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Case Report

A Case of Autoimmune Hepatitis Associated with Idiopathic Thrombocytopenic Purpura and Chronic Thyroiditis

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Autoimmune hepatitis (AIH) is frequently associated with extrahepatic autoimmune disorders such as rheumatoid arthritis, Sjögren's syndrome, and chronic thyroiditis, but the association with idiopathic (immune) thrombocytopenic purpura (ITP) is rare. We report a 46-year-old Japanese woman who presented with severe thrombocytopenia, elevated levels of aminotransferases, immunoglobulin (Ig) G, and platelet-associated IgG (PAIgG), positive anti-nuclear antibody, and hypothyroidism. After a diagnosis of coexisting AIH, ITP, and chronic thyroiditis, the patient was treated with 30 mg/day of prednisolone orally. The patient responded to such treatment: showing an increase in the number of platelets and decrease of serum levels of aminotransferases, IgG, and PAIgG to within normal ranges. Discrimination of ITP from liver cirrhosis as a cause of severe thrombocytopenia seen in chronic liver disease is important because complications and therapy are quite different. Prednisolone as a treatment for AIH should be also effective for ITP, and therefore, ITP should be considered when liver dysfunction is accompanied by severe thrombocytopenia, particularly in the autoimmune types of liver diseases.

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Key Words: *autoimmune hepatitis, idiopathic thrombocytopenic purpura, chronic thyroiditis, immunoglobulin G, platelet-associated immunoglobulin G, prednisolone*

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Introduction

Autoimmune hepatitis (AIH) is a chronic necroinflammatory liver disorder that occurs predominantly in women and is characterized by the presence of circulating autoantibodies and hypergammaglobulinemia.[1] Affected individuals often have concurrent extrahepatic autoimmune disorders such as rheumatoid arthritis, Sjögren's syndrome (SjS), and chronic thyroiditis,[2] but association with idiopathic (immune) thrombocytopenic purpura (ITP) has been rarely reported in Japan.[3-9]

In the present report, we describe a patient of AIH associated with ITP and chronic thyroiditis who was successfully treated with prednisolone.

Case Report

A 46-year-old Japanese woman was referred to Nagasaki University Hospital, Japan, in March 1998 for investigation of elevated levels of serum aminotransferases and thrombocytopenia. Fourteen months previously she was found to have elevated levels of aminotransferases with aspartate aminotransferase (AST) level of 97 IU/l and alanine aminotransferaese (ALT) level of 147 IU/l associated with 2-month history of anorexia and general malaise. She was not a smoker, and reported an average alcohol intake of <25 g/day for 8 years. The family history was negative for liver diseases and the patient denied exposure to agents relevant to hepatitis including blood transfusion or drugs. Physical examination on admission showed no hepatosplenomegaly, jaundice, or mucocutaneous bleeding.

Laboratory data on admission (Tables 1 and 2) showed severe thrombocytopenia, and elevated levels of erythrocyte sedimentation rate, total bilirubin, hepato-biliary enzymes, and gamma-globulin. Serum levels of immunoglobulin (Ig) G and IgM were

Table 1. Laboratory data on admission (1)

Test	Results	Normal range
Peripheral blood		
White blood cells (/μ^3)	2,700	(3,600 – 8,500)
Red blood cells (x10^4/μ^3)	427	(390 – 500)
Hemoglobin (g/dl)	13.1	(11.0 – 14.5)
Platelets (x10^4/μ^3)	3.2	(15 – 38)
Prothrombin time (%)	95	(82 – 127)
Activated partial thromboplastin time (second)	30.6	(25.2 – 34.4)
Fibrinogen (mg/dl)	229	(168 – 329)
Erythrocyte sedimentation rate (mm/hr)	60	(10 – 20)
Blood chemistry		
Total bilirubin (mg/dl)	1.8	(0.2 - 1.0)
Direct bilirubin (mg/dl)	1.0	(0 – 0.5)
Total protein (g/dl)	8.7	(6.2 - 8.0)
Albumin (g/dl)	3.6	(3.8 - 4.9)
Gamma-globulin (g/dl)	3.18	(0.7 - 1.5)
Aspartate aminotransferase (IU/l)	462	(11- 39)
Alanine aminotransferase (IU/l)	520	(4 -33)
Lactate dehydrogenase (IU/l)	427	(202 – 435)
Alkaline phosphatase (IU/l)	443	(88 - 270)
Leucine aminopeptidase (IU/l)	161	(40 - 100)
Gamma-glutamyl transpeptidase (IU/l)	180	(0 - 50)
Cholinesterase (ΔpH/hr)	0.89	(0.6 - 1.3)
Thymol turbidity test (U)	32.5	(0 – 4)
Zinc turbidity test (U)	41.8	(4 –12)
Total cholesterol (mg/dl)	179	(111 - 247)
Tumor markers		
Alpha-fetoprotein (ng/ml)	80	(<10)
Des-gamma-carboxy prothrombin (mAU/ml)	48	(<40)

Table 2. Laboratory data on admission (2)

Test	Results	Normal range
Immunology		
Immunoglobulin G (mg/dl)	3,879	(972 - 2,010)
Immunoglobulin M (mg/dl)	461	(67 - 359)
Immunoglobulin A (mg/dl)	447	(90 - 445)
CH50 (U/ml)	36.2	(20 - 60)
C3 (mg/dl)	57	(42 - 107)
C4 (mg/dl)	11.7	(14 - 40)
Anti-nuclear antibody	x2,560	(diffuse pattern)
Anti-dsDNA antibody (IU/ml)	198	(<12)
Anti-ssDNA antibody (AU/ml)	197	(<25)
Anti-mitochondrial antibody	(-)	(<x20)
Anti-smooth muscle antibody	x640	(<x40)
Rheumatoid factor (IU/ml)	27	(<14)
Anti-Ro/SS-A antibody (ID)	60.9	(gray zone: 7 - 20)
Anti-La/SS-B antibody (ID)	3.2	(gray zone: 10 - 25)
Anti-platelet antibody	(-)	
Platelet-associated immunoglobulin G (ng/10^7 cells)	274.2	(9 – 25)
Thyroid function tests		
Free T3 (pg/ml)	2.1	(2.7 – 4.5)
Free T4 (ng/dl)	0.8	(1.0 – 1.8)
Thyroid stimulating hormone (μU/ml)	6.26	(0.3 –3.2)
Thyroid test	x1,600	
Microsome test	x400	
Hepatitis virus markers		
IgM antibody to hepatitis A virus	(-)	
Hepatitis B surface antigen (HBsAg)	(-)	
Antibody to HBsAg (anti-HBs)	(-)	
Hepatitis B e antigen (HBeAg)	(-)	
Antibody to HBeAg (anti-HBe)	(-)	
Antibody to hepatitis B core antigen (anti-HBc)	(-)	
Antibody to hepatitis C virus (anti-HCV) (COI*)	0.4	(<1.0)

*Cut-off index (second-generation enzyme-linked immunosorbent assay).

elevated. Rheumatoid factor, anti-nuclear antibody (ANA), antibodies against single-stranded DNA and double-stranded DNA, anti-smooth muscle antibody, and anti-Ro/SS-A antibody were positive, but anti-mitochondrial antibody was negative. Anti-platelet antibody was negative, but platelet-associated IgG (PAIgG) was positive. Thyroid function tests revealed hypothyroidism with positive results of thyroid test (anti-thyroglobulin particle agglutination) and microsome test (anti-thyroid microsomal particle agglutination). All tests for serum markers of hepatitis A, B, or C virus infections were negative. Abdominal computed tomography (CT) showed mild splenomegaly but no hepatobiliary mass or stones. Thyroid ultrasonography

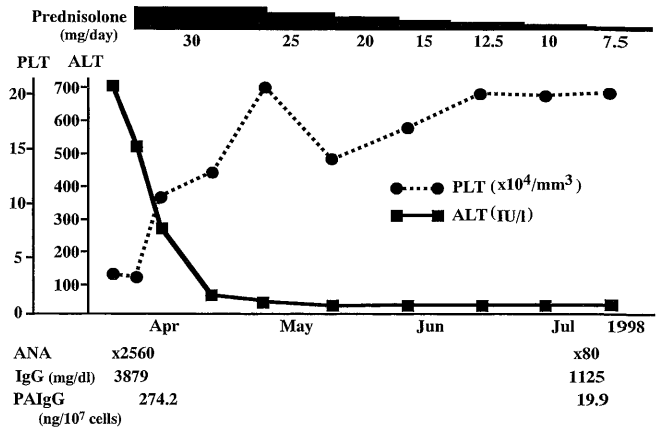

Figure 1. Clinical course. Administration of prednisolone reduced serum alanine aminotransferase (ALT), anti-nuclear antibody (ANA), immunoglobulin (Ig) G, and platelet-associated IgG (PAIgG), and also increased platelet (PLT) count.

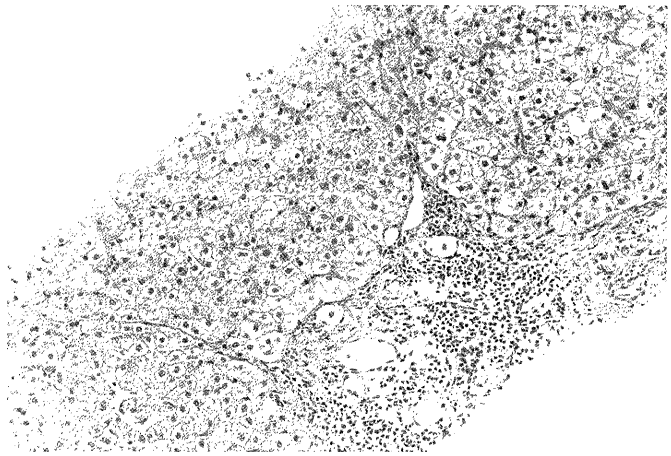

Figure 2. Histopathological examination of the liver biopsy specimen obtained in June 1998 showing fibrous portal expansion with predominantly lymphoplasmacytic infiltrates but no interface hepatitis. (H-E stain, x100)

revealed no thyroid swelling or mass. Bone marrow aspirate showed normoplastic marrow with an increase in the number of megakaryocytes. Schirmer's test was negative. According to the revised scoring system for the diagnosis of AIH,[10] an aggregate score was 17 before treatment, indicative of "definite AIH" based on the following individual scores: female gender (+2); ALP:AST ratio <1.5 (+2); serum IgG 1.5-2.0 times above normal (+2); ANA titer 1:2560 (+3); seronegative for hepatitis viral markers (+3); no drug history (+1); average alcohol intake <25 g/day (+2); other autoimmune disease ITP (+2).

The diagnosis of AIH, ITP, and chronic thyroiditis was made based on the aforementioned clinical and laboratory findings. Because of the severe thrombocytopenia, liver biopsy was not performed at that stage. The patient was treated with 30 mg/day

of prednisolone, and thereafter the number of platelets increased and the serum levels of aminotransferases, IgG, and PAIgG returned to within normal limits (Figure 1). Examination of a percutaneous liver biopsy specimen obtained in June 1998 showed fibrous portal expansion with predominantly lymphoplasmacytic infiltrates but no interface hepatitis (Figure 2). The dose of prednisolone was tapered and was maintained at 7.5 mg/day. She remains well and results of liver function tests at the latest follow-up in June 2001 were within normal range. The aggregate AIH score increased to 20 after treatment and liver biopsy (predominantly lymphoplasmacytic infiltrates on liver histology; +1, complete response to therapy; +2), again indicative of "definite AIH".[10]

Discussion

A specific feature of AIH is the association of extrahepatic immune-mediated syndromes.[2] According to a nationwide survey in Japan,[11] extrahepatic autoimmune disorders were present in 229 (28%) of 817 patients with AIH, and the most frequent disorders were rheumatoid arthritis (10%), SjS (10%), and chronic thyroiditis (10%). However, the association of ITP in patient with AIH has been rarely reported in Japan, and the prevalence is around 2%.[4, 12]

The etiopathological association between AIH and ITP is obscure at present. ITP is an autoimmune disease characterized by a low platelet count, mucocutaneous bleeding, normal bone marrow findings, and the absence of other causes of thrombocytopenia in which anti-platelet autoantibodies such as PAIgG induces platelet destruction.[13, 14] Pfueller et al. reported that of 24 patients with AIH, 13 (54%) had low platelet counts and 17 (71%) had elevated levels of PAIgG.[15] The same group also reported that 12 (92%) of 13 AIH patients with thrombocytopenia had elevated levels of PAIgG, and overall, PAIgG levels in AIH correlated with the degree of thrombocytopenia and increased levels of serum IgG.[15] The clinical course of our patient was in line with this finding because serum levels of PAIgG and IgG decreased simultaneously after prednisolone treatment.

Another possible mechanism is an AIH-SjS-ITP association. As described above, AIH frequently associates with SjS, and the prevalence of complicating thrombocytopenia in patients with SjS has been reported to be approximately 15%.[16, 17] However, our patient did not suffer from SjS because of the lack of xerostomia and keratoconjunctivitis, and the negative result of Schirmer's test. Systemic lupus erythematosus (SLE)-associated hepatitis should also be considered in our patient because thrombocytopenia caused by peripheral immune destruction is relatively common in SLE (20-40%).[18] However, the diagnostic criteria of SLE were not fulfilled in our patient,[19] and the international AIH score indicated our patient as "definite AIH".

Thrombocytopenia frequently occurs in chronic liver diseases, and may often be considered a predictive sign of evolution to liver cirrhosis. This is thought to be due to the sequestrating function of an enlarged spleen (hypersplenism), the presence of anti-platelet antibodies, and/or impaired production of thrombopoietin in cirrhotic patients.[20, 21] Discrimination of ITP from liver cirrhosis as a cause of severe thrombocytopenia is important because complications and therapy are quite different. In most cases of ITP, marked splenomegaly is seldom seen and the liver function tests such as serum albumin, cholinesterase, and prothrombin time are not so impaired. Indeed, prednisolone administered as a treatment for AIH was also effective for ITP in our patient. Therefore, ITP should be considered when liver dysfunction is accompanied by severe thrombocytopenia, particularly in the autoimmune types of liver diseases.[15]

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