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Abstract

A 34-year-old woman infected with human T cell leukemia virus type-I(HTLV-I) with recurrent thrombocytopenia and various autoantibodies is described. The platelet counts fluctuated between 1.3 x 10(4)/microliters and 14.8 x 10(4)/microliters without any medical treatment, and thrombocytopenia improved with a decrease of platelet-associated IgG (PA-IgG). Autoantibodies such as rheumatoid factor, antinuclear factor, anti-Sm, anti-RNP and anti-SSA antibodies were also recognized. Marker analysis of peripheral mononuclear cells showed an increase in the proportion of CD 25+ cells, CD 3+ HLA-DR+ cells, CD4+ HLA-DR+ cells and CD8+ HLA-DR+ cells. The recurrent thrombocytopenia and development of various autoantibodies in this HTLV-I carrier are speculated to be due to the alteration of B cell functions by T cells infected with HTLV-I.

KEYWORDS: recurrent thrombocytopenia, HTLV-I, HTLV-I carier

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— Brief Note —

A Human T cell Leukemia Virus Type-I Carrier with Recurrent Thrombocytopenia and Various Autoantibodies

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A 34-year-old woman infected with human T cell leukemia virus type-I(HTLV-I) with recurrent thrombocytopenia and various autoantibodies is described. The platelet counts fluctuated between $1.3 \times 10^4/\mu l$ and $14.8 \times 10^4/\mu l$ without any medical treatment, and thrombocytopenia improved with a decrease of platelet-associated IgG (PA-IgG). Autoantibodies such as rheumatoid factor, antinuclear factor, anti-Sm, anti-RNP and anti-SSA antibodies were also recognized. Marker analysis of peripheral mononuclear cells showed an increase in the proportion of CD 25+ cells, CD 3+ HLA-DR+ cells, CD 4+ HLA-DR+ cells and CD 8+ HLA-DR+ cells. The reccurrent thrombocytopenia and development of various autoantibodies in this HTLV-I carrier are speculated to be due to the alteration of B cell functions by T cells infected with HTLV-I.

Key words : recurrent thrombocytopenia, HTLV-I, HTLV-I carrier

Human T cell leukemia virus type-I (HTLV-I) is known to be the causative agent not only adult T-cell leukmeia (ATL) (1), but also of chronic progressive myelopathy [HTLV-I-associated myelopathy (HAM)] (2). In addition, recent investigations suggest a pathogenic role of HTLV-I in some bronchioloalveolitis (3, 4), and some chronic inflammatory arthropathy (5). In the present paper we describe a woman HTLV-I carrier with recurrent thrombocytopenia and various autoantibodies.

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Case Report

A 34-year-old woman was referred to our hospital because of arthralgia and thrombocytopenia. The patient was diagnosed as having idiopathic thrombocytopenic purpura (ITP) in October 1988. Examination of the blood showed a platelet count of $2.9 \times 10^4/\mu l$. Platelet-associated IgG (PA-IgG) was 167 ng/10^7

platelets and serological examination revealed positivity for anti-HTLV-I antibody. A biopsied specimen of bone marrow showed normocellular marrow with normal megakaryopoiesis. The serum immunoglobulin level was not elevated. Rheumatoid factor (RF), antinuclear factor (ANF) and anti-DNA antibodies were negative. She was observed without any medical treatment, and she begun to feel arthralgia of the left elbow, left fingers and left 2nd and 4th toes from the beginning of October 1989. The serum immunoglobulin level was increased (IgG; 2, 500 mg/dl) and ANF was also found to be positive. Then, she was referred to our hospital on December 4, 1989. The patient is a nurse and her father died of malignant lymphoma.

Physical examination on admission revealed a well-nourished female with moderate swelling of the tonsils. No lymphadentpathy was noted. The head and neck were normal. The lungs were clear, and the heart was normal. Abdominal examination was negative; the liver and spleen were not felt, and no masses were palpated. Neurological examination was negative. Erythrocyte sedimentation rate was 30 mm/h. Examination of the blood showed a red blood cell count of $434 \times 10^4/\mu l$, hemoglobin of 11.8 g/dl, Platelets count of $8.1 \times 10^4/\mu l$, a white blood cell count of $5,100/\mu l$ with 44 % segmented neutrophils, 15 % band forms, 32 % lymphocytes, and 9 % monocytes. Atypical lymphocytes suggesting ATL were not found. Bone marrow aspirate showed 1.4 % myeloblatst, 4.0 % promyelocytes, 10.4 % myelocytes, 7.2 % metamyelocytes, 14.2 % band forms, 12.6 % segmented neutrophils, 4.2 % eosinophils, 0.8 % basophils, 3.2 % monocytes, 30.6 % lymphocytes, 1.6 % plasma

