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CASE REPORT

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A case of systemic lupus erythematosus with postpartum hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome and concomitant high phosphatidylserine-dependent anti-prothrombin antibody levels

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Abstract In August 1994, a 19-year-old woman presented to her dermatologist with a slight fever, arthralgia, and a butterfly rash. Discoid lupus erythematosus was suspected, and serological testing yielded positive results for antinuclear antibody. She was diagnosed with systemic lupus erythematosus without organ failure and was treated with only nonsteroidal antiinflammatory drugs. She became pregnant in June 2001, at age 26. In November her obstetrician noted that she had severe hypertension, edema of the low limbs, and proteinuria. On admission, she was diagnosed with severe preeclampsia, and cesarean section was performed. On hospital day 3 the patient developed sudden epigastric pain and vomiting. Laboratory tests revealed thrombocytopenia, liver dysfunction, and microangiopathic hemolytic anemia, leading to a diagnosis of HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. Plasma exchange was performed for 5 days. The thrombocytopenia, liver dysfunction, and proteinuria diminished quickly. Later testing revealed a high titer of plasma phosphatidylserine-dependent anti-prothrombin antibody. This case is useful for exploring the relations between SLE, HELLP syndrome, and anti-prothrombin antibody.

Key words Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome · Phosphatidylserine-dependent anti-prothrombin antibody · Plasma exchange · Preeclampsia · Systemic lupus erythematosus (SLE)

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Introduction

The frequency of preeclampsia complicating a normal pregnancy ranges from about 3% to 5%. Conversely, the rate of preeclampsia complicating pregnancies in patients with systemic lupus erythematosus (SLE) ranges from 20% to 30%.[1] However the onset of preeclampsia is not always related to the activity of the SLE. It was reported recently that anti-prothrombin antibody is often detected in the serum of the patients with SLE.[2] This antibody is also detected in the serum of the patients with preeclampsia and eclampsia.[3] Anti-prothrombin antibody has thus been suggested as a factor contributing to the pathophysiology of preeclampsia associated with SLE.

We encountered a case of SLE with HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, which is characterized by three signs; hemolysis, elevated liver enzymes and low platelet count. Anti-prothrombin antibody may contribute to the pathogenesis of HELLP syndrome because HELLP syndrome is also a form of severe preeclampsia. However, no previous case reports have described HELLP syndrome with concomitant anti-prothrombin antibody. The present report describes a patient with SLE, postpartum HELLP syndrome, and concomitant high titers of phosphatidylserine-dependent anti-prothrombin antibody. Relations between anti-prothrombin antibody and HELLP syndrome were examined.

Case report

In August 1994, a 19-year-old woman presented to her dermatologist with slight fever, arthralgia, and a butterfly rash. Laboratory test results demonstrated leukopenia and the presence of antinuclear antibody. SLE without organ failure was diagnosed, and treatment was initiated using only nonsteroidal antiinflammatory drugs.

The patient became pregnant in June 2001, at 26 years of age. In November, at 26 weeks of pregnancy, she displayed severe hypertension (152/118 mmHg), edema of the lower limbs, and proteinuria (0.3 g/day). The next day, her blood pressure had increased to 220/150 mmHg, and she was admitted to our hospital. On admission, her body weight was 57.6 kg, representing an increase of 4 kg over 2 weeks. Her heart rate was 120 beats/min and regular, and she was fully oriented. Her liver, spleen, and superficial lymph nodes were not palpable. Slight facial rash, tender eruptions on both hands, and severe edema of the lower limbs were apparent.

Laboratory data revealed slight thrombocytopenia ($12.6 \times 10^4/\mu l$) and hypoproteinemia (5.8 g/dl). The liver enzymes were elevated: aspartate aminotransferase (AST) 45 IU/l (normal 11–39 IU/l), alanine aminotransferase (ALT) 58 IU/l (normal 5–40 IU/l), γ-glutamyl-transpeptidase 103 IU/l (normal 6–35 IU/l), and lactate dehydrogenase (LDH) 618 IU/l (normal 190–440 IU/l). C-reactive protein (0.57 mg/dl; normal <0.30 mg/dl) was also slightly elevated. Haptoglobin levels were normal. The antinuclear antibody titer was 1:40, but complement levels were normal, and negative results were obtained for anti-DNA antibody. Lupus anticoagulant (dRVVT) was negative but anti-β_2-glycoprotein 1 antibody was 4.1 U/ml (normal <3.5 U/ml). Both direct and indirect Coombs' tests yielded negative results. Total proteinuria was 0.3 g/day (Table 1).

