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**Acquired deficiency of von Willebrand factor-cleaving protease in a patient suffering from acute systemic lupus erythematosus**

SIR, Thrombotic thrombocytopenic purpura (TTP) is a well-known complication in established rheumatic diseases, especially in patients with systemic lupus erythematosus (SLE) (estimated incidence 1–4%). Post-mortem examination of SLE patients suggests that this association may be present in a significantly higher percentage of SLE patients succumbing to multi-organ system failure [1, 2].

TTP is a syndrome characterized by the pentad of thrombocytopenia, haemolytic microangiopathy, fluctuating neurological deficits, renal dysfunction and fever [3]. However, it has been observed that many patients with TTP may lack one or more of these criteria. The complete clinical pentad, characteristic of TTP, is entirely present in only about 30–40% of patients [4]. TTP may precede the onset of SLE or occur late in the course of the disease, and may occur in either quiescent or active lupus disease states [2].

A 12-yr-old girl was referred to our hospital after a 3-week history of increasing fatigue. Physical examination was normal except for a symmetrical malar rash and petechial bleeding on all four limbs. She was alert, had moderate temperature elevation (up to 38.5°C), and normal renal function and urinalysis. Laboratory data showed profound thrombocytopenia ( $9 \times 10^9/l$ ) and anaemia (haemoglobin 64 g/l) (Fig. 1). Her blood smear revealed anisocytosis and schistocytes. The lactate dehydrogenase (LDH) level was 1887 U/l whereas creatinine was normal. The coagulation profile was normal and no fibrin degradation products were detected. Anti-cardiolipin IgM, IgA and IgG antibodies (ACA) were in the normal range, while lupus anticoagulant and anti- $\beta_2$ -glycoprotein I IgM, IgA and IgG antibodies were absent. Antibodies against platelet glycoproteins (anti-IIb/IIIa, -Ia/IIa and -Ib) and anti-HLA antibodies were negative. After administration of 0.8 g/kg intravenous immunoglobulins, the direct Coombs test was positive (anti-IgG-positive, anti-C3d-negative). Bone marrow examination showed increased erythropoiesis and megakaryopoiesis. She was highly positive for anti-nuclear, anti-Smith antigen, anti-nuclear ribonucleoprotein, anti-histone, anti-SSA and anti-SSB antibodies. Double-stranded DNA antibodies were detectable (*Crithidia* assay). Levels of complement factors C3 and C4 were low. As our patient fulfilled four of 11 American Rheumatism Association (ARA) criteria (malar rash, haemolytic anaemia/thrombocytopenia, antinuclear antibodies, anti-double-stranded DNA/Smith antibodies), the diagnosis of SLE was made. Low C3 and C4 complement levels indicated active disease. Cardiac manifestation of SLE was ruled out by normal echocardiography. The patient received prednisone, methylprednisolone pulse therapy and intravenous immunoglobulins (Fig. 1). Packed red cell

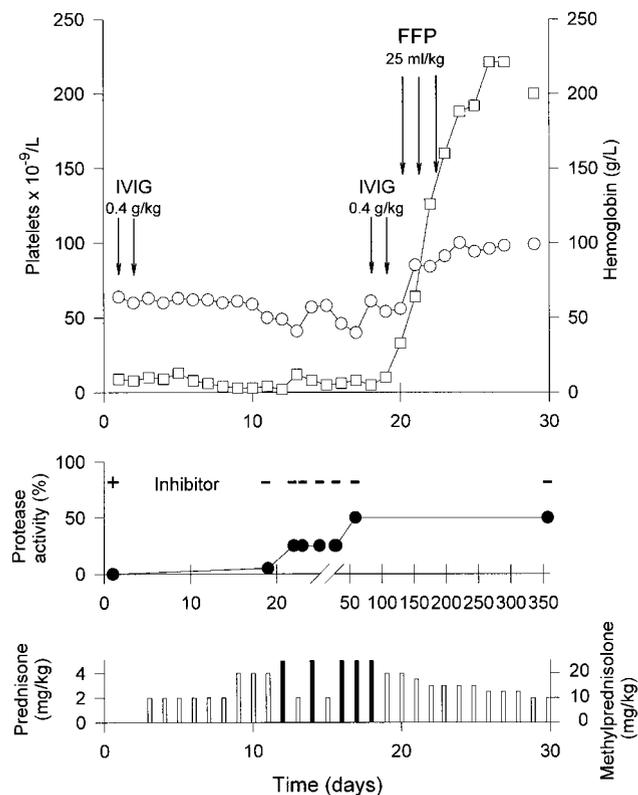


FIG. 1. Time course of laboratory parameters in the patient with SLE and TTP in relation to therapy with intravenous IgG (IVIG), infusion of FFP, prednisone (open bars) and methylprednisolone (solid bars).  $\circ$  = haemoglobin;  $\square$  = platelet count;  $\bullet$  = vWF-cleaving protease activity; + and - indicate the presence and absence, respectively, of a circulating inhibitor of the vWF-cleaving protease.

