CASE REPORT

An Anti-nuclear Antibody-negative Patient with Systemic Lupus Erythematosus (SLE) Accompanied with Anti-ribosomal P Antibody (anti-P)

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Abstract

We report a case of an anti-nuclear antibody (ANA)-negative patient with systemic lupus erythematosus (SLE) accompanied with anti-phospholipid antibody syndrome (APS) and lupus nephritis (LN). Histological examination of placenta obtained by an artificially-induced abortion revealed multiple thromboses in the placental villi. Histology of biopsied kidney tissue revealed minimal change with deposits of immunoglobulin and complement. Anti-ribosomal P antibodies (anti-P) and lupus anticoagulant (LAC) were positive and anti-double stranded DNA antibody (anti-DNA) showed only a slightly positive titer in her serum. The intensity of proteinuria of the patient was correlated with the anti-P, but not anti-DNA titers.

Key words: lupus nephritis, antiphospholipid antibody syndrome, lupus anticoagulant, placental thrombosis

Introduction

Systemic lupus erythematosus (SLE) is a prototype autoimmune disease. Various kinds of autoantibodies such as anti-nuclear antibodies (ANA), anti-cytoplasmic antibodies and anti-plasma membrane antibodies are present in sera of SLE patients (1). ANA is a diagnostic hallmark for SLE, having a frequency of 95% or greater in patients with SLE (2). ANA-negative patients with SLE have also been reported (3). ANA-negative SLE patients have been known to have a higher prevalence of both anti-Ro antibody, one of the anti-cytoplasmic antibodies, and cutaneous manifestation, as well as a lower prevalence of both central nervous system (CNS) and renal involvement than ANA-positive SLE patients (4, 5). In addition to anti-phospholipid antibodies (aPL), one of the anti-plasma membrane antibodies, and other autoantibodies are often detected in patients with ANA-negative SLE (4). Anti-phospholipid antibodies cause anti-phospholipid antibody syndrome (APS), which is characterized by the presence of thromboembolic symptoms (6, 7). Recurrent fetal loss due to thrombosis of the placenta is one of the most prominent symptoms of APS (8). Anti-ribosomal P antibodies (anti-P), one of the anti-cytoplasmic antibodies, have also been found in patients, with a prevalence of 5 to 42% (9-14). Anti-P is believed to be associated with neuro-psychiatric disorders (12, 15, 16), as well as liver and kidney lesions in patients with SLE (17, 18).

Here, we report a case of an ANA-negative, but lupus anticoagulant (LAC) and anti-P-positive, SLE patient who presented with a thrombosis in the placental villi of placenta taken from an artificially-induced abortion, and immune deposits in biopsied kidney tissue. The clinical significance of LAC and anti-P in ANA-negative SLE patients is discussed.

Case Report

A 28-year-old woman has been suffering from low grade fever, facial erythema, cervical lymphadenopathy, epigastric discomfort, polyarthritis and headache since February 2001. The patient visited Ohta Nishinouchi Hospital, in Koriyama, Japan, on April 12, 2001. Laboratory data of the patient were as follows: white blood cells (WBC); 3,100/mm³ (normal, 3,500-9,000), complement; 1 1.9 IU/ml (normal, 30-50), lower positive titer of anti-dsDNA antibody; 8 IU/ml (normal, less than 6), positive lupus anticoagulant, and proteinuria; 30 mg/dl. A diagnosis of SLE, based on the revised ACR criteria for SLE, complicated with APS was made. Two weeks later she was recognized to be pregnant.

Prednisolone (PSL) at doses of 20 mg/day and aspirin at a dose of 81 mg/day were administrated. However, the levels of proteinuria were increased at 2 g/day. She was hospitalized at the Division of Rheumatology, Ohta Nishinouchi Hospital on May 25, 2001. On admission, a fever of 38.7°C, facial erythema,
swollen cervical lymphnodes and polyarthritis in both elbows, wrists and knees were noted. No signs of Raynaud’s phenomenon, oral aphtha, or alopecia were observed. Heart sounds were clear with regular sinus rhythm, a pulse rate of 88/min and a blood pressure of 108/68 mm Hg. No rales were audible in the lung fields. No edema was observed in her face or lower legs. No signs of deep vein thrombosis, brain infarction and lung infarction were observed.

