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CASE REPORT

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Thrombotic microangiopathic hemolytic anemia in systemic lupus erythematosus associated with antiphospholipid antibodies: usefulness of monitoring coagulation–fibrinolysis markers

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Abstract We report on a 24-year-old woman with systemic lupus erythematosus and lupus anticoagulant who developed chronic thrombotic microangiopathic hemolytic anemia. The patient responded well to a combination of plasma exchange and anticoagulant therapy. Changes in the molecular markers for coagulation and fibrinolysis corresponded with the disease activity. We suggest that thrombotic microangiopathic hemolytic anemia should be suspected when anemia and thrombocytopenia of unknown etiologies occur in systemic lupus erythematosus. In such cases, the evaluation of molecular markers for coagulation and fibrinolysis might be helpful both for diagnosis and for assessing the response to therapy.

Key words Hemolytic anemia · Systemic lupus erythematosus · Antiphospholipid antibody · Plasma exchange · Molecular markers for coagulation and fibrinolysis

Introduction

Thrombotic microangiopathic hemolytic anemia (TMHA) is a rare complication of systemic lupus erythematosus (SLE). The pathophysiological features of TMHA are intravascular hemolysis and thrombocytopenia due to microthrombus formation in small vessels. The major clinical indications of TMHA are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), but TMHA is known to be associated with pregnancy, malignancy, certain drugs, and collagen vascular diseases. Clinical presentations of TMHA are thrombocytopenia, microangiopathic hemolytic anemia, fever, neurological manifestations, and renal involvement.[1] Neurological abnormalities are predominant in the course of TTP, whereas renal insufficiency predominates in HUS. TMHA may be underdiagnosed in SLE patients because of the similarity of the clinical manifestations to those of central nervous system lupus or lupus nephritis. In particular, when microangiopathic hemolytic anemia is not severe, it is difficult to differentiate TMHA from other types of anemia associated with SLE. Antiphospholipid antibodies are frequently observed in SLE patients and are associated with thrombotic events, recurrent fetal loss, and thrombocytopenia. Recently, an association between antiphospholipid antibodies and TTP has been reported. Here we report on a patient with SLE and antiphospholipid antibodies who developed chronic TMHA. A combination of plasma exchange and anticoagulant therapy was effective for the treatment of TMHA. Evaluating changes in the molecular markers for coagulation and fibrinolysis was found to be useful for diagnosing TMHA and for assessing the efficacy of treatment.

Case Report

A 24-year-old woman presented in March 1996 with polyarthritis. Laboratory tests revealed a high titer for antinuclear antibody, a false-positive serologic test for syphilis, and hypocomplimentemia. She was admitted to St. Marianna University Hospital in September 1996 because of nasal bleeding, generalized edema with massive proteinuria, and progressive anemia during the past 3 weeks.

On admission, examination revealed her blood pressure to be 160/130 mmHg, body temperature 38.5°C, and generalized edema. The patient was alert and neurological examination was normal. Laboratory tests showed the following results: urinalysis, 3+ proteinuria with hematuria; erythro-

