Cholestatic Jaundice as the Predominant Presentation in a Patient with Autoimmune Hepatitis

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Autoimmune hepatitis is a heterogeneous liver disease of unknown etiology. It is predominant in females and characterized by elevation of transaminase, hypergammaglobulinemia and circulating autoantibodies. Interface hepatitis and plasma cell infiltration are the main findings on liver biopsy. However, deep cholestatic jaundice is rarely seen. We present here an unusual case of type 1 autoimmune hepatitis with hyperbilirubinemia as the initial and predominant presentation. Although rare, autoimmune hepatitis should be considered in patients with cholestasis without history of drug or viral hepatitis. [*J Chin Med Assoc* 2008;71(1):45–48]

Key Words: autoantibody, autoimmune hepatitis, jaundice

Introduction

Autoimmune hepatitis (AIH) is a chronic and unresolving hepatic parenchymal necroinflammation of unknown cause. The disease is rare in Asian countries. Specific circulating organ-nonspecific autoantibodies and high serum globulin level are the main characteristics of the disease. Three types of AIH have been defined. The most common and typical form, type 1, is predominant in females and seropositive for both antinuclear antibody (ANA) and/or anti-smooth muscle antibody (SMA). AIH type 2 is male-dominant and seropositive for anti-liver/kidney microsome type 1 (anti-LKM-1) antibodies. Type 3 AIH is characterized by the presence of antibodies against soluble liver antigen/hepatic pancreatic antigen (SLA-LP). The disease spectrum can range from mild to severe. Most patients present with nonspecific symptoms such as nausea, vomiting, anorexia, weight loss, fatigue and mild intermittent jaundice. However, deep jaundice is rare in Eastern countries. The diagnosis depends on the presence of characteristic autoantibodies and the fulfillment of criteria proposed by the International Autoimmune Hepatitis Group.[1]

Here, we report a case of type 1 AIH with the initial and predominant presentation of hyperbilirubinemia. Jaundice was dramatically responsive to prednisolone treatment.

Case Report

A 48-year-old female was admitted to the gastroenterology ward of Taipei Veterans General Hospital because of marked jaundice. She had no history of alcohol intake, blood transfusion or drug or Chinese herbal medicine usage in the past 3 months. Progressive jaundice had persisted for 2 months without a definite diagnosis at a local hospital prior to this admission. She was alert but appeared jaundiced. On physical examination, she had icteric sclera, no palmar erythema, no shifting fullness and no abdominal tenderness. On admission,

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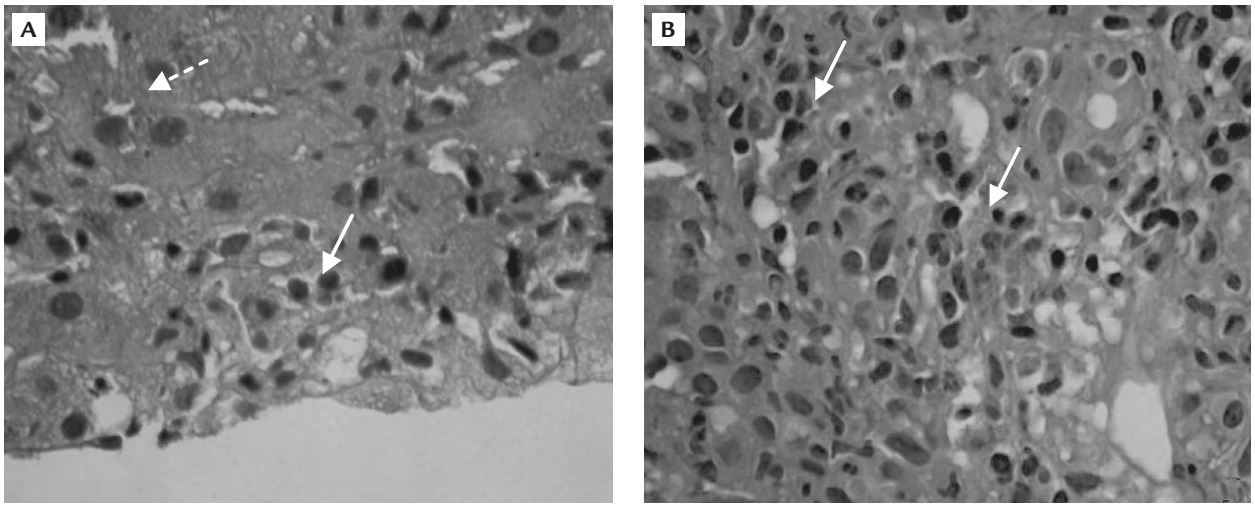

Figure 1. Histologic findings of the liver specimen (hematoxylin & eosin, 1,600×): (A) necrosis of liver parenchyma with plasma cell infiltration (solid arrow) and cholestasis (broken arrow); (B) edema in the portal tract and infiltration of plasma cells and lymphocytes (arrows); diffuse ballooning, necrosis of hepatocytes and bile stasis with bile duct changes are shown.

her serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALK-P) and total bilirubin were 686 U/L (normal, 0–40 U/L), 819 U/L (normal, 5–45 U/L), 134 U/L (normal, 10–100 U/L) and 19.2 mg/dL (normal, 0.2–1.6 mg/dL), respectively. Prothrombin time was 14.4 seconds, with international normalized ratio of 1.2 (1.0–1.2). Anti-hepatitis A immunoglobulin M (anti-HAV IgM), hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg), anti-hepatitis B core IgM (anti-HBc IgM), anti-hepatitis C virus (HCV) antibody, anti-Epstein Barr virus IgM, anti-cytomegalovirus IgM, and antimitochondria antibody (AMA) were negative. Test for anti-SMA was positive and ANA titer was 1:320 of speckled form. Hypergammaglobulinemia (IgG) was 2,340 mg/dL (normal, 751–1,560 mg/dL). The ratio of ALK-P and ALT, as defined by the Autoimmune Hepatitis Scoring System, was 0.19. Abdominal sonography revealed thickening of the gallbladder wall, which was compatible with hepatitis.

Liver needle biopsy was performed 5 days after admission. Histology of the liver specimen showed diffuse hepatocellular ballooning and necrosis, with occasional giant cell transformation and bile stasis. Mixed inflammatory cell infiltrates, including plasma cells, eosinophils, lymphocytes and a few acidophil bodies, were present in the periportal area. Cholangitis with bile duct changes were noted (Figure 1). These findings were compatible with AIH with diffuse lobular compartment.

Human leukocyte antigen (HLA) typing demonstrated a phenotype of DR4, DR14, DR52 and DR53. The diagnosis of AIH was supported by histologic findings and the criteria of the International Autoimmune Hepatitis Group (Table 1). Steroid therapy was started as soon as the diagnosis was confirmed. The starting prednisolone dose was 50 mg/day. One week after treatment, the biochemical markers of AST, ALT and total bilirubin levels had dramatically improved (Figure 2).

Liver biochemistry and bilirubin levels flared up once due to poor drug compliance by the patient, but both were soon restored to within normal ranges after reinstitution of the low-dose prednisolone.

Table 1. The International Autoimmune Hepatitis Group score of the patient before treatment

Category	Factor	Score
Gender	Female	+2
ALK-P:AST (or ALT)	0.19	+2
IgG (upper limit of normal)	1.5×	+2
ANA, anti-SMA	1:320	+3
AMA	Negative	
Viral marker of active infection	Negative	+3
Hepatotoxic drugs	None	+1
Alcohol	None	+2
Concurrent immune disease	None	+2
Other autoantibodies	Not detected	
Histologic features	Interface hepatitis	+3
HLA	DR4+	+1
Pretreatment score		21

ALK-P = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; IgG = immunoglobulin G; ANA = antinuclear antibody; SMA = smooth muscle antibody; AMA = antimitochondria antibody; HLA = human leukocyte antigen.

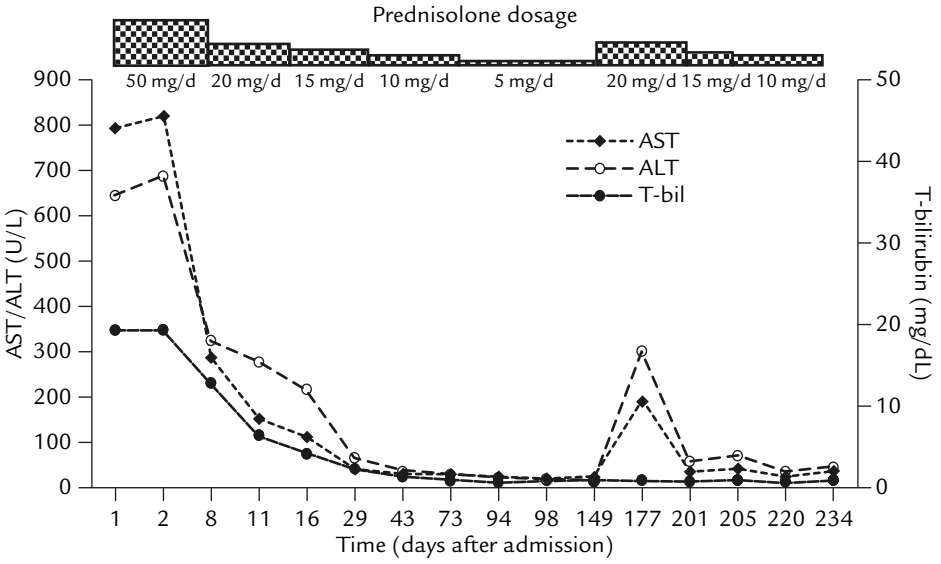

Figure 2. Clinical course of the patient. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and total bilirubin level before and after prednisolone treatment are shown. All these biochemical markers dramatically improved after prednisolone administration.