Laboratory data on admission were as follows: increased level of C-reactive protein (CRP); 0.73 mg/dl (normal, less than 0.2), WBC; 3,800/mm³, lymphocytes; 684/mm³, hemoglobin; 8.8 g/dl, platelets; 16.2x10⁹/mm³, PT; 97.9% (normal, more than 70), APTT; 33.6 seconds (normal, 29–44), TT; more than 100% (normal, more than 70), bleeding time; 1 minute (normal, less than 4), aspartate aminotransferase (AST); 18 IU/l, alanine aminotransferase (ALT); 14 IU/l, BUN; 13.0 mg/dl, creatinine; 0.48 mg/dl, lower than normal levels of hemolytic complement (CH50); 10.1 IU/ml (normal, 30–50), C3; 48.9 mg/dl (normal, 86–160), C4; 5.4 mg/dl (normal, 17–45), immune complex by a C1q binding method; 5.1 μg/ml (normal, less than 2.9), false-positive for syphilis test, positive lupus anticoagulant [tested by “Gradipore” (MEDICAL & BIOLOGICAL LABORATORIES CO., LTD, Tokyo) based on diluted Russel’s viper venom time], low positive titer of anti-dsDNA antibody at 9 IU/ml (normal, less than 6), low positive titer of anti-cardiolipin IgG antibody at 14.0 GPL (normal, less than 10) and high positive titer of anti-P at 250 index (normal, less than 10) tested using a commercial ELISA kit. However, serum ANA in an indirect immunofluorescence test using Hep2 cell substrates was negative in three repeated tests. None of anti-RNP, anti-Sm, anti-Ro, anti-La, anti-Scl-70 or anti-β2GPI antibody was detected using routine commercial ELISA kits. Urinalysis revealed proteinuria at 225 mg/dl. RBC (at 10 to 20 cells in one field at x40 magnification), numerous WBC and bacteria were observed in sediment without urinary cast. Her HLA loci were A24, A26, B35, B60, CW3, DR14 and DQ1.

Persistent fever of 37.5–38.5°C and exacerbation of facial erythema, lymphadenopathy, polyarthritis, proteinuria and hypocomplementemia prompted an increase in the prednisolone dose to 40 mg/day. Subsequently, facial erythema, cervical lymphadenopathy, polyarthritis as well as the fever were ameliorated. However, proteinuria of 2.0 g/day or greater and hypocomplementemia of less than 20 IU/ml continued.

To avoid a poor prognosis, an artificially-induced abortion was performed on June 6th, 2001, at the 11th week of gestation under permission of both the patient and her husband. One week after the induced abortion, her proteinuria levels decreased. Moreover both anti-P and LAC titers diminished one month after the induced abortion (Fig. 1). Histological examination of the placenta obtained at the time of the induced abortion revealed multiple micro-thrombosis in the small vessels in the placental villi (Fig. 2). Pathohistology of renal biopsy tissue obtained on July 7, 2001, revealed a mild mesangial proliferation (Fig. 3A) with moderate deposits of immunoglobulin...
Anti-P Antibody in ANA Negative SLE

Figure 2. Pathohistology of placenta obtained at the artificially-induced abortion performed at the 11th week of gestation. Multiple thrombi are evident in placental vessels (arrows) (HE stain, x50).

Discussion

Patients with ANA-negative SLE have been reported to have a higher prevalence of skin rashes and mucous membranous ulcers and a lower prevalence of renal and central nervous system involvement than ANA-positive patients (4, 5). Furthermore, Meyer et al reported that the prevalence of arterial and venous thrombosis with thrombocytopenia in ANA-negative patients with SLE was higher than ANA-positive patients, and also that anti-phospholipid antibody (aPL) and lupus anticoagulant (LAC) were common in ANA-negative patients with SLE (6).