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cyte sedimentation rate, 57 mm/h; hemoglobin, 7.4 g/dl; hematocrit, 21.9%; platelets, 66000/mm^3; serum creatinine, 1.7 mg/dl; urea nitrogen, 32 mg/dl; LDH, 720 units/L. Prothrombin time was 68% and activated partial thromboplastin time (APTT) was 57.4 s (normal control 27 s). C3 was 25 mg/dl, C4 was 2 mg/dl, and CH50 was under 10 U/ml. Antinuclear antibody (ANA) was positive with a titer of 1280. Anti-double-stranded DNA antibody (116 units/ml), LE cells, and platelet-associated IgG (PA IgG) were all positive, but direct and indirect Coombs' tests were negative. Antibodies for cardiolipin-2-glycoprotein I complex were positive with a low titer (5.3 U/ml) and lupus anticoagulant was positive. The latter was diagnosed by the criteria of the Scientific and Standardization Committee of the ISTH in 1995[2] by both the APTT- and dilute Russell's Viper Venum Time (DRVVT)-based assays. The patient was treated with methylprednisolone pulse therapy (0.5 g/m^2), followed by a high dose of oral prednisolone (1 mg/kg) (Fig. 1). Despite this high-dose corticosteroid therapy, the anemia progressed with reticulocytosis (Hb, 5.1 g/dl; reticulocytes, 117%) and thrombocytopenia (99000/μl), and renal function gradually deteriorated (serum creatinine, 1.8 mg/dl; urea nitrogen, 74 mg/dl; total protein, 4.2 g/dl; serum albumin, 2.9 g/dl; protein excretion, 7.3 g/day). After a second course of methylprednisolone pulse therapy (1.0 g/m^2), these was an improvement in renal function accompanied by decreased serum anti-double-stranded DNA antibody and an increased serum complement level. However, anemia persisted with reticulocytosis and moderate thrombocytopenia. PAIgG decreased to normal levels, but lupus anticoagulant was still positive. In addition to the elevated LDH levels (1087 IU/l) and very low serum haptoglobin levels (<10 mg/dl), a peripheral blood smear showed schistocytes, helmet cells, and tear drop cells (Fig. 2). Sustained elevations of thrombomodulin (56.1 TU/ml), D-dimer (2.9 μg/ml), and thrombin–antithrombin complex (TAT; 4.2 mg/dl) suggested the formation of microthrombi and continuing endothelial damage (Fig. 3). Under the diagnosis of TMHA, anticoagulant therapy with dipyridamole and warfarin was administered. This therapy was partially effective in decreasing coagulation and fibrinolysis markers, but did not improve the anemia or thrombocytopenia (Fig. 1). When anticoagulant therapy was suspended to allow renal biopsy, plasma thrombomodulin, D-dimer, and TAT levels became elevated again. A renal biopsy specimen showed cellular proliferation with crescent formation compatible with WHO IV A. No glomerular thrombosis was diagnosed. The patient underwent plasma exchange with fresh frozen plasma (2 × 3 l), followed by resumption of the anticoagulation therapy. An improvement in anemia and thrombocytopenia accompanied by normalization of the molecular makers for coagulation and fibrinolysis was obtained.

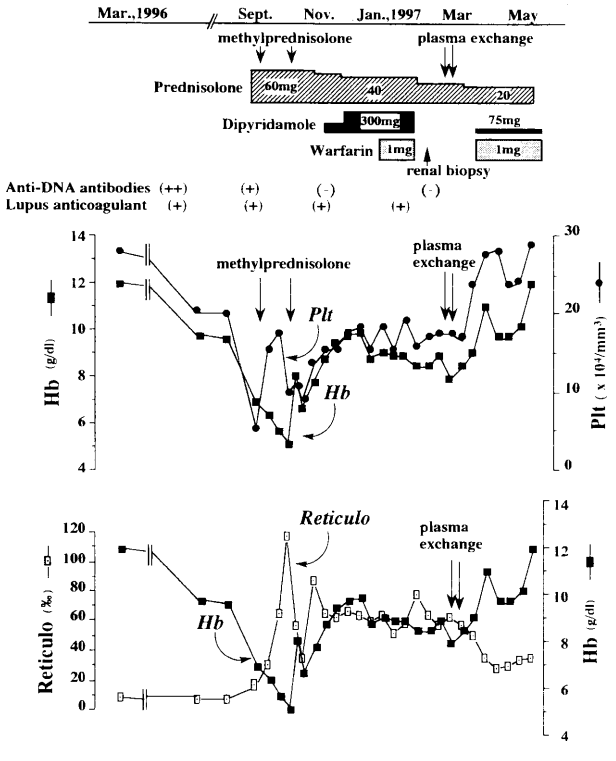

Fig. 1. Serial changes in hemoglobin, platelets, and reticulocytes during the course of the disease. *Hb*, hemoglobin; *Plt*, platelets; *Reticulo*, reticulocytes

