Primary Biliary Cirrhosis-Autoimmune Hepatitis Overlap Syndrome Concomitant with Systemic Sclerosis, Immune Thrombocytopenic Purpura

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Abstract

A 58-year-old Japanese woman presented with chronic fluctuating liver dysfunction with purpura. Raynaud’s phenomenon had been diagnosed 4 years previously. At the initial examination, skin biopsy showed limited cutaneous systemic sclerosis (SSc). Laboratory investigations revealed liver dysfunction. Anti-nuclear antibodies, anti-mitochondria M2 antibody, anti-thyroglobulin antibody, and platelet-associated IgG were positive. Primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH) were diagnosed serologically, clinically and histologically. Immune thrombocytopenic purpura (ITP) was diagnosed by bone marrow puncture, clinical and laboratory findings, and Helicobacter pylori IgG was positive. She was treated with prednisolone 30 mg/day, ursodeoxycholic acid 600 mg/day, and a 7-day course of lansoprazole plus amoxicillin and clarithromycin. Thrombocytes increased rapidly and transaminase improved at day 7. We report a rare case of PBC-AIH overlap syndrome with concurrent ITP and SSc which suggest the presence of shared genetic susceptibility factors in multiple autoimmune conditions including PBC, AIH, ITP and SSc.

Key words: primary biliary cirrhosis (PBC), autoimmune, hepatitis (AIH), systemic sclerosis (SSc), immune thrombocytopenic purpura (ITP)

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Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterized by gradual destruction of the interlobular bile ducts leading to damage of the hepatocytes. The etiology remains unknown. The rate of disease progression is quite variable, but typically the disease is slowly progressive (1). Approximately half of PBC patients are affected by at least one additional autoimmune disease. A significant subgroup of patients (20%) has multiple additional autoimmune conditions. These multiple autoimmune disease cases include combinations of Sjögren’s syndrome, autoimmune thyroid disease, rheumatoid arthritis and scleroderma (2).

Autoimmune hepatitis (AIH) associated with connective tissue disorder is regarded to be rare. However, West et al (3) reviewed a case series of patients with AIH and reported that patients with AIH may be at increased risk for developing systemic CTD, while a review of literature reveals that systemic CTD may be at increased risk of developing AIH. The so-called “PBC-AIH overlap syndrome” has been defined as the concurrent manifestation of the main characteristics of the two conditions at the same time in the

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same patient (4-6). In a comparative study, patients with PBC-AIH overlap syndrome presented with characteristic features of PBC (anti-mitochondrial M2 antibodies and bile duct damage compatible with PBC), but a more hepatic picture than a cohort of typical PBC patients (7). Here, we report a case of PBC-AIH overlap syndrome with cutaneous systemic sclerosis (SSc) and immune thrombocytopenic purpura (ITP).

Case Report

In 2009, a 58-year-old Japanese woman was admitted to a local hospital because of chronic fluctuating liver dysfunction. She had been diagnosed with Raynaud’s phenomenon 4 years earlier. A skin biopsy from the left forearm showed irregularly thickened collagen bundles in the dermis and degenerated bundles of collagen fibers, with perivascular inflammatory infiltrate of mononuclear cells, and mildly reduced sweat and sebaceous glands (Fig. 1a). She fulfilled the criteria of systemic sclerosis (scleroderma) proposed by the American College of Rheumatology (8) and was classified as limited cutaneous SSc (lcSSc) according to the classification system proposed by LeRoy et al (9). She was transferred to our hospital for thorough investigation of liver dysfunction.

Her physical findings on admission to our hospital were as follows: body temperature, 36.8°C; pulse, 69 beats/min and regular; blood pressure, 122/77 mmHg; respiratory rate 16/min; no anemic sign at the conjunctiva palpebra; and icteric finding at conjunctiva bulbi. No flapping tremor or palmar erythema was observed. Superficial lymph nodes were not palpable. She had purpura on the left side of her leg. Physical examination of her hands revealed findings characteristic of scleroderma; namely, her skin was tight, smooth, glistening, and white (Fig. 1b). The lungs were normal on auscultation, chest radiograph, and electrocardiogram. The initial laboratory findings were as follows. Hematological data showed normal white blood cell count (5.40 × 10³/μL; normal range, 3.3-9.0 × 10³/μL), slightly reduced red blood cell count (3.68 × 10¹²/μL; normal range, 4.30-5.70 × 10¹²/μL), and reduced platelet count (4.50 × 10¹²/μL; normal range, 140-340 × 10¹²/μL). Erythrocyte sedimentation rate was 45 mm/h. Blood biochemical data were total bilirubin 1.3 mg/dL (normal range: 0.2-1.2 mg/dL), direct bilirubin 0.3 mg/dL (normal range: 0.0-0.2 mg/dL), aspartate aminotransferase (AST) 406 IU/L (normal range: 10-40 IU/L), alanine aminotransferase (ALT) 481 IU/L (normal range: 5-45 IU/L), alkaline phosphatase 308 IU/L (normal range: 100-325 IU/L), γ-guanosine triphosphate 155 IU/L (normal range: <30 IU/L), blood urea nitrogen 10.6 mg/dL (normal range: 8.0-26 mg/dL), creatinine 1.2 mg/dL (normal range: 0.47-0.71 mg/dL), IgG 2,020 mg/dL (normal range: <0.3 U/mL) and platelet associated IgG (PAIgG: 50.5 ng/10⁷ cell; normal range: 5.0-25.0 ng/10⁷ cell) were positive. Abdominal ultrasonography and computed tomography, conducted to examine the cause of hepatic dysfunction, detected no abdominal mass lesion. The patient also had no splenomegaly. Gastrointestinal fibroscopy revealed short segment Barrett’s esophagus and gastric bleeding related to portal hypertensive gastropathy. *Helicobacter pylori* IgG (18 U/mL; normal range: <10 U/mL) was positive. A liver biopsy showed epithelial damage in interlobular bile duct, intraepithelial lymphocytes and periductal lymphoplasmacyte infiltration, resembling chronic nonsuppurative destructive cholangitis (CNSDC) (Fig. 2a, b). PBC was diagnosed clinically and histologically according to the criteria proposed by the Japanese Joint Research Group for Autoimmune Hepatitis (10). Moreover, liver biopsy showed moderate to severe portal fibrosis with partial