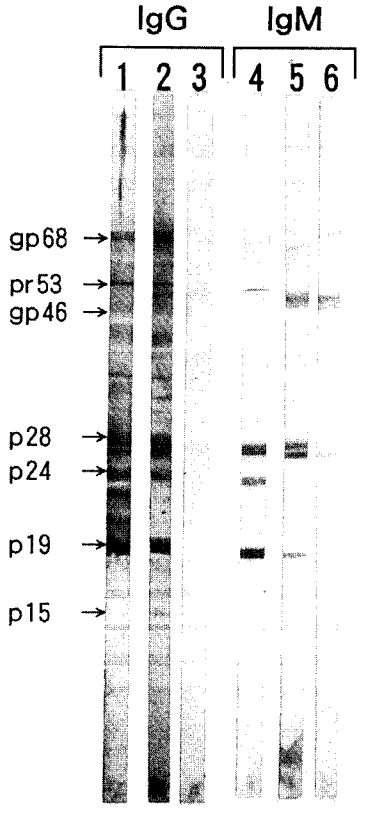

Fig. 1 Western blot anlalysis (6, 7) using sera obtained from an ATL patient (lanes 1 and 4), the present case (lanes 2 and 5) and a healthy control (lanes 3 and 6) using MT-2 cell lysate. Reactivities of IgM and IgG antibodies against MT-2 cell lysates were recognized in ATL patient and the present case.

Table 1 Serological examination on admission

CRP	(−)	Coombs test	
HBsAg	(−)	Direct	(−)
Wa-R	(−)	Indirect	(+)
RF	(+)	Antinuclear factor	Sp (++)
IgG	2450 mg/dl	Anti-DNA antibody	4.6 IU/l
IgA	270 mg/dl	Anti-Sm antibody	×32
IgM	300 mg/dl	Anti-RNP antibody	×42
C3	56 mg/dl	Anti-SSA antibody	×32
C4	13 mg/dl	Anti-SSB antibody	(−)
CH50	29 U/l	PA-IgG	260.4 ng/10^7 platelets

cells, 0.6 % reticulum cells and 8.6 % erythroblasts. Morphological abnormalities were not observed in hematopoietic cells. Liver function tests were negative, blood levels of urea nitrogen, creatinine, amylase and electrolytes were within normal limits. Rentogenological examinations of the lungs, bones and joints were negative, and electrocardiogram was also negative. Ultrasonographic examination of the abdomen disclosed a small cyst of the left kidney. No hepatosplenomegaly was noted. A titer of anti-HTLV-I antibody was 1:512 by the gelatin particle aggultination test. Western blot analysis (6, 7) using MT-2 cell lysate revealed IgG and IgM antibodies (Fig. 1). Southern blot analysis of DNA obtained from patient's peripheral mononucler cells showed a smear pattern indicating a random integration of HTLV-I proviral DNA (data not shown). Serum levels of IgG and CH50 were 2,450 mg/dl and 29 U/l, respectively. Serological examinations revealed that RF, indirect Coombs test, ANF, anti-Sm, anti-RNP and anti-SSA antibodies were positive. PA-IgG was 260.4 ng/10^7 platelets (Table 1). The proportions of CD4+ cells and CD8+ cells were 41.4 % and 32.1 %, respectively. Further analysis of surface markers revealed an increase in the proportions of CD25+ cells (8.1 %), CD3+HLA-DR+cells (21.5 %), CD4+HLA-DR+cells (11.7 %) and CD8+HLA-DR+cells (12.4 %) (Table 2). Retrospective analysis of hematological findings disclosed the fluctuation of platelet counts (Fig. 2), and she was diagnosed to be a HTLV-I carrier with recurrent thrombocytopenia. Latent systemic lupus erythematosus (SLE) was also suspected from serological findings. She was discharged on January 10, 1990 and observed without any medical treatment. On January 24,