Preeclampsia was diagnosed according to the criteria of the Japan Society of Obstetrics and Gynecology.[4] Although a nicardipine drip (3.6 mg/h) was utilized, her blood pressure remained elevated. Despite minimal SLE activity, the possibility of progressing to life-threatening maternal complications (eclampsia) led to the decision to deliver the baby immediately.

Cesarean section was performed that night. The baby weighed 450 g at birth and died 3 days later. Pathohistological study of the placenta revealed that many of the villi were smaller than normal. Failure of the fetus to grow was thought to be secondary to general placental failure. Spotty necrosis with neutrophil infiltration was noted in the maternal-side decidua. Cultures yielded negative results, and no abnormal changes in placental vessels were identified.

After delivery, the patient displayed gradual stabilization of blood pressure without administration of any antihypertensive agents. However, approximately 50 h after childbirth, the patient developed sudden, severe epigastric pain, right subchondral pain, and vomiting. Pentazocine was prescribed, but symptoms remained undiminished. Laboratory data at that time indicated thrombocytopenia ($9.1 \times 10^4/\mu l$) and progressive liver dysfunction (AST 163 IU/l; ALT 146 IU/l; LDH 882 IU/l). The fibrinogen degradation products concentration was 9 μg/ml. Disseminated intravascular coagulation was not present. Computed tomography (CT) showed pleural effusion, and abdominal CT revealed slight ascites around the liver. A peripheral blood specimen revealed red blood cell fragmentation (Fig. 1). The presence of microangiopathic hemolytic anemia was confirmed. Further testing revealed elevation of transaminase levels (AST 172 IU/l; ALT 170 IU/l), worsened thrombocytopenia ($2.0 \times 10^4/\mu l$), and a drop in hemoglobin concentration to 7.6 g/dl (Fig. 2). Slight purpura was seen on the lower limbs at that time.

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome were rejected as diagnoses because of the absence of symptoms involving the central nervous system or colon, as well as the lack of predominant renal involvement: creatinine 0.8 mg/dl (normal

Table 1. Laboratory data on admission

Peripheral blood	
WBC	$9.4 \times 10^3/\mu l$
Neutrophils	77.0%
Lymphocytes	16.2%
Monocytes	6.0%
Eosinophils	0.3%
Basophils	0.5%
RBC	$4.30 \times 10^6/\mu l$
Hemoglobin	12.8 g/dl
Hematocrit	38.7%
Platelets	$12.6 \times 10^4/\mu l$
AT-III	95%
FDP	7 μg/ml
Urinalysis	
Protein	288.8 mg/day
Blood chemistries	
Total protein	5.8 g/dl
Albumin	3.4 g/dl
T. bilirubin	0.6 mg/dl
AST	45 IU/l
ALT	58 IU/l
ALP	658 IU/l
LDH	618 IU/l
γ-GTP	103 IU/l
BUN	25 mg/dl
Creatinine	0.8 mg/dl
Na	134 mEq/l
K	4.5 mEq/l
Cl	104 mEq/l
Ca	8.9 mg/dl
Ferritin	43.2 ng/ml
Serological tests	
CRP	0.57 mg/dl
IgG	675 mg/dl
IgA	185 mg/dl
IgM	63 mg/dl
Hp	52 mg/dl
CH_{50}	33.0 U/ml
ANA	40×, diffuse
a-DNA Ab	<2.0 IU/ml
a-Sm Ab	–
a-SS-A Ab	–
PA IgG	43.2 ng/10^7 cells
LAC	1.0 index
a-β2GP1 Ab	4.1 U/ml
a-PT IgM Ab	16.2 U/ml
a-PT IgG Ab	13.5 U/ml
D-Coomb's test	–
I-Coomb's test	–

WBC, white blood cell count; RBC, red blood cell count; AT-III, antithrombin III; FDP, fibrin degradation product; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyl transpeptidase; BUN, blood urea nitrogen; CRP, C-reactive protein; IgG, immunoglobulin G; Hp, haptoglobin; CH_{50}, 50% hemolyzing dose of complement; ANA, antinuclear antibody; Ab, antibody; a-, anti; PA IgG, platelet-associated immunoglobulin G; LAC, lupus anticoagulant; a-β2GP1 Ab, anti-β2-glycoprotein 1 antibody; D, direct; I, indirect