![Figure 1](image-url)
necrosis associated with portal fibrosis (Fig. 2a, c). Inflammatory activity and the stage of fibrosis were classified as A2F2, according to the Inuyama classification (11). Cirrhosis was not evident. Autoimmune hepatitis was diagnosed provisionally. A final diagnosis of AIH was established on the basis of a positive antinuclear antibody test, high titer 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 (12). The patient had a post-treatment AIH score of 13 (probable AIH) according to the system proposed by the revised International Autoimmune Hepatitis Group (12). A bone marrow puncture showed normal cellular marrow with normal maturation of the erythrocytes, normal maturation of granulocytes and relatively increased megakaryocytes (Fig. 3). Immune thrombocytopenic purpura (ITP) was diagnosed from clinical and laboratory findings (13).

The patient received prednisolone 30 mg/day; ursodeoxycholic acid 600 mg/day; and a 7-day course consisting of lansoprazol 30 mg twice a day (b.i.d.), amoxicillin 750 mg and clarithromycin 200 mg b.i.d. Platelet count increased slowly without further treatment from 4.5×10^3/μL at day 1 to 15.3×10^3/μL at day 7. Transaminase levels began to decline after the administration of prednisolone for 3 days, and eventually were normalized in one month (Fig. 4).

### Discussion

The PBC-AIH overlap syndrome is a disease entity proposed by Popper and Schaffner (14) and has clinical features of both PBC and AIH. The histological characteristics of the disease are marked periportal necrosis, widespread bridging necrosis and CNSDC that are characteristic of PBC, together with a mixed finding of highly proliferated cholangiocytes and normal interlobular biliary tracts (15). The present patient, diagnosed with overlap syndrome, had high serum levels of ALT and IgM, showing mixed features of PBC and AIH.

Patients who have an overlap between AIH and PBC pose...
a major therapeutic dilemma. Ursodeoxycholic acid is a safe and life-extending therapy for most patients with PBC (16), whereas corticosteroids with or without azathioprine markedly improve survival in patients with AIH (17). Treatment with UDCA improves serum transaminase levels in patients with type 1 AIH, but change of histological activity after UDCA treatment has been controversial (18). Furthermore, the duration from treatment initiation to normalization of serum ALT levels is longer in UDCA treatment compared with corticosteroid treatment (19). Further studies are necessary to define the optimal therapeutic strategies in patients with overlapping PBC and AIH.

The detection of AIH overlap syndromes appears to depend on the selection of specific diagnostic criteria. Uniform application of a systematic algorithm, therefore, is warranted to accurately determine the prevalence in different populations. The revised International Autoimmune Hepatitis Group (IAIHG) scoring system is a valuable tool for the diagnosis of classical AIH (12). However, the applicability of the IAIHG criteria for the diagnosis of variant forms of AIH is questionable (20, 21). The IAIHG score for the present case was 13, and is classified as probable AIH. In a study of PBC patients, probable AIH overlap was diagnosed in 19%, with no case of definite AIH overlap identified using the revised IAIHG scoring system (20).

The precise mechanism underlying ITP remains largely unknown. Immune dysregulation and the development of autoantibodies appear to play a major role (22). Autoantibodies are present in the plasma of patients with ITP. In approximately 50-70% of these patients, the antibodies recognize one or more platelet surface glycoproteins (GP) including GPIb-IIIa, GPIb-IX and GPIa-II (22). In general, hypersplenism is suspected as a cause of thrombocytopenia in PBC. However, some patients with PBC exhibit autoantibodies; Dixon et al proposed the measurement of PAIgG in patients with PBC patient (23). As for the underlying mechanism of thrombocytopenia in PBC, a report has indicated that the glycoprotein complex of platelets and mitochondrial M2 antigen has similar amino acid sequences and they cross-react (24). ITP associated with PBC-AIH overlap syndrome is very rare, and our search of literature yielded only one case (25).

In Japan, the current standard first-line regimen for the eradication of *H. pylori* consists of a proton pump inhibitor, amoxicillin and clarithromycin for 1 week (26). The present patient received a 7-day course of triple therapy of lansoprazol, amoxicillin, and clarithromycin. There is growing evidence of an association between *H. pylori* eradication and platelet recovery in patients with ITP (27, 28). The evidence is strongest in Japan, where *H. pylori* eradication is now recommended as an initial treatment for *H. pylori*-positive ITP patients (29).

Although the prevalence of PBC concomitant with SSc is not clear, approximately 15% of patients with PBC have been reported to have SSc, mostly the variant of lcSSc (30). Concurrent autoimmune hepatitis and SSc is unusual. A Japanese patient with CREST syndrome and autoimmune hepatitis was reported (31). Marie et al (32) reported two patients with CREST variant of SSc, who developed autoimmune hepatitis. They proposed that since liver involvement may precede skin manifestations, the evaluation for SSc is appropriate when autoimmune hepatitis is noted. This evalu-
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References