Discussion

TMHA is only rarely observed in cases of SLE. For example, Nesher et al.[1] suggested that TMHA occurs in about 2–3% of SLE patients. However, there has been an increase in reported cases of SLE-related TMHA in recent years. The major clinical indications of TMHA are TTP and HUS. The patient in this study exhibited none of the typical central nervous system symptoms seen in TTP. Instead, she manifested nephrotic syndrome and decreased renal function. Although renal function recovered after the methylprednisolone pulse therapy, hematological abnormalities (anemia and thrombocytopenia) persisted. Therefore, in

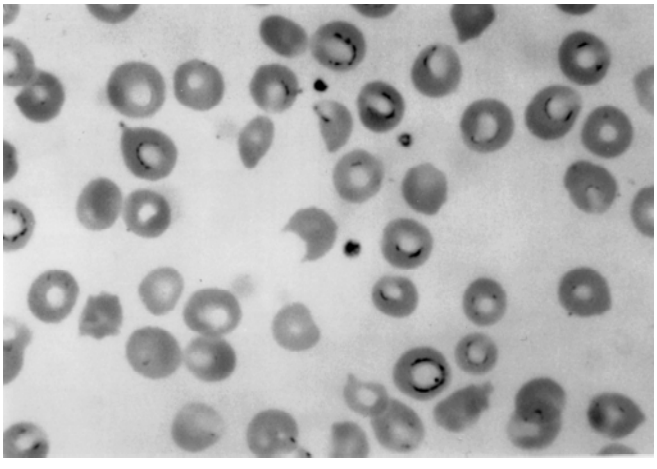

Fig. 2. A peripheral blood smear shows schistocytes, helmet cells, and tear drop cells

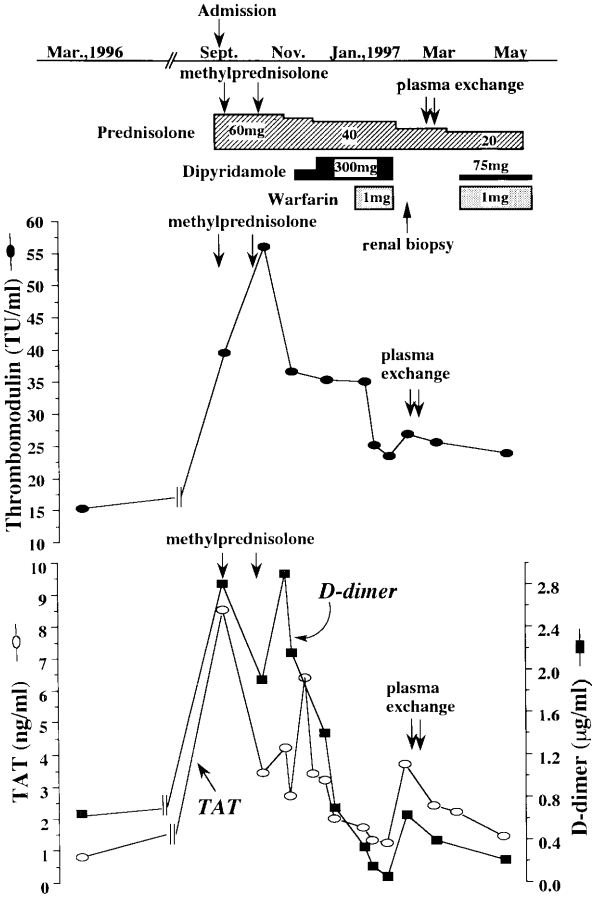

Fig. 3. Serial changes in the molecular markers for coagulation and fibrinolysis during the course of the disease. *TAT*, thrombin–antithrombin complex

this case, the clinical course was different from that of typical HUS.