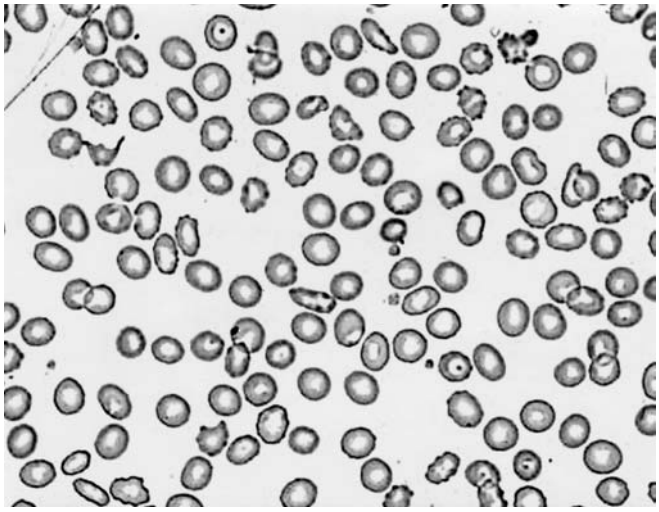

Fig. 1. Peripheral blood specimen, revealing many clastic erythrocytes

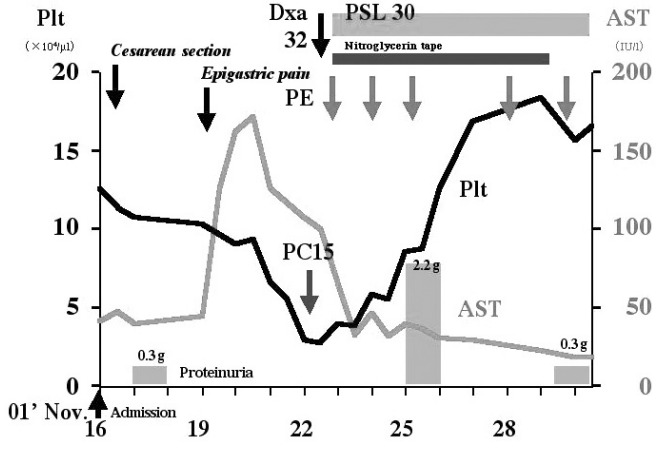

Fig. 2. Clinical course. *Dxa*, dexamethasone; *PSL 30*, prednisclone 30 mg/day; *Plt*, platelet count; *AST*, aspartate aminotransferase; *PE*, plasma exchange; *PC15*, platelet concentrate 15 unit

0.5–0.9 mg/dl). HELLP syndrome of the postpartum period was diagnosed in accordance with the criteria proposed by Sibai et al.[5]: presence of hemolytic anemia with red blood cell fragmentation, elevated liver enzymes (AST > 70 IU/l; LDH > 600 IU/l), and low platelet count ($<10.0 \times 10^4/\mu l$).

Dexamethasone is reportedly effective for antepartum HELLP syndrome[6] and was prescribed at a dose of 32 mg/day on hospital day 6. Abdominal pain decreased, but pancytopenia remained. Plasma exchange was conducted for 5 days from hospital day 6, as we did not wait for the effect of steroids because of the acute thrombocytopenia. Her platelet count began to increase on hospital day 7, and the hemoglobin level improved to 10.0 g/dl. Proteinuria, which had transitionally increased to 2.2 g/day, decreased to 0.3 g/day by December 1. After dexamethasone therapy, the patient was started on prednisolone at a dose of 30 mg/day. Prednisolone dose was gradually tapered to 20 mg/day, and the patient was discharged on hospital day 33.

Frozen plasma obtained before the plasma exchange was later analyzed. Levels of phosphatidylserine-dependent anti-prothrombin antibody were measured using the following methods. Phosphatidylserine was distributed over enzyme-linked immunosorbent assay (ELISA) plates. Prothrombin was then added to each well in the presence of 5 M $CaCl_2$. Phosphatidylserine–prothrombin complexes formed as an antigen. Plasma samples were then added to the wells, and the aggregation of antibody with complex was measured. The results showed phosphatidylserine-dependent anti-prothrombin antibody immunoglobulin G (IgG) levels of 13.5 U/ml (normal <2 U/ml) and IgM 16.2 U/ml (normal <13 U/ml) in plasma. After 6 months the phosphatidylserine-dependent anti-prothrombin antibody IgG titer had decreased to 4.2 U/ml, and IgM was 10.6 U/ml.

