Autoimmune Hepatitis Associated with Pulmonary Arterial Hypertension

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Abstract

A 46-year-old woman presented with arthralgia. She had a history of fluctuating liver function impairment for 6 months. Laboratory investigations revealed elevated liver function test results, positive antinuclear antibodies and elevated serum IgG. The histological findings of a liver biopsy were interface hepatitis accompanied by plasmocytic infiltration with bridging fibrosis. There was no evidence of cirrhosis on pathological examination and no portal hypertension on endoscopic and radiographic studies. Autoimmune hepatitis was diagnosed, and treatment with prednisolone improved the liver dysfunction. After 6 months, she complained of dyspnea. Doppler echocardiography showed a dilated right ventricle, severe tricuspid insufficiency, and systolic pulmonary arterial pressure indicative of pulmonary arterial hypertension. We report this rare case of autoimmune hepatitis with pulmonary arterial hypertension.

Key words: autoimmune hepatitis, pulmonary arterial hypertension

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Introduction

Autoimmune hepatitis (AIH) has been shown to be associated with a number of other autoimmune diseases (1, 2). Patients with AIH may be at increased risk for developing systemic connective tissue disease (CTD) (3). While AIH and CTD are different entities, the boundary between the two disorders can be indistinct (3). Pulmonary arterial hypertension (PAH) occurs in a variety of conditions including CTD and some rheumatic diseases (4). PAH is characterized by progressive obliteration of small vessels in the pulmonary vascular bed leading to permanently increased pulmonary vascular resistance and elevated pulmonary artery pressure, which may result in right heart failure and premature death. However, treatment options for patients with PAH have evolved to help prolong their survival and improve their quality of life. Early identification of PAH and its underlying or concurrent pathology is important for treatment outcome (5). We report a rare case of AIH with PAH, which was diagnosed from investigating multiple serological markers.

Case Report

A 46-year-old woman was admitted to our hospital with a low-grade fever and arthralgia. The patient had a history of fluctuating liver function impairment for 6 months. She denied alcohol and drug use. On admission, her temperature was 37°C, pulse rate was 70/min, respiration rate was 18/min, and blood pressure was 110/70 mmHg. Physical examination detected no palpable cervical lymph node, but moderate jaundice was found. Auscultation of the heart and the lungs were normal. The abdomen was soft with normal bowel sounds. The edge of the liver was detected at 3 cm below the right costal margin.

Her initial laboratory findings were as follows: White blood cell count (5.40×10^3/μL; normal range, 3.3-9.0×10^3)
was within normal range. Red blood cell count was slightly reduced (3.17×10^4/μL; normal range, 4.30-5.70×10^4/μL). Platelet count (16.7×10^3/μL; normal range, 140-340×10^3/μL) was within normal range. Total bilirubin (4.2 mg/dL; normal range: 0.2-1), direct bilirubin (3.2 mg/dL; normal range, 0.0-0.4), aspartate aminotransferase (AST) (159 U/L; normal range, 5-35), and alanine aminotransferase (ALT) (149 U/L; normal range, 5-45) were elevated. Alkaline phosphatase (ALP) (361 IU/L; normal range: 100-325) was slightly high. Prothrombin time was reduced (48%; normal range, 70-100). Tests for antibodies to Epstein-Barr nuclear antigen and viral capsid antigen (IgG) were both positive. Urinalysis was normal. Viral serological tests were negative for anti-HCV, anti-hepatitis B core antigen, and anti-hepatitis B surface antigen. HCV-RNA was not detected in serum by polymerase chain reaction. The concentrations of IgG, IgM, and IgA were 4808 mg/dL (normal range: 870-1,700), 551 mg/dL (normal range: 110-410), and 253 mg/dL (normal range: 46-260), respectively. The test for anti-nuclear antibodies was positive, at a titer of 1:2,560 and showing homogenous pattern. Anti-mitochondria antibody was negative. Human leukocyte antigens (HLA) typing was DR-4, DR14.

