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CASE REPORT

Association of primary biliary cirrhosis with idiopathic thrombocytopenic purpura

Nobuyuki Toshikuni, Ryumei Yamato, Haruhiko Kobashi, Ken Nishino, Nobu Inada, Ritsuko Sakanoue, Mitsuhiko Suehiro, Yoshinori Fujimura, Gotaro Yamada

Nobuyuki Toshikuni, Ryumei Yamato, Ken Nishino, Nobu Inada, Ritsuko Sakanoue, Mitsuhiko Suehiro, Yoshinori Fujimura, Gotaro Yamada, Department of Internal Medicine, Center for Liver Diseases, Kawasaki Hospital, Kawasaki Medical School, Okayama 7008505, Japan
Haruhiko Kobashi, Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama 7008558, Japan
Author contributions: Toshikuni N wrote the paper; Toshikuni N, Yamato R and Kobashi H treated the present patient; Nishino K, Inada N, Sakanoue R, Suehiro M, Fujimura Y and Yamada G gave helpful comments on the present case.
Correspondence to: Nobuyuki Toshikuni, Dr, Department of Internal Medicine, Center for Liver Diseases, Kawasaki Hospital, Kawasaki Medical School, 2-1-80 Nakasange, Okayama 7008505, Japan. n.toshikuni@gmail.com
Telephone: +81-86-2252111 Fax: +81-86-2328343
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Abstract

Although both primary biliary cirrhosis (PBC) and idiopathic thrombocytopenic purpura (ITP) are autoimmune diseases, the association of the 2 diseases is rare. Here, we report a case of ITP that developed during the follow-up of PBC in a 74-year-old man. The patient had been diagnosed with PBC 12 years previously, and had received treatment with ursodeoxycholic acid. The platelet count decreased from approximately 60 × 10^9/L to 8 × 10^9/L, and the association of decompensated liver cirrhosis (PBC) with ITP was diagnosed. Steroid and immune gamma globulin therapy were successful in increasing the platelet count. Interestingly, human leukocyte antigen genotyping detected the alleles DQB1*0601 and DRB1*0803, which are related to both PBC and ITP in Japanese patients. This case suggests common immunogenetic factors might be involved in the development of PBC and ITP.

Key words: Primary biliary cirrhosis; Idiopathic thrombocytopenic purpura; Anti-platelet autoantibody; Platelet surface glycoprotein complex; Human leukocyte antigen

Peer reviewers: Yukihiro Shimizu, Dr, Kyoto Katsura Hospital, 17 Yamada-Hirao, Nishikyo, Kyoto 615-8256, Japan; Tom H Karlsen, MD, Institute of Immunology, Rikshospitalet University Hospital, N-0027 Oslo, Norway; Shinji Shimoda, MD, PhD, Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan

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INTRODUCTION

Primary biliary cirrhosis (PBC) is a chronic liver disease characterized by progressive biliary injury as a result of an underlying autoimmune process. PBC is often associated with extrahepatic autoimmune diseases such as Sjögren's syndrome and chronic thyroiditis. Idiopathic thrombocytopenic purpura (ITP) is a well-defined autoimmune disease, but the association of PBC with ITP is rare. However, cases of simultaneous occurrence of PBC and ITP as well as ITP after liver transplantation for PBC have been reported[1-4]. We describe a case in which ITP developed during the follow-up of PBC in an elderly man and discuss the possible mechanisms underlying the association of the 2 diseases.

CASE REPORT

A 74-year-old man was referred to our hospital in November 2000 because of liver dysfunction detected during a medical checkup. The patient had been diagnosed with nephrotic syndrome in 1995. Laboratory examinations showed elevated serum hepatobiliary enzymes and IgM, and the presence of antimitochondrial antibodies. Serologic markers for Hepatitis B and C viruses were negative. Histopathologic examination of a liver biopsy specimen obtained at laparoscopy revealed non-suppurative destructive cholangitis in the portal area (Figure 1). The diagnosis of PBC (Scheuer stage 3) was confirmed and ursodeoxycholic acid, 900 mg daily, was started. In January and June 2002, the patient underwent endoscopic variceal ligation plus endoscopic injection sclerotherapy as well as argon plasma coagulation for worsening esophageal varices.