Discussion

In 1982, Weinstein reported 29 cases of HELLP syndrome during pregnancy.[7] Presenting symptoms for this syndrome include sudden epigastric pain and vomiting. HELLP syndrome is based on gestosis and occurs in 10%–15% of preeclampsia cases and in 30%–50% of eclampsia cases. The crisis usually starts between weeks 24 and 34 of pregnancy but is reported to develop during the postpartum period in rare cases,[8] as in our case.

With regard to the relation between SLE and HELLP syndrome, both SLE and preeclampsia, preceding HELLP syndrome, share a common pathogenesis: endothelial injury. As mentioned previously, the frequency of preeclampsia is known to be higher in patients with SLE. We evaluated the reports of five SLE patients with HELLP syndrome.[9–13] Analysis revealed three patients with exacerbation of their SLE and two with no SLE activity accompanying the development of HELLP syndrome. No relation was apparent between SLE activity and the development of HELLP syndrome. Similar results were obtained for a relation between SLE activity and the development of preeclampsia.

These results could not explain whether endothelial injuries due to high SLE activity contributed to preeclampsia and HELLP syndrome. The role of anti-phospholipid antibody was thus investigated. Laboratory results revealed no elevation of anti-DNA antibody, and normocomplementemia. The present patient was not administered lupus anticoagulant and received only a small titer of anti-β_2-glycoprotein 1 antibody. Complications of antiphospholipid syndrome were clinically possible, but the status at that time did not satisfied the "Sapporo criteria."[14]

Interestingly, further plasma studies at the initiation of the HELLP syndrome revealed the existence of phosphatidylserine-dependent anti-prothrombin antibody. Anti-prothrombin antibody is one of the anti-phospholipid antibodies that has recently been thought to have a strong relation with thrombosis.[15]

Prothrombin comprises four domains: Gla, catalytic, and the Kringle 1 and 2 domains. Antibody against fragment 1

(anti-fragment 1 antibody) consists of Gla and Kringle 1 domains and is associated with preeclampsia. Antibody against prothrombin 1 (anti-prothrombin 1 antibody), which comprises the Kringle 2 and catalytic domains, is associated with repeated abortion in the presence of gestosis.[3] We did not analyze the concentrations of anti-fragment 1 antibody and anti-prothrombin 1 antibody in our case. However, high titers of phosphatidylserine-dependent anti-prothrombin antibody were detected in plasma samples from the patient despite a lack of SLE exacerbation.

Following treatment, her liver dysfunction and thrombocytopenia resolved and have not recurred. This patient also displayed anti-β_2-glycoprotein 1 antibody, but the titer of anti-β_2-glycoprotein 1 antibody was maintained, whereas the phosphatidylserine-dependent anti-prothrombin antibody titer had decreased after 6 months.

Phosphatidylserine-dependent anti-prothrombin antibody may be capable of inducing preeclampsia and HELLP syndrome in pregnant SLE patients. The patient reported no past history of infection following endothelial injury or operations such as tooth extraction in the current case. This antibody was thought to be associated with the present pathogenesis.

The mainstay of treatment for HELLP syndrome is immediate delivery of the child, usually via cesarean section. However, our patient displayed no improvements in liver dysfunction or thrombocytopenia, so treatment with dexamethasone was selected.[16] Vasodilators were also prescribed in an effort to control her blood pressure. As the condition of the patient appeared to be resistant to steroids, plasma exchange was performed.[17] The effect of plasma exchange for HELLP syndrome is attributed to the exclusion of toxic factors that induce vasospasm, such as thromboxane A_2 and endothelin. In addition, plasma exchange is thought to remove anti-prothrombin antibodies, which were detected in our patient, as well as other unknown antiphospholipid antibodies, leading to improvements. Isler et al. recently reported that dexamethasone treatment is effective for postpartum HELLP syndrome.[18] Although corticosteroids may have produced good results in this case, we believe that plasma exchange a better option for treating postpartum HELLP syndrome.