Abdominal ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) were conducted to investigate the cause of hepatic dysfunction. The patient had no splenomegaly. Electronic gastroduodenal endoscope depicted no esophageal or gastric varices. There was no evidence of portal hypertension on endoscopic and radiographic studies. Liver biopsy showed moderate to severe portal fibrosis with partial nodular formation of parenchyma, interface hepatitis, and moderate to severe portal inflammation consisting of lymphocytes and plasma cells. Rosette arrangement of hepatocytes was commonly observed in periporal zones. However, interlobular bile ducts were hardly involved. Inflammation activity and the stage of fibrosis were classified as A3F3 according to the Inuyama classification (6) (Fig. 1). Cirrhosis was not evident. Autoimmune hepatitis was diagnosed provisionally. A final diagnosis of AIH was established on the basis of a positive anti-nuclear antibody test, high titers of serum globulin, no evidence of current hepatitis virus infection, histological findings, and a good response to corticosteroid therapy, all of which met the diagnostic criteria for type 1 AIH (7). The patient had a pre-treatment AIH score of 26 according to the system proposed by the International Autoimmune Hepatitis Group (7).

Prednisolone (40 mg/day) was started on the fifth hospital day, after the diagnosis of AIH. The patient’s elevated bilirubin levels began to decline after the administration of steroids for 3 days, and eventually normalized in one month. Other liver function tests including AST and ALT also decreased to normal ranges concomitantly. IgG declined gradually and returned to normal range after approximately a year (Fig. 4). She was maintained on prednisolone at 2 mg/day.

**Figure 1.** Histological findings of liver biopsy. Liver biopsy shows moderate to severe portal inflammation infiltrated by lymphocytes and plasma cells (a), interface hepatitis (b) (arrow), portal fibrosis with nodular formation (c) and (d) rosette arrangement of hepatocytes (arrow) in periporal zone. (a, b, d: Hematoxylin and Eosin staining; c: Masson-trichrome stain). Magnification for a, b and c: ×100; for d, ×400.
After 6 months, she complained of exercise-induced dyspnea for the previous month. CTD is characterized by polyarthralgia, arthritis, low grade fever, erythema, sicca symptom, and Raynaud’s phenomenon. However, the patient showed none of these characteristic symptoms. Echocardiography revealed a dilated, hypertrophied right ventricle and septal flattening in a parasternal short axis view (Fig. 2a). Continuous Doppler echocardiography revealed a dilated right ventricle, severe tricuspid insufficiency and systolic pulmonary arterial hypertension (Fig. 2b). Ventilation/perfusion scan of lungs did not suggest the presence of thromboembolism. Right heart catheterization disclosed severe pulmonary arterial hypertension with a mean right atrial pressure of 24 mmHg (normal: <6 mmHg), systolic PAP of 95 mmHg (normal: <30 mmHg), mean PAP of 54 mmHg (normal: <14 mmHg), and cardiac output of 2.43/min/m² body surface area (normal: >2.9/min/m²). Immunological studies showed a positive test for anti-nuclear antibodies at a titer of 1: 640 with homogenous staining pattern, while anti-DNA was 14 IU/mL (normal: <6), RAHA titer was \( \times 80 \) (normal: \( \times <40 \)), anti-RNP was 25.9 pU/mL (normal: <15), anti-Scl was 6.0 U/mL (normal: <16), anti-SS-A was 109.0 U/mL (normal: <10.0), and anti-SS-B was
26.6 U/mL (normal: <15.0). Other assays including anti-ds-DNA, anti-Smith, anti-Scl-70, anti-centromere, anti-Jo1, perinuclear anti-neutrophil cytoplasmic antibody (P-ANCA) and cytoplasmic ANCA (C-ANCA) were negative. The serum circulating immune complex was 1.39 g/mL (normal: <1.23 g/mL), C3 was 96 mg/dL (normal: 85-135), and C4 was 15 mg/dL (normal: 13-35).

Pulmonary arterial hypertension (PAH) is the most ominous complication of collagen vascular diseases (4). The patient was judged to be class II according to the WHO Classification of Functional Status of Patients With Pulmonary Hypertension (8). Under right cardiac catheterization, she was given sildenafil at 60 mg/day. Her general status further improved to WHO class I by sildenafil. SPAP and mean PAP (mPAP) decreased from 92 and 57 to 61 and 33 mmHg, respectively. Pulmonary vascular resistance (PVR) decreased from 15 to 6.4 Wood’s units. She was judged to be quite responsive to oral sildenafil (Fig. 4).