In September 2007, the patient was admitted for the

Table 1 Laboratory data on admission

		Normal ranges			Normal ranges
WBC	4×10^9/L	3.5-8.5	IgG	2217 mg/dL	870-1700
RBC	3.44×10^{12}/L	4.2-5.5	IgA	478 mg/dL	110-410
Hb	10.4 g/dL	13.5-17.0	IgM	217 mg/dL	35-220
Plt	8×10^9/L	150-350	CRP	0.11 mg/dL	⩽ 0.3
PT-INR	1.14	0.9-1.08			
APTT	30.6 s	25-40	HBsAg	(-)	
Fibrinogen	301 mg/dL	178-384	HCV RNA	(-)	
AST	39 IU/L	10-35	ANA	× 640	
ALT	21 IU/L	7-42		Nucleolar	
ALP	390 IU/L	110-360	AMA	× 160	
LAP	48 IU/L	30-80	MPO-ANCA	(+)	
γGTP	29 IU/L	5-60	Anti-Jo-1	(-)	
T-Bil	0.5 mg/dL	0.2-1.2	Anti-DNA	(-)	
ChE	144 IU/L	168-470	Anti-SSA	(+)	
T-Cho	107 mg/dL	130-220	Anti-SSB	(-)	
TP	6.8 g/dL	6.5-8.0	Anti-Scl	(-)	
Alb	2.7 g/dL	3.8-5.3			
BUN	14 mg/dL	8.0-20			
Cr	0.92 mg/dL	0.6-1.10	PAIgG	13200 ng/10^7 cells	9-25

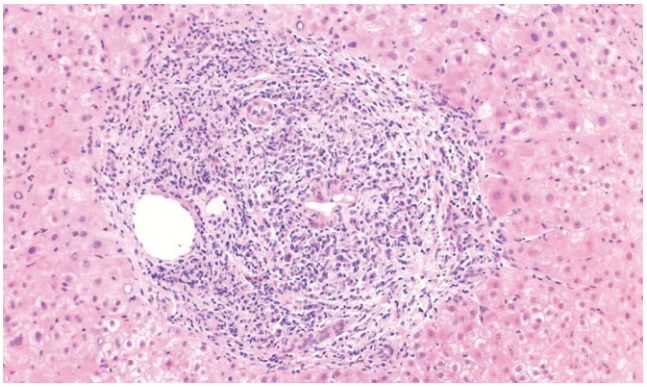

Figure 1 A liver biopsy specimen obtained at laparoscopy showing marked infiltration of lymphocytes and plasma cells, and degeneration of interlobular bile ducts in the portal area (HE, × 100).

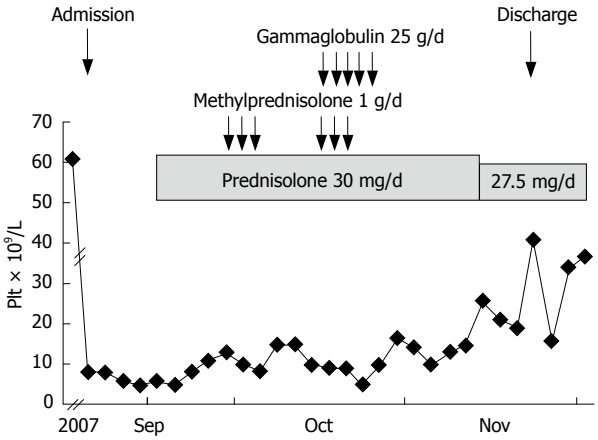

Figure 2 The clinical course of the patient.

treatment of recurrent esophageal varices. The platelet count had ranged between 52×10^9/L and 69×10^9/L for several years, but it was noted to decrease from 61×10^9/L in June 2007 to 8×10^9/L just before admission. Before the deterioration of thrombocytopenia, the patient had no infectious diseases and received no other medication. On admission, the patient had neither purpura nor bleeding episodes. Table 1 shows the laboratory data on admission. The platelet-associated IgG level was markedly high. Bone marrow biopsy revealed normocellular marrow without cellular atypia. Ultrasonography and magnetic resonance imaging revealed a cirrhotic liver with splenomegaly, ascites, and gallstones. The spleen size had remained unchanged from previous imaging examinations. Based on these findings, the association of PBC (decompensated liver cirrhosis) with ITP was diagnosed. Human leukocyte antigen (HLA) genotyping determined by polymerase chain reaction-sequencing-based typing or polymerase chain reaction-sequence specific primers (SRL, Inc., Tokyo, Japan) detected A*02010101, B*400201, C*030401, C*07020101, DPB1*0501, DQA1*0103, DQA1*030101, DQB1*030201, DQB1*060101, DRB1*080201, and DRB1*080302. The 13C urea breath test for *H pylori* infection was negative.