The renal abnormalities can be partly explained by lupus nephritis, and renal involvement was proven by a biopsy which revealed diffuse proliferative glomerulonephritis (WHO IV A). However, the patient showed sustained anemia with increased reticulocytes, thrombocytopenia, an elevated serum LDH level, and a very low serum haptoglobin level, although Coombs' test was negative. In addition, a peripheral blood smear revealed schistocytes, helmet cells, and tear drop cells. We serially monitered the plasma levels of thrombomodulin, D-dimer, and TAT during the patient's course of treatment, and their high levels indicated the occurrence of vascular endothelial injury with subsequent coagulation and fibrinolysis. These findings suggested the development of intravascular hemolysis with microthrombi formation due to endothelial damage, which are features consistent with TMHA. Recently, molecular markers for coagulation and fibrinolysis have been used to diagnose various coagulation disorders. An evaluation of these markers may also be useful for the diagnosis of TMHA in SLE, especially when patients lack typical symptoms of TTP or HUS.

Recent reports have indicated that antiphospholipid antibodies or lupus anticoagulant is associated with more than half of all SLE cases with TMHA.[1] In this case study, lupus anticoagulant was positive by both APTT- and DRVVT-based assays, although only a low level of IgG was specific against cardiolipin –β2GPI complex. Antiphospholipid antibodies have been reported to be associated with arterial and venous thrombosis, recurrent fetal loss, and thrombocytopenia due to their various effects on endothelial cells, coagulation factors and regulators, and platelets.[3] The very high plasma thrombomodulin level in this case might have been partly due to renal impairment, because the level decreased with the recovery of renal function following methylprednisolone pulse therapy. However, the persistently high thrombomodulin levels indicated progressive vascular endothelial damage. Previous reports have suggested that lupus anticoagulant induces platelet aggregation and decreases the production of prostacyclin by endothelial cells.[4] Thus, lupus anticoagulant might play an important role in the development of TMHA via vascular injury and platelet activation, since it was persistently exhibited in this patient despite the normalization of serum anti-DNA antibodies and complement level.

The efficacy of plasma exchange for TTP or HUS in SLE patients has been reported in recent years. The mortality rate is improved by plasma exchange when compared with treatment with classical corticosteroid regimens.[1] Plasma exchange may control TMHA by the removal of immune complexes, antiphospholipid antibodies, large molecular von Willebrand factor, and platelet-activating substances, as well as by preventing the proteolytic fragmentation of von Willebrand factor.[5] In this patient, a combination of plasma exchange and anticoagulation improved TMHA and normalized the molecular markers for coagulation and fibrinolysis.

This case suggests that TMHA should be suspected when anemia of unknown etiology occurs together with thrombocytopenia in SLE, especially in antiphospholipid antibody-positive patients, even when there are no typical signs of TTP or HUS. The evaluation of coagulation and fibrinolysis markers might be useful for the diagnosis of TMHA, and plasma exchange combined with anticoagulation may be an effective treatment.

References

1. Nesher G, Hanna VE, Moore TL, Hersh M, Osborn TG. Thrombotic microangiopathic hemolytic anemia in systemic lupus erythematosus. Semin Arthritis Rheum 1994;24:165–72.
2. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for diagnosis of lupus anticoagulant: an update. Thromb Haemost 1995;74:1185–90.
3. Hughes GR. The antiphospholipid syndrome: ten years on. Lancet 1993;342:341–4.
4. Schorer AE, Wickham NW, Watson KV. Lupus anticoagulant induces a selective defect in thrombin-mediated endotherial prostacyclin release and platelet aggregation. Br J Haematol 1989;71:399–407.
5. Mannucci PM, Lombardi R, Lattnada A, Ruggenenti P, Viguano GL, Barbui T, et al. Enhanced proteolysis of plasma von Willebrand factor in thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome. Blood 1989;74:978–83.