Conclusions

We treated an SLE patient who presented with HELLP syndrome during the postpartum period, with a concomitant high titer of phosphatidylserine-dependent anti-prothrombin antibody. SLE was not exacerbated during pregnancy, but the course of the pregnancy was complicated by preeclampsia and the subsequent appearance of the HELLP syndrome. The pathogenesis of HELLP syndrome remains unclear at this time. The relations between connective tissue diseases (e.g., SLE) and anti-phospholipid antibodies appear interesting, and further analysis of this relation is crucial to a better understanding of this phenomenon.

References

1. Branch DW, Silver RM. Autoimmune disease and pregnancy: maternal and fetal implications in systemic lupus erythematosus and antiphospholipid syndrome. In: Bronson RA, ed. Reproductive immunology. Cambridge: Blackwell Science; 1996. p. 443.
2. Munoz-Rodriguez FJ, Reverter JC, Font J, Tassies D, Cervera Espinosa G, Carmona F, et al. Prevalence and clinical significance of anti-prothrombin antibodies in patients with systemic lupus erythematosus or with primary antiphospholipid syndrome. Haematologica 2000;85:632–7.
3. Akimoto T, Akama T, Saitoh M, Kono I, Sumida T. Antiprothrombin autoantibodies in severe preeclampsia and abortion. Am J Med 2001;110:188–91.
4. Nakabayasi M, Isono S. Preeclampsia. Taketani Y, eds. Comprehensive handbook of women's medicine. vol 23. Tokyo: Nakayama-Shoten; 1998. p. 55–73.
5. Sibai BM, Ramdan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes and low platelets (HELLP syndrome). Am J Obstet Gynecol 1993;169:1000–6.
6. O'Brien JM, Milligan DA, Barton JR. Impact of high-dose corticosteroid therapy for patients with HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. Am J Obstet Gynecol 2000;183:921–4.
7. Weinstein L. Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. Am J Obstet Gynecol 1982;142:159–67.
8. Esan K. Postpartum HELLP syndrome after a normotensive pregnancy. Br J Gen Pract 1997;47:441–2.
9. Minakami H, Idei T, Koike T, Tamada T, Yasuda Y, Hirota N. Active lupus and preeclampsia: a life threatening combination. J Rheumatol 1994;21:1562–3.
10. Fehr T, Cahomas G, Weber C, Fontana A, Schaffner A. Foetal loss, liver necrosis and acute lupus erythematosus in a patient with antiphospholipid antibody syndrome. Lupus 2001;10:576–9.
11. Kato Y, Yoshitake A, Saotome T, Jishi K, Ichimaru K, Sato T, et al. A gravida case of HELLP syndrome with systemic lupus erythematosus. Shusanki Igaku 1991;21:1077–80.
12. Iwasaki T, Ogata A, Hamano T, Kakishita E. A case of HELLP syndrome with systemic lupus erythematosus. Ryumachi 1999; 39:403.
13. Tabushi Y, Kamei K, Yokote T, Kagiya M, Hayashi M, Takeuchi T, et al. A gravida case of systemic lupus erythematosus with HELLP syndrome and hemophagocytic syndrome. Nihon Rinsho Meneki Gakkai Kaishi 1999;22:278.
14. Lockshin MD, Sammaritano LR, Schwartzman S. Validation of Sapporo criteria for antiphospholipid syndrome. Arthritis Rheum 2000;43:440–3.
15. Atsumi T, Ieko M, Bertolaccini ML, Ichikawa K, Tsutsumi A, Matsuura E, et al. Association of autoantibodies against the phosphatidylserine-prothrombin complex with manifestations of the antiphospholipid syndrome and with the presence of lupus anticoagulant. Arthritis Rheum 2000;43:1982–93.
16. Matthew JT, Siva T. HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome: the benefit of corticosteroids. Am J Obstet Gynecol 1999;181:304–9.
17. Kimura T, Noda Y. Usefulness of plasma exchange for severe HELLP syndrome. Jpn J Apheresis 1999;18:90–4.
18. Isler CM, Magann EF, Rinehart BK, Terrone DA, Bass JD, Martin JN Jr. Dexamethasone compared with betamethasone for glucocorticoid treatment of postpartum HELLP syndrome. Int J Gynaecol Obstet 2003;80:291–7.