

Successful treatment of acquired hypoprothrombinemia without associated lupus anticoagulant using intravenous immunoglobulin

Acquired hypoprothrombinemia is usually associated with a lupus anticoagulant, but cases without associated neutralizing antibodies have also been reported.^{1,2} We describe here a patient with acquired hypoprothrombinemia due to accelerated clearance of prothrombin by non-neutralizing antibodies. Intravenous immunoglobulin therapy resulted in prompt improvement.

Case Report. An 83-year old previously healthy Chinese man presented in October 1998 with 'flu-like symptoms and a sudden onset of frank hematuria and skin bruises. There was no history of snakebite or drug intake. Physical examination was unremarkable except multiple skin bruises.

On admission, his hemoglobin was 10.9 g/dL. Platelet and white cell counts were normal. Prothrombin time (PT), and activated partial thromboplastin time (APTT) were 27.9 and 90.6 seconds respectively. Plasma urea, creatinine and liver enzymes were normal. Mid-stream urine showed no bacterial growth. Lupus anticoagulