INTERNAL MEDICINE

□ CASE REPORT □

Autoimmune Hepatitis Associated with Immune Thrombocytopenic Purpura

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Abstract

Although autoimmune hepatitis (AIH) is frequently complicated with chronic thyroiditis or other autoimmune disorders, reports on its association with immune thrombocytopenic purpura (ITP) are scarce. We herein describe a case of AIH associated with ITP. A 75-year-old Japanese woman was admitted to our hospital due to increased aminotransferase levels and severe thrombocytopenia. Elevated serum immunoglobulin G (IgG) was detected, and tests for platelet-associated IgG and anti-nuclear antibody were positive. Following the diagnosis of AIH-associated ITP, prednisolone treatment of 0.6 mg/kg/day resulted in a decrease in the aminotransferase levels and an increased platelet count.

Key words: autoimmune hepatitis, immune thrombocytopenic purpura, corticosteroid

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Introduction

Type 1 autoimmune hepatitis (AIH) is a progressive liver disorder predominantly affecting women that is characterized by the presence of circulating autoantibodies [antinuclear antibody (ANA) and/or anti-smooth muscle antibody (ASMA)], hypergammaglobulinemia, and a favorable response to immunosuppressive therapy (1-5).

Individuals affected with AIH often have concurrent non-hepatic autoimmune disorders, such as chronic thyroiditis (9.2%), Sjögren's syndrome (7.2%), and rheumatoid arthritis (2.8%), but associations with immune thrombocytopenic purpura (ITP) are rare (1.4%) (5).

In the present report, we describe the clinical outcome of a patient with AIH associated with ITP who was successfully treated with prednisolone (PSL).

Case Report

A 75-year-old Japanese woman was admitted to the National Hospital Organization Shinshu Ueda Medical Center, Japan, in July 2013 for further investigation of elevated serum aminotransferase levels and thrombocytopenia. She had begun experiencing anorexia and general malaise one month prior. She was 153 cm in height and weighed 47 kg. She had no apparent fever or bleeding tendency. A physical examination at presentation revealed mild hepatomegaly and jaundice. The laboratory data from her referring institution were aspartate aminotransferase (AST) 935 IU/L, alanine aminotransferase (ALT) 913 IU/L, total bilirubin 7.7 mg/dL, and platelet count 2.8×10^4/μL. She had been diagnosed with essential hypertension three years prior and was taking a candesartan cilexetil/amlodipine besilate compound product. She had no other underlying diseases or medical history. The woman neither smoked nor drank. Her family history was negative for liver or autoimmune disease, and she denied exposure to agents relevant to hepatitis, such as blood transfusion or herbal (kampo) medicine.

The laboratory data on admission at our facility (Table 1, 2) showed severe thrombocytopenia and increased levels of hepato-biliary enzymes and gamma-globulin. Elevated serum immunoglobulin G (IgG) was noted as well. Tests for ANA and ASMA were positive. Platelet-binding IgG (PBIgG) was negative, but platelet-associated IgG (PAIgG) was 894 ng/10^7 cells (nl: <47). *Helicobacter pylori*

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Table 1. Laboratory Findings on Admission.

<Peripheral Blood>			<Biochemistry>			<Serology>		
WBC	3,100	/μL	TP	7.5	g/dL	CRP	0.7	mg/dL
Neutro	65.0	%	Alb	3.6	g/dL	IgM	106	mg/dL
Lymph	23.2	%	ZTT	29.0	KU	IgG	2,309	mg/dL
Mono	8.5	%	TTT	20.9	KU	IgA	332	mg/dL
Eosino	2.6	%	AST	801	IU/L	Type IV collagen 7s	87	ng/mL
Baso	0.7	%	ALT	857	IU/L			
RBC	414×10⁴	/μL	γ-GTP	152	IU/L	<Hormone>		
Hb	11.9	g/dL	T. Bil	8.3	mg/dL	TSH	1.02	μU/mL
Plt	2.8×10⁴	/μL	D. Bil	5.8	mg/dL	FT3	2.01	pg/mL
Ret	0.83	%	ALP	865	IU/L	FT4	1.62	ng/dL
			LDH	455	IU/L			
<Coagulation>			BUN	15.7	mg/dL	<Tumor Marker>		
PT%	80.3	%	Cr	0.6	mg/dL	AFP	3.3	ng/mL
PT-INR	1.07	INR	Na	140	mmol/L			
APTT	31.3	sec	K	4.1	mmol/L			
Fibrinogen	127	mg/dL	Cl	109	mmol/L			
FDP	5.6	μg/mL						

Ret: reticulocyte, FDP: fibrin/fibrinogen degradation products

Table 2. Laboratory Findings on Admission (2).

<Immunology>			<Viral Maker>		<Immunogenetic Analysis>	
ANA (Speckled)	×80		HBs Ag	(-)	HLA DRB1	*0405/*1501
ASMA	×160		HBs Ab	(-)		
AMA	(-)		HBc Ab	(-)		
AMA(M2)	(-)		IgM-HA Ab	(-)		
Anti-LKM1 Ab	(-)		IgM-HBc Ab	(-)		
PAIgG	894	ng/10⁷ cells	HCV Ab	(-)		
PBIgG	(-)		HCV-RNA	(-)		
Anti-DNA Ab	(-)		HEV-IgA	(-)		
Anti-ENP Ab	(-)		EBV-IgG	(±)		
Anti-Sm Ab	(-)		EBV-EBNA	(+)		
Anti-Ro/SSA Ab	(-)		VCA-IgG	(+)		
Anti-Ls/SSB Ab	(-)		VCA-IgM	(-)		
Tg Ab	>4,000	U/mL	CMV-IgM	(-)		
TPO Ab	283	U/mL	CMV-IgG	(-)		
H. pylori Ab	(-)		HSV-IgG	(+)		
			HSV-IgM	(-)		

ANA: anti-nuclear antibody, ASMA: anti-smooth muscle antibody, AMA: anti-mitochondria antibody, anti-LKM1 Ab: anti-liver/kidney microsome type 1 antibody, PAIgG: platelet-associated IgG, PBIgG: platelet-binding IgG, Tg antibody: anti-thyroglobulin antibody, TPO antibody: anti-thyroperoxidase antibody, *H. pylori* Ab: *Helicobacter pylori* antibody, EBV: Epstein-Barr virus, CMV: cytomegalovirus, HSV: herpes simplex virus, HLA: human leukocyte antigen

IgG testing was negative. Her thyroid-stimulating hormone and free-thyroxin levels were within normal ranges, although anti-thyroglobulin (Tg) and anti-thyroperoxidase (TPO) antibodies were positive. The diagnostic criteria for disseminated intravascular coagulation (DIC) proposed by the Japanese Ministry of Health, Labor and Welfare were not satisfied in this patient (score: 4). Tests for the hepatitis A, B, C, and E viruses, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus were all negative. Her human leukocyte antigen (HLA) typing pattern was DRB1*04:05 and DRB1*15:01. Enhanced abdominal computed tomography showed no cirrhosis or splenomegaly. A bone marrow examination uncovered normoplastic marrow with platelet depletion and a megakaryocyte count of 30/μL (Fig. 1).

A diagnosis of ITP was made based on the above clinical and laboratory findings. According to the criteria of the International Autoimmune Hepatitis Scoring System (6), the patient's pre-treatment clinical score without histology was 16 (female: +2, ALP (alkaline phosphatase)/ALT ratio: +2, IgG level: +2, ANA titer: +2, anti-mitochondrial antibody (AMA): 0, viral markers: +3, drugs: +1, alcohol: +2 and immune disease: +2), and indicative of definite AIH. Thus, we diagnosed her as having type 1 AIH associated with ITP. Liver biopsy was not performed at the time due to severe thrombocytopenia.

The patient promptly began treatment with 30 mg/day (0.6 mg/kg/day) of PSL on Day 5 of admission, which quickly restored her liver enzyme levels to within normal limits (Fig. 2). A percutaneous liver biopsy specimen was obtained on Day 14 (Fig. 3) since the platelet numbers had increased to approximately 10×10⁴/μL. Her post-biopsy score was 19. Tissue histology revealed centrilobular necrosis (Fig. 3a and c), infiltration of lymphocytic and plasma cells, and mild interface hepatitis around the portal vein (Fig. 3a and d). The inflammatory activity and fibrosis stage were classified as A1F1 (Fig. 3a and b) according to the Metavia scoring system (7).

Following an uneventful treatment course, the patient's se-

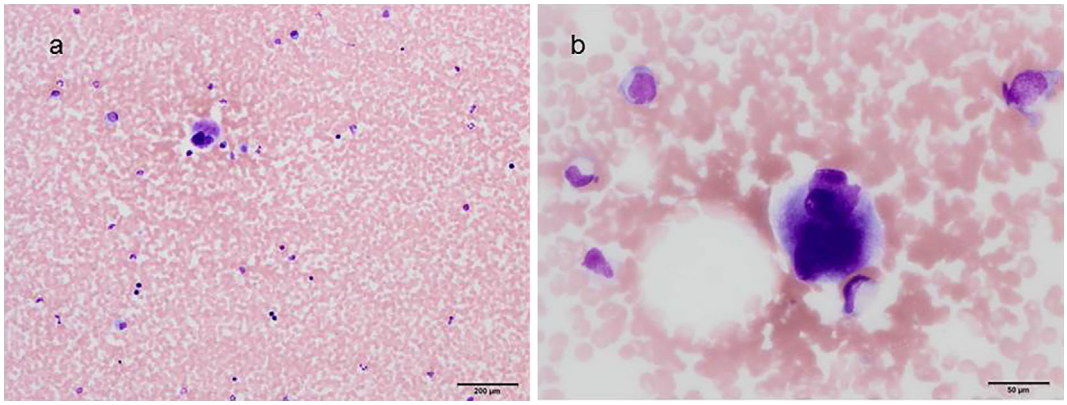

Figure 1. **The histological findings of a bone marrow examination. (a) Normoplastic marrow with platelet depletion was evident. (b) Megakaryocytes without dysplasia were present. Magnification: (a) ×40, Hematoxylin and Eosin (H&E) staining; (b) ×400, H&E staining.**

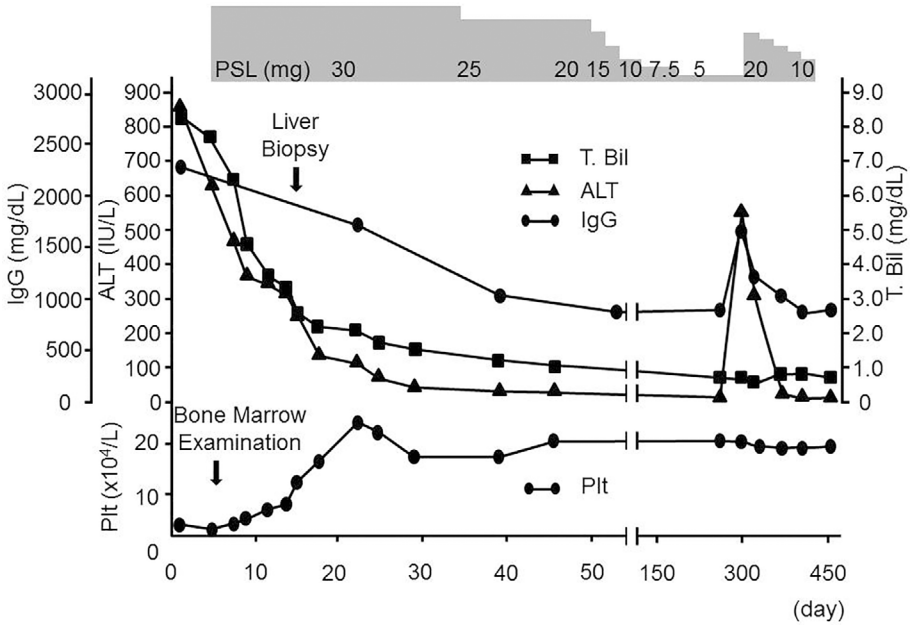

Figure 2. **Clinical course.**

rum transaminase and IgG levels became elevated without thrombocytopenia due to a recurrence of AIH when PSL was tapered to 5 mg/day. Restoring the steroid dose to 20 mg/day normalized her laboratory findings, and the serum transaminase and IgG levels and platelet count have since remained normal for over 19 months with a maintenance dose of 10 mg/day PSL (Fig. 2). Her PAIgG levels decreased to near-normal values (54 ng/10^7 cells). Informed consent was obtained from the patient for inclusion in the study.

Discussion

AIH is defined as a chronic liver disease with unknown etiological factors that is associated with aberrant autoreactivity and a genetic predisposition (1-5). In contrast, ITP is an acquired autoimmune disorder mediated by antibodies against platelet membrane glycoprotein (GP) Ib or IIb/IIIa complexes and thrombopoietin receptor (8-10). The precise mechanism underlying ITP remains elusive (11), and ITP complicating AIH is rare and of uncertain pathogenesis (12-14). In Japan, given that type 1 AIH represents the overwhelming majority (15) of AIH cases, all reported cases of AIH associated with ITP have been type 1.

Nagase et al. summarized 16 cases of AIH associated with ITP appearing in the Japanese literature (12). While AIH preceded ITP in 5 cases, the disorders manifested simultaneously in the others. In agreement with these findings, Wada et al. reported on a patient with a six-year history of AIH who developed ITP (13), and Yamaike et al. described an additional case of simultaneous AIH and ITP occurrence (14). Relapses of AIH and/or ITP were not found in any case. In our patient, either AIH and ITP developed simultaneously or AIH shortly preceded ITP, because liver histology (biopsied 9 days after commencing steroid therapy) showed very mild fibrosis (Fig. 3b). The first-line ther-

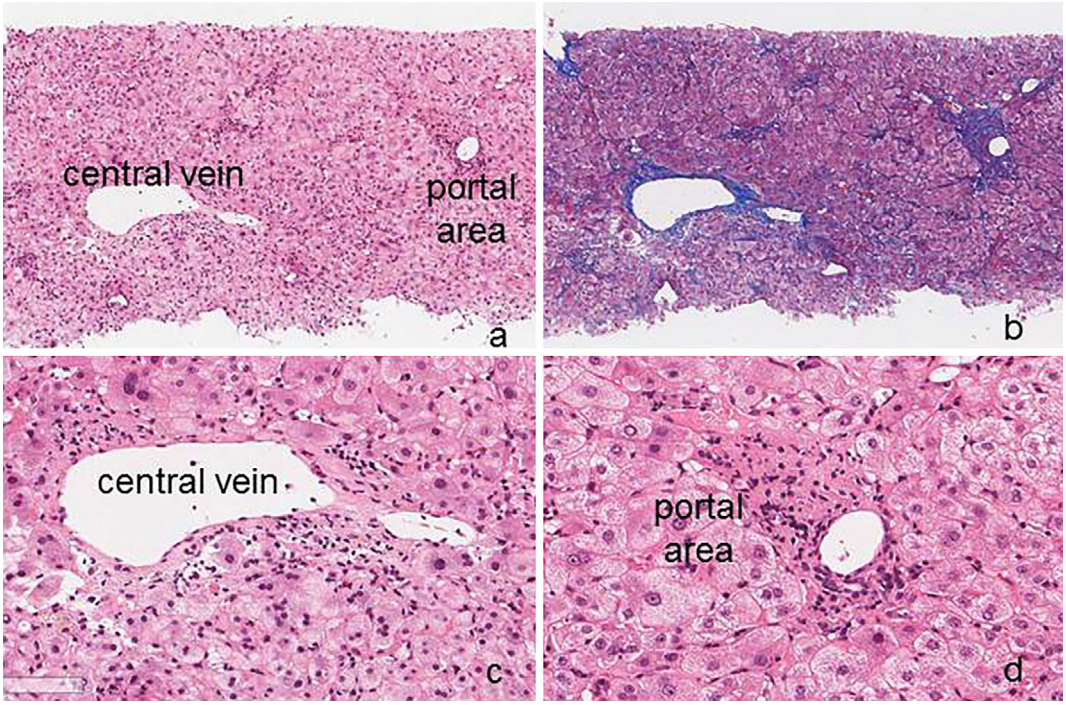

Figure 3. **The histological findings of liver biopsy. (a) The pathological diagnosis was mild chronic hepatitis. (b) Mild portal and perivenular fibrosis was seen. (c) The specimen exhibited centrilobular necrosis. (d) The specimen showed infiltration of inflammatory cells consisting of lymphocytes and plasma cells, with mild interface hepatitis in the portal zone. Magnification: (a) ×40, Hematoxylin and Eosin (H&E) staining; (b) ×40, Azan-Mallory staining; (c) and (d) ×400, H&E staining.**

apy for both AIH and ITP is corticosteroids (1-5). Roughly 24-50% of AIH patients experience relapse during steroid tapering or withdrawal (1, 15). Approximately 75% of patients with ITP respond to corticosteroids, but only 5-30% achieve a sustained remission (16). To our knowledge, the present case is the first of its kind, showing relapsing AIH and non-relapsing ITP during steroid tapering. We suspected that the response thresholds of the two diseases to PSL were different in our subject.

HLA regions have been strongly associated with autoimmune disease. HLA class II molecules on antigen-presenting cells play a crucial role in triggering the immune response, which begins with the recognition of peptide antigens in the HLA class II groove by the T-cell receptor of CD4 T cells through direct contact of both molecules. We previously reported that the most influential gene associated with type 1 AIH susceptibility was HLA-DRB1*04:05 (17, 18), while DRB1*15:01 conferred disease resistance (19). Kuwana et al. described several relationships between HLA and ITP. Strong associations between anti-GP autoantibodies and HLA class II genes have been identified, as follows: anti-GPIIb-IIIa antibody association with DRB1*04:05 and DQB *04:01; and anti-GPIb-IX antibody with DRB1*08:03 and DQB1*06:01 (20). The HLA typing pattern in the present case was DRB1*04:05 and DRB1*15:01. Thus, the DRB1* 04:05 allele may be linked to AIH associated with ITP. However, it is difficult to explain the low frequency of AIH with ITP, although the immunologically different mechanisms of the two disorders, which remain unresolved, may be involved.

Since ITP and AIH manifest as autoimmune-mediated disorders, the treatment for both conditions is PSL. Here, AIH recurred after PSL tapering but ITP did not. This differential immunosuppressive effect is of clinical interest and may provide insights into the mechanisms and interplay of autoimmune diseases.

The authors state that they have no Conflict of Interest (COI).

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