Discussion

AIH is an inflammatory disease of the liver characterized by hypergammaglobulinemia, presence of autoantibodies, and elevation of liver function tests. Piecemeal necrosis and plasma cell infiltrates are typical findings on liver biopsy. A clinical diagnosis depends on the exclusion of other liver diseases that resemble AIH. The International Autoimmune Hepatitis Group established criteria for the diagnosis of the disease.[1,2] These criteria define patients into 2 groups, as probable or definite disease. Differentiation between the 2 diagnoses of AIH rely mainly on the degree of serum gammaglobulin (IgG) elevation, titers of autoantibodies (ANA, SMA, anti-LKM-1), and exposure to alcohol, medications or infectious agents that could cause liver injury.[1,3] Appropriate immunosuppressive therapy based on an accurate diagnosis can achieve maximum response.

In the case we report here, the patient presented with deep jaundice as her primary symptom. In the typical presentation of AIH, the aminotransferase levels of liver enzymes are usually elevated higher than the levels of total bilirubin, ALK-P and γ-glutamyl transferase, a picture that looks like viral hepatitis. Consequently, AIH must be taken into consideration for differential diagnosis, especially in areas endemic for viral hepatitis. Though mild elevation of bilirubin is a common presentation of AIH and presents in 83% of patients, the majority of cases experience a level of bilirubin elevation that is less than 3-fold the upper limit of normal.[4] It was reported that only 18.2% of a total of 22 Chinese AIH patients presented with jaundice as the initial symptom, and the mean value of total bilirubin was 4.8 mg/dL in the female group.[5,6] The elevated bilirubin level that was over 10-fold the upper limit of normal in the current case was extremely rare. Some might suggest that the hyperbilirubinemia was the consequence of biliary tract destruction secondary to severe hepatic necroinflammation. However, hyperbilirubinemia should persist longer in that case. The dramatic response of bilirubin level to prednisolone treatment excluded this possibility. Serum ALK-P level is commonly elevated (81%) in AIH cases, but high-degree elevation is less common.[7] Hypergammaglobulinemia in AIH is a selective elevation of IgG subclass. This unique feature of AIH matched that of our patient except for the marked elevation in serum total bilirubin level.

Sometimes, AIH can have a cholestatic pattern, which merits a thorough imaging study to rule out biliary obstruction. In this patient, deep jaundice accompanied by elevated aminotransferase levels were the main presenting symptoms. This unusual presentation expanded the differential diagnoses to include conditions such as drug hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis. This patient had no history of drug or herbal medication abuse. Approximately 80% of patients with AIH present with significant high titers of ANA and/or anti-SMA autoantibodies.[7,8] This patient had a raised ANA titer and presence of anti-SMA. The absence of AMA and

no abnormality in the biliary system on sonography study excluded other possibilities.

There is a strong genetic basis associated with type 1 AIH.[9] The principal susceptible gene in Asians is HLA-DR4,[10] which concurs with this patient's HLA typing. The pretreatment score of the modified criteria of the International Autoimmune Hepatitis Group in this case was 21, therefore, the diagnosis of type 1 AIH was definite.

The histologic feature of AIH is interface hepatitis. The inflammation is confined to the periportal regions (interface hepatitis) or may sometimes involve the entire lobule (lobular hepatitis).[11] The presence of plasma cells is a typical feature that is abundant at the interface. Rosettes of hepatocytes are common in the periportal area.[11] The liver pathology of this patient showed these typical features, which enhanced the diagnostic score.

Responsiveness to corticosteroid treatment with marked improvement in the serum levels of aminotransferases and total bilirubin is another practical clue to the diagnosis of AIH. In our patient, steroid therapy was started as soon as the diagnosis was made. The clinical and biochemical responses were remarkable within days. Currently, steroid therapy remains the mainstay of therapy, and the suggested initial dosage is prednisone 1 mg/kg/day, with a maintenance dose of 20 mg/day in Western populations. The rate of remission with this treatment was approximately 80%.[12] On the contrary, a lower dose regimen of steroid was instituted in Taiwanese and Singapore populations, which demonstrated remission rates of 87.5% and 89%, respectively.[5,13] The average time to remission was shorter in the Taiwanese group.[5] In the present patient, biochemical markers returned to normal ranges within 4 weeks with low-dose steroid treatment, and treatment was continued for 2 years.

In conclusion, AIH is a multifaceted disease that can mimic other causes of hepatitis indiscriminately and respond well to steroid therapy. Cholestatic jaundice is rare in AIH,[10] but should not be overlooked. Although rare, AIH should be listed in the differential diagnosis in patients with cholestasis without a history of drug or viral hepatitis.

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