concentrates had to be transfused twice because of worsening anaemia and additional symptoms, such as haematuria. On day 15 she developed neurological symptoms with temporary aphasia and weakness of her left hand, which prompted neuroradiological investigation. Magnetic resonance imaging showed ischaemic lesions in the basal ganglia that were consistent with thrombotic occlusions of lenticulostriate arteries; cerebrovascular vasculitis was excluded. Repeated Coombs tests during immunosuppressive treatment were negative and schistocytes increased steadily. LDH rose to above 9000 U/l but creatinine remained within the normal range. The clinical picture, with cerebrovascular ischaemia, microangiopathic haemolytic anaemia and thrombocytopenia, suggested the diagnosis of TTP (day 19 after admission). She received fresh-frozen plasma (FFP) (25 ml/kg) daily on three consecutive days (days 19–21) while steroid treatment was maintained. Within 5 days after starting infusions of FFP, the platelet count returned to normal ( $>150 \times 10^9/l$ ). The haemolysis ceased with the disappearance of schistocytes and the normalization of LDH. She was discharged 2 weeks later in good general condition with normalized whole blood count and

urine parameters. Neurological sequelae were left-sided hemiparesis and dysidiadochokinesis of the left hand. At the last visit (day 357), 1 yr after the acute bout of TTP, she was still under immunosuppressive treatment with low-dose steroids and azathioprine. She was in remission for SLE and TTP and residual neurological symptoms of hemiparesis had almost completely disappeared. Anti-nuclear, anti-SSA and anti-Smith antibodies were still elevated while anti-phospholipid antibodies were negative.

The activity of von Willebrand factor (vWF)-cleaving protease and the presence of a protease inhibitor were determined retrospectively in frozen plasma samples according to methods described previously [5]. As controls, 16 adult patients, aged 28–79 yr, who had been referred to the Central Haematology Laboratory (University Hospital, Bern) for thrombophilia investigation and had high levels of ACA, were tested for vWF-cleaving protease activity. Three of these 16 patients had SLE according to ARA criteria, whereas the remaining 13 patients had not. All 16 had normal vWF-cleaving protease activity (100%).

In our patient, vWF-cleaving protease activity was undetectable on the day of admission to the hospital before any therapy and this deficiency was found to be due to a circulating inhibitor. On day 19, after 17 days of immunosuppressive treatment and just after the first plasma infusion, the vWF-cleaving protease activity was still very low ( $<5\%$ ) and an inhibitor was no longer detectable. The activity of vWF-cleaving protease rose to 25% on day 22 and to 50% on day 59. One year later, the protease activity was still 50% (Fig. 1). The vWF-cleaving protease activity in the patient's father and mother was 100 and 50% respectively.

Recent reports have shown a clear association of vWF-cleaving protease deficiency with TTP [5–7]. Our patient is the first SLE patient with concomitant TTP in whom autoantibodies against the vWF-cleaving protease were detected. The partial deficiency of vWF-cleaving protease (50%) that remained despite clinical and biochemical remission of TTP may be inherited, as the patient's mother showed only about 50% activity. It should be noted that obligate heterozygous carriers of the protease deficiency have thus far always been found to be asymptomatic [8].

Another interesting point is that our patient was completely negative for anti-phospholipid antibodies during the whole observation period. Several instances of TTP have been reported in SLE patients with positive anti-phospholipid antibodies [9], suggesting that these antibodies may be associated with platelet aggregation and endothelial damage in patients with TTP. Because anti-phospholipid antibodies have been found in non-SLE patients with TTP [10], it cannot be excluded that anti-phospholipid antibodies may also contribute to the development of TTP in patients with SLE.

In the present study, we demonstrated that all 16 thrombophilic patients with elevated ACA had normal vWF-cleaving protease activity, indicating that the presence of ACA and of vWF-cleaving protease

inhibitors are not necessarily associated pathophysiological phenomena. This view is supported by observations of Porta *et al.* [2], who found normal levels of anti-phospholipid antibodies in each of 10 patients with TTP.

We believe that in SLE patients with Coombs-negative haemolytic anaemia, schistocytes in the peripheral blood smear, and thrombocytopenia, the assay of vWF-cleaving protease and of its inhibitor may provide additional, helpful information for the delineation, earlier detection and therapy of life-threatening TTP-associated complications with a high mortality rate.

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