**Discussion**

We report a rare case of AIH with PAH from which we obtained multiple immunologic data. PAH includes idiopathic PAH (IPAH) and pulmonary hypertension associated with various conditions such as CTD, congenital systemic-to-pulmonary shunts, portal hypertension and human immunodeficiency virus (HIV) infection (8). All these conditions manifest similar pathological obstructive changes of the pulmonary microcirculation, suggesting shared pathobiological processes across the disease spectrum of PAH (9). The pathology of the pulmonary artery has been described in a case of fatal pulmonary arterial hypertension with non-cirrhotic portal fibrosis. Autopsy revealed classical plexogenic pulmonary arteriopathy in the lung pathological finding (10).

Recently, portopulmonary hypertension (PPH) is defined as the development of pulmonary arterial hypertension complicated by portal hypertension with or without advanced hepatic disease. Despite the rarity of PPH (2% of the patients with portal hypertension), its clinical implications are significant (11, 12). In the present case, gastrointestinal fiberscope showed no esophageal and gastric varices, and CT scan depicted no gastro-renal shunt; therefore, the etiology of PAH was unlikely to be associated with portal hypertension. Unfortunately hemodynamic study of liver-portal circulation was not undertaken.

Since the presence of PAH has been extensively described in the course of various CTDs (4), we investigated the association of PAH with CTDs. In a recent study on community-based rheumatology practices in the US, the prevalence of PAH was 13.3% in patients with systemic sclerosis and mixed connective tissue disease as analyzed by echocardiography (13). These data were confirmed in a British study that adopted hemodynamic confirmation by right heart catheterization using a diagnostic algorithm, which found a prevalence of 12% in patients with systemic sclerosis (14). PAH appears to be less commonly associated with systemic lupus erythematosus; however, well-controlled prospective
trials are lacking and retrospective studies reported a prevalence of up to 14% as assessed by echocardiography (15). Patients with AIH may be at an increased risk of developing systemic CTD (3). Moreover, there appears to be shared susceptibility alleles for AIH and CTD in addition to shared autoantibodies (3). On the other hand, Morrison et al (16) reported an association of type 1 AIH with PAH, although the association is quite rare. Their case series described the clinical and pathologic findings of seven consecutive patients with progressive and fatal pulmonary hypertension which was not explained by predisposing cardiac or pulmonary diseases. Bertino et al (17) reported a case of AIH/PAH with correlated diagnostic and therapeutic implications, and proposed the possibility to classify this condition in the context of a more complex “overlap syndrome”.

In the liver biopsy, there were many abnormal vessels. Most vessels in a liver biopsy can be easily identified as lymphatic vessels or blood vessels by a combination of D-2 40 (lymph vessels) and CD34 (blood vessels) immunostaining. D2-40 stains the endothelium of a small lymphatic vessel but not that of the adjacent capillary, while CD34 stains the endothelium of a portal vein, capillary and arteriole. Using this method, we found that the abnormal vessels in the liver biopsy of the present case were dilated lymphatic vessels (Fig. 3). Previous report showed that the number of lymphatics and areas occupied by the lymphatics do not differ significantly with the activity of hepatitis, but differ significantly in association with the degree of liver fibrosis. These changes are thought to be caused by the disturbance of microcirculation associated with liver fibrosis and lobular distortion (18).

As for clinical manifestations, the present patient had anti-nuclear antigen, anti-SS-A, anti-SS-B, and anti-RNP antibodies, but no signs or symptoms suggestive of a systemic autoimmune disease, and did not fulfill the classification criteria for defined diseases. Such conditions have been defined as undifferentiated connective tissue diseases (UCTD) (19). The most characteristic symptoms of UCTD are represented by arthritis and arthralgias, Raynaud’s phenomenon and leukopenia, while neurological and kidney involvement is virtually absent. Eighty percent of these patients have a single autoantibody specificity; more frequently anti-SS-A and anti-RNP antibodies. Stable UCTD are considered a distinct clinical entity, and therefore it has been proposed to define those conditions as UCTD. Classification criteria have also been proposed and studies to better define them are under way (19). Patients with signs and symptoms suggestive of a systemic autoimmune disease but not fulfilling the classification criteria for defined diseases are commonly encountered in clinical practice. Although many aspects of these conditions have been studied and clarified, there is still no agreement on how best to identify UCTD patients after disease onset. However, such identification is of paramount importance, and further analysis is necessary to improve the sensitivity and specificity of the proposed classification criteria (19).

Therefore, in cases of PAH, thorough immunological and hepatic function studies are always recommended in order to ensure an early diagnosis and a prompt treatment for AIH, thus preventing the risk of a rapid progression to severe cirrhosis and pulmonary hypertension (16).

References
