Long-lasting remission and successful treatment of acquired factor VIII inhibitors using cyclophosphamide in a patient with systemic lupus erythematosus

F. Trotta, G. Bajocchi, R. La Corte, S. Moratelli and L.-Y. Sun

Division of Rheumatology, Arcispedale S. Anna, Centre for the Study of Thrombosis and Haemostasis, University of Ferrara, Italy and Department of Immunology, Gu Lou Hospital, Nanjing, China

Abstract

Acquired deficiency of clotting factor VIII (FVIII) is a rare bleeding diathesis seldom encountered in systemic lupus erythematosus (SLE). Reduction of FVIII activity by autoantibodies can cause potentially life-threatening situations. Herein, an SLE patient with a positive lupus anticoagulant (LAC) test who abruptly developed metrorrhagia 4 yr after diagnosis is reported. Coagulation tests revealed FVIII activity reduced to 3% and a prolonged aPTT. FVIII inhibitor(s) were found to be as high as 3.0 Bethesda Units. Plasmapheresis, immunoglobulins, prednisolone and FVIII plasma concentrates induced the cessation of metrorrhagia, but the clotting tests were barely improved. One month later, extensive ecchymosis appeared and worsened, despite re-administration of the previous therapy. Pulse cyclophosphamide followed by oral administration was then started with normalization of coagulation parameters and long-lasting disease remission.

Key words: Systemic lupus erythematosus, Factor VIII, Acquired deficiency, Metrorrhagia, Treatment, Cyclophosphamide.
The values of factor IX (73%), factor XII (86%), vWRFicof (60%), factor V (99%) and factor X (94%) were normal. LAC, detected by kaolin clotting time, was present. Anticardiolipin antibodies (ELISA), fibrin split products and the syphilis test (VDRL) were negative.

Initial treatment consisted of plasmapheresis three times a week, prednisolone (50 mg/day i.v.) and one infusion of FVIII plasma concentrate (2000 IU) which induced cessation of metrorrhagia within a week. However, the clotting tests did not become completely normal. The patient was discharged taking prednisolone 25 mg/b.i.d.

One month later, a massive haemorrhage recurred with ecchymosis on the lower limbs and hips, for which the patient was readmitted to hospital. Prednisolone (50 mg/day i.v.), gammaglobulins (0.4 g/kg/day i.v. for 3 days) and FVIII plasma concentrate (3000 IU/day for 2 days) were started. Despite the treatment, the ecchymosis worsened, along with a progressive decline of the Hb down to 7.7 g/dl. In following check-ups, FVIII activity ranged between 3 and 14%. Pulse cyclophosphamide (750 mg/m² i.v.) was then started and followed by an oral dose of 100 mg/day. Both clinical and laboratory improvement were evident after ~2 weeks. Once discharged, the patient underwent combined therapy with 2 mg/kg/day of cyclophosphamide and 25 mg/b.i.d. of prednisolone. Factor VIII activity rose to 42% and FVIII inhibitor(s) disappeared after 1 month (Fig. 1). Menses started again. After 1 month of therapy, cyclophosphamide was stopped because of leucopenia (WBC 2000/mm³) and prednisolone was gradually tapered off to 22.5 mg/day. Four years later, FVIII activity is still within normal levels and no haematological disorder has recurred.

Discussion

In autoimmune diseases, haemorrhages are a significant cause of morbidity and mortality for several reasons. Firstly, the acquired haemophilac, unlike hereditary haemophiliaics, is unprepared for haemorrhagic episodes. Secondly, a sudden major bleeding can be the first symptom revealing the presence of a circulating anticoagulant(s). Thirdly, the cause of the bleeding may be further complicated, especially in SLE, by the overlapping of different types of coagulant inhibitors [4, 5], such as in our case. Nonetheless, one-third of the patients present amelioration of haemorrhages by means of spontaneous clearance of the inhibitors [6].

Owing to the rarity of the cases, controlled therapy trials are lacking, so the management of these patients is largely tentative. When reviewing 20 yr of literature, there was no consensus on the treatment of SLE associated with FVIII inhibitors. Corticosteroids were administered in SLE and Sjögren’s syndrome overlap [7]; corticosteroids and 1-deamino-8-D-arginine vasopressin (DDAVP) in an SLE-like serology [8]; combined immunosuppressive therapy with corticosteroids, azathioprine, cyclophosphamide and cyclosporin followed by immunoglobulins in a case of SLE [9]; corticosteroids in a rheumatoid arthritis patient with positive LAC [4]; corticosteroids and cyclophosphamide to treat an overlap between mixed connective tissue disease and SLE [10]; tranexamic acid and corticosteroids post-partum with anti-DNA antibodies [11]; immunoglobulins, cyclophosphamide and cyclosporin in SLE [12]; plasmapheresis, corticosteroids, cyclophosphamide, methotrexate, immunoglobulins and vincristine in two SLE patients [13]. Notably, in our case, corticosteroids, plasmapheresis and FVIII plasma concentrates halted the bleeding with only a partial improvement of the laboratory tests. Disappearance of the circulating FVIII inhibitor(s) and normalization of the clotting tests were noticed only after adding cyclophosphamide.

Lacking a standardized treatment, a careful check-up of laboratory data is critical to evaluate the response to therapy and the risk of a new emergency. Looking at our and other cases in the literature, it seems that the best approach is to monitor both inhibitors and activity of FVIII sequentially, in order to demonstrate their divergent progression with time. We feel that neither the disappearance of bleeding nor the low titre of inhibitors per se have a trustworthy prognostic role in excluding a relapse. In our case, repeated measurements always detected a low titre (3.0 BU) of circulating inhibitor(s), but bleeding definitively stopped after the steady progressive enhancement of FVIII. This observation also supports the hypothesis that a low titre of the inhibitor(s) is related to responsiveness to immunosuppressive treatment [14].

In conclusion, even a low titre of FVIII inhibitor(s) must keep clinicians alert until FVIII activity progressively increases. The reciprocal progression over time of FVIII and its inhibitor could identify cases in which cyclophosphamide is regarded as first-line treatment.

References