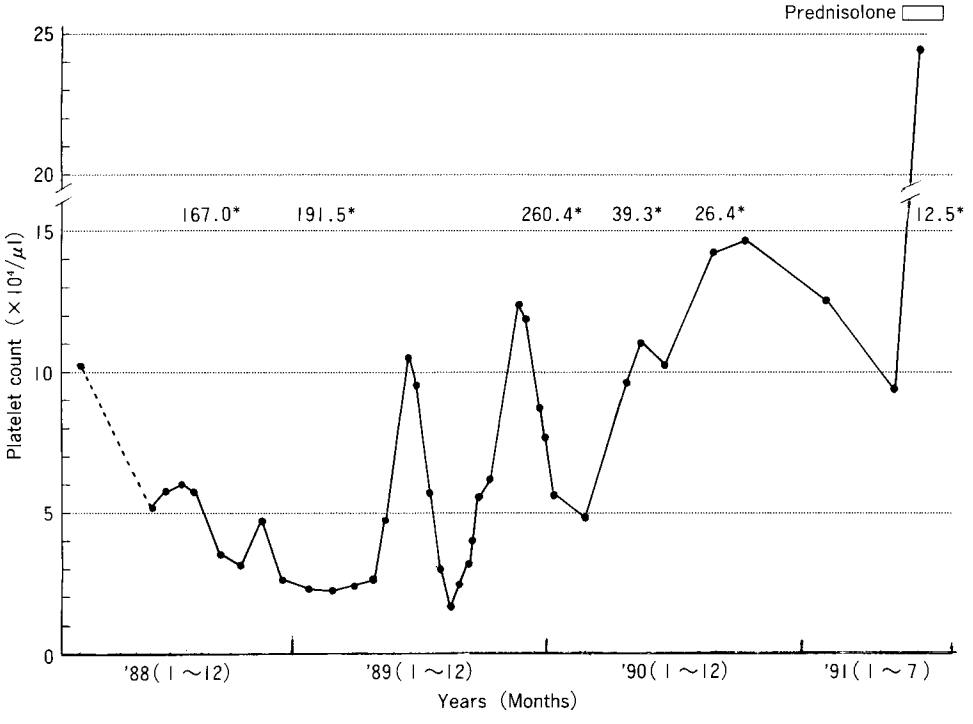

Fig. 2 Time course of platelet counts. *PA-IgG (ng/10^7 platelets)

Table 2 Surface markers of peripheral mononuclear cells on admission

CD 3	73.3 %	CD4+2H4+	14.3 %
CD 4	41.4 %	CD4+4B4+	22.3 %
CD 8	32.1 %	CD3+HLA-DR+	21.5 %
CD20	22.4 %	CD4+HLA-DR+	11.7 %
CD25	8.1 %	CD8+HLA-DR+	12.4 %

1991 she was diagnosed to be at the 18th week of pregnancy. At that date, the platelet count was $12.3 \times 10^4/\mu l$. On April 21, 1991 a caserean section was done due to the toxic pregnany. After the section platelet count decreased to $9.3 \times 10^4/\mu l$, prednisolone (30 mg per day as initial dose) was administered in order to prevent the exacerbation of latent SLE. Prednisolone was tapered and she was observed without any medical treatment at July 1991 when the platelet count was $20.8 \times 10^4/\mu l$.

Discussion

The patient's birth place is in the southwest of Shikoku Island, Japan, an area known to be endemic for ATL or HTLV-I. Western blotting analysis confirmed that she was a carrier of HTLV-I. Southern blotting analysis of DNA obtained from the patient's mononuclear cells also disclosed a random integration of HTLV-I proviral DNA. HTLV-I is known to be the causative agent not only of ATL but also of HAM (1, 2). Recent investigations raise interesting problems with respect to its pathogenic role in some chronic diseases; Sugimoto *et al.* (3) reported HAM patiets with T-lymphocyte alveolitis associated with micronodular shadows in chest X-ray films, increase of total cell counts and proportion of lymphocytes in lavage fluid and infiltrations of lymphocytes in alveolar structure. Kimura (4) proposed a clinical entity of HTLV-I associated bronchiolo-alveolar disorder (HABA) to idiopathic interstitial pneumonitis or diffuse panbronchiolitis showing positive anti-HTLV-I antibody and/or HTLV-I related reactions. Nishioka *et al.* (5) reported patients with chronic inflammatory arthropathy with high HTLV-I antibody titers in both sera and synovial fluid. HTLV-I carriers with uveitis (8), dermatomyositis (9) and thrombocytopenic purpura (10) have been also reported.

The present paper describes a woman carrier of HTLV-I showing recurrent thrombocytopenia and various autoantibodies. Cyclic or recurrent thrombocytopenia is a rare disorder characterized by fluctuations in platelet levels. Menitove *et al.* (11) have reported cases with cyclic thrombocytopenia, in which total PA-IgG varied inversely with platelet levels, and suggested that platelet-reactive autoantibodies were of pathogenic significance in some patients with this disease. In the present case platelet counts fluctuated between $1.3 \times 10^4/\mu l$ and $14.8 \times 10^4/\mu l$ without any medical treatment, and the thrombocytopenia improved with a decrease of PA-IgG. Furthermore, various autoantibodies such as RF, ANF, anti-Sm, anti-RNP and anti-SSA antibodies were also recognized. The mechanism of the development of various autoantibodies in this case is still obscure. It is reported that alloreactive T cell clones infected with HTLV-I, which originally provided allospecific help only to B cells expressing the DRI antigen, were found to stimulate B cells of any HLA-D/DR phenotype to produce immunoglobulin in culture (12). In HAM patients the proportions of activated T cells were found to be increased in their peripheral blood, and polyclonal gammopathy was also observed in most of the patients (13). In the present case an increase in the proportions of CD3+HLA-DR+, CD 4+HLA-DR+ and CD8+HLA-DR+ cells was also recognized. The alteration of B cell functions by T cells infected with HTLV-I is speculated to be one of the possible causes of the development of various autoantibodies in this HTLV-I carrier.

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