Recently, anti-P, one of the anti-cytoplasmic, was specifically found in patients with SLE (19), particularly in those complicated by neuropsychiatric disorders (12, 15, 16) and liver and kidney lesions (17, 18). Moreover, Chindalare et al reported that the titer of anti-P was correlated with the activity of renal lesions in 13 patients with SLE (20). The patient presented in this report suffered from proteinuria with high positive titers of anti-P but low positive titers of anti-dsDNA antibody. Therefore, the anti-P in our patient may be associated with the renal lesions.

The importance of female sex hormones in the production of autoantibodies and the occurrence of SLE had been extensively discussed (21-24). In the present patient, proteinuria was ameliorated after the artificially-induced abortion, in accordance with the decrease in the titers of both anti-P and LAC. These results suggest that the patient’s pregnancy may have played some role in the production of anti-P and LAC and the resultant proteinuria. Measurement of the level of each complement component revealed no inherited deficiency of complement...

Figure 3. Pathohistology of biopsied kidney tissue showed a mild mesangial proliferation in the glomerulus [A] (HE stain, x100). Immunofluorescent micrographs of the biopsied kidney tissue showed positive staining of mesangium and capillary walls of the glomerulus by anti-human IgG antibody [B] (x100) and anti-human C1q antibody [C] (x100).
components (C1q; 9.1 mg/dl, C3; 55.4 mg/dl, C4; 3.3 mg/dl, C5; 13.3 mg/dl, C6; 5.1 mg/dl, C7; 6.0 mg/dl, C8; 5.7 mg/dl, and C9; 7.1 mg/dl) (25).

Studies have shown that immune complex (IC) composed of anti-dsDNA antibody activates the complement cascade, whereas anti-phospholipid antibody does not (26, 27). Recently, however, Munakata et al reported that some anti-phospholipid antibody ICs activate the complement cascade (28). In the present patient, hypocomplementemia was observed along with higher positive titers of LAC and anti-P but lower positive titers of anti-DNA. In addition, a prominent deposition of immunoglobulins and complement components were observed in the glomerulus of the biopsied kidney tissue. Therefore, it is plausible that LAC and/or anti-P antibody, clustered with IgG anticardiolipin in the patient, could activate complement cascade and cause internal organ damage such as LN. Recently, Ghirardello et al reported that anti-P is strongly clustered with IgG anticardiolipin antibodies in lupus sera, even if they are independently elucidated (19). In the present patient, anti-P may have clustered with LAC, and these two autoantibodies may have participated together to bring about renal lesions unrelated to the anti-DNA titers. Furthermore, pathogenetic potentials of anti-P in LN have been reported (29, 30). Recently it has been reported that anti-β2GPI antibody as well as LAC is closely related with thromboembolic events in patient with APS (31, 32). Positive LAC without anti-β2GPI antibody were observed in this patient. In our case it may be possible to speculate LAC, not anti-β2GPI antibody, causes micro-thrombosis in the small vessels in the placental villi.

ANA-negative SLE is considered to be as heterogeneous as ANA-positive SLE. Previous reports have indicated the existence of two major subpopulations in ANA-negative SLE patients. The first manifests cutaneous involvement with anti-Ro antibody, which is one of the anti-cytoplasmic antibodies, and the second exhibits secondary APS with aPL, which is one of the anti-plasma membrane antibodies. In general, in these two major two subpopulations of ANA-negative SLE, renal involvement as well as CNS involvement is less common than in ANA-positive SLE cases. The present patient may indicate the existence of a third subpopulation of ANA-negative SLE; one exhibits renal lesions with anti-P. We have treated two other ANA-negative SLE patients of 120 SLE patients belonging to our Division of Rheumatology (unpublished data). One patient suffered from LN and the other suffered from CNS lupus, while both had high titers of anti-P in their active phase of the disease. Detailed evaluation of anti-P will provide more precise clinical information for patients with ANA-negative SLE.

In conclusion, we report an ANA-negative SLE patient accompanied with APS and LN, in whom high positive titers of both anti-P and LAC were observed. The serum level of anti-P, but not anti-DNA, was correlated with the disease activity and the amount of proteinuria. The measurement of anti-P is useful for characterization of the clinical features of SLE and to predict the outcome of SLE patients, in particular ANA-negative SLE patients.

References