Figure 2 shows the clinical course. Oral prednisolone, 30 mg daily, for ITP was started on day 11, and diuretic therapy combined with albumin infusion for ascites was performed. As the platelet count did not increase notably, pulse therapy with intravenous methylprednisolone, 1 g daily, was added on d 22 to 24. However, the response was weak and temporary. On d 31, mild melena was identified. The patient was given a trial of intravenous immune gamma globulin therapy, 25 g daily, on d 32 to 36, combined with a second round of intravenous methylprednisolone pulse therapy on d 32 to 34. Because a moderate response was observed, prednisolone was continued, and the platelet count increased slowly. The ascites was relatively well controlled with diuretics at discharge. Considering the decompensated liver cirrhosis and the platelet count, we determined the patient required careful follow-up of esophageal varices without prophylactic endoscopic therapy.

DISCUSSION

Because immunogenetic factors are believed to influence the development of autoimmune diseases, the relationship between HLA alleles and susceptibility to PBC and ITP has been investigated[5-8]. In Japanese patients with PBC, the frequency of DPB1*0501, DQA1*0103, DQB1*0601, and DRB1*0803 is increased[5,6]. On the other hand, those with ITP have an increased frequency of DRB1*0410[7], and strong associations between anti-platelet surface glycoprotein autoantibodies and HLA alleles have been reported, including an association of anti-glycoprotein Ⅱb/Ⅲa antibody with DQB1*0401 and DRB1*0405, and of anti-glycoprotein Ⅰb/Ⅸ antibody with DQB1*0601 and DRB1*0803[8]. Of these HLA alleles, DPB1*0501, DQA1*0103, DQB1*0601, and DRB1*0803 were detected in the present case. It should be noted that DQB1*0601 and DRB1*0803 are related to both PBC and ITP. The frequency of a combination of the 2 HLA alleles in patients with PBC and ITP is significantly higher than that in general population[6,8]. Furthermore, it is estimated patients with a combination of the 2 HLA alleles are at least several-fold more susceptible to PBC and ITP. The 2 HLA alleles might be common immunogenetic factors for the development of PBC and ITP, and the mechanism underlying ITP development might be anti-glycoprotein Ⅰb/Ⅸ antibody-mediated platelet destruction. Unfortunately, anti-glycoprotein autoantibodies were not examined. Immunogenetic analyses should shed light on the mechanism of the association of PBC with ITP.

The present patient already had thrombocytopenia related to liver cirrhosis at the onset of ITP. Based on an evaluation of platelet kinetics, a recent study has shown reduced platelet production and enhanced platelet turnover in patients with liver cirrhosis[9]. Hypersplenism, as observed in the present case, is well known to enhance platelet turnover; the pathologically enlarged and congested spleen accelerates the sequestration and destruction of platelets. Another mechanism of thrombocytopenia in liver cirrhosis is anti-platelet autoantibody-mediated platelet destruction. Kajihara *et al*[10] have revealed a similar profile of the anti-glycoprotein Ⅱb/Ⅲa autoantibody response between patients with liver cirrhosis and those with ITP, and concluded that immune-mediated platelet destruction may contribute, at least in part, to cirrhotic thrombocytopenia. In the present case, an autoimmune response to platelets might have been induced or enhanced by the underlying liver cirrhosis.

Panzer *et al*[11] have reported autoantibodies eluted from a patient with PBC and ITP precipitate glycoprotein Ⅱb/Ⅲa of autologous and allogeneic platelets and bind to an epitope of the rat 70-kDa mitochondrial protein M2. Furthermore, computer analysis of published peptide sequences of the mitochondrial protein and glycoprotein Ⅱb/Ⅲa showed partial amino acid sequence homology, suggesting the possibility of a common antibody-binding site. In another study, it was suggested the development of the immune phenomenon in PBC may also involve immune-mediated platelet destruction[12]. There might be a mechanism by which PBC-related autoantibodies cross-reacting with platelet surface autoantigens cause ITP.

In summary, we experienced a rare case of the association of PBC with ITP. HLA genotyping suggests that common immunogenetic factors might be involved in the development of PBC and ITP.

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