33	Immunoglobulin M	286 mg/dl
PT%	49%	Immunoglobulin G	1,928 mg/dl
Ammonia	71 μg/dl	HBsAg	–
Total cholesterol	88 mg/dl	Anti-HBs	–
Blood urea nitrogen	12 mg/dl	Anti-HBc	–
Creatinine	0.56 mg/dl	IgM-HBc	–
C-reactive protein	2.9 mg/dl	HBV DNA	–
Alpha-fetoprotein	9.0 ng/ml	IgM-HA	–
PIVKA-II	37 mAU/ml	Anti-HCV	–
Total protein	6.5 g/dl	HCV RNA	–
Albumin	3.3 g/dl	Antinuclear antibody	×640
Aspartate aminotransferase	3,334 IU/l	AMA	×40
Alanine aminotransferase	2,602 IU/l	AMA-M2	14 IU/ml
Lactate dehydrogenase	568 IU/l	Anti-smooth muscle antibody	–
Alkaline phosphatase	795 IU/l		

AMA = Antimitochondrial antibody; Anti-HBc = hepatitis B core antibody, total; Anti-HBs = hepatitis B surface antibody; Anti-HCV = hepatitis C virus antibody; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus DNA; IgM-HA = hepatitis A antibody immunoglobulin M; IgM-HBc = hepatitis B core immunoglobulin M antibody; M2 = pyruvate dehydrogenase complex-E2 (PDC-E2); PIVKA-II = protein induced by vitamin K absence II; PT-INR = prothrombin time international normalized ratio.

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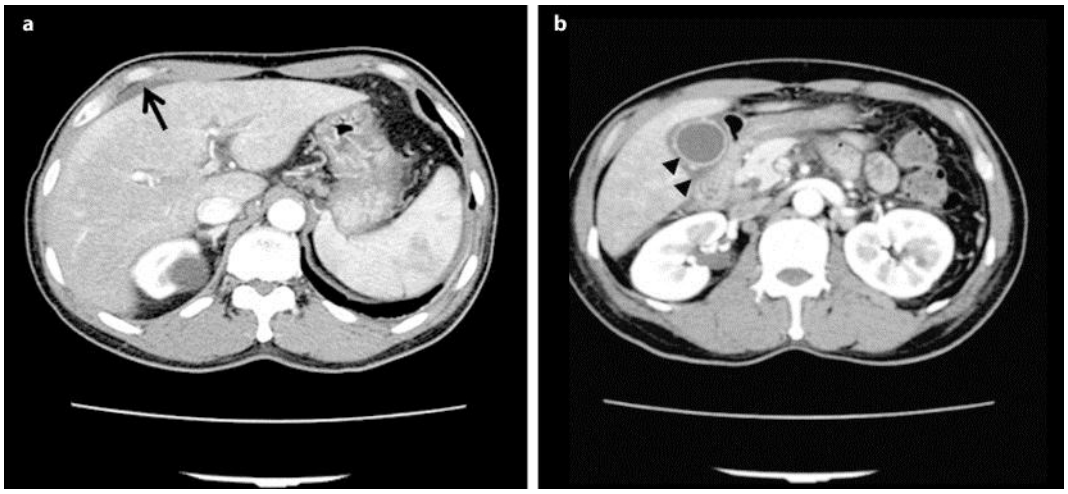

Fig. 1. Computed tomography on admission showed minimal ascites (arrow) and mild hepatosplenomegaly (**a**) with a thickened gall bladder wall (arrowheads) (**b**). These indicated severe liver injury.

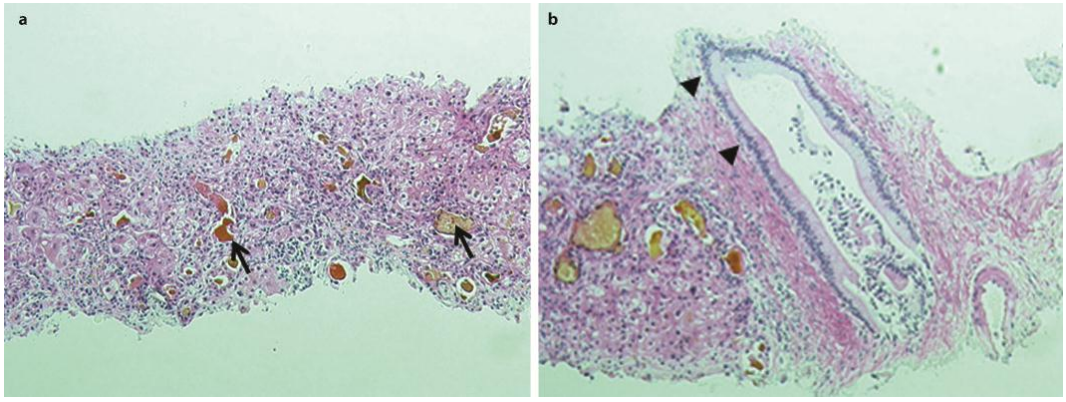

Fig. 2. Liver biopsy showed submassive hepatic necrosis and cholestasis (arrows) (hematoxylin and eosin; original magnification 40×) (**a**) and florid bile duct regions (arrowheads) (hematoxylin and eosin; original magnification 200×) (**b**). The architecture of the liver was preserved, indicating no cirrhosis, but revealed submassive hepatic necrosis, findings compatible with overlap syndrome with characteristics of both PBC and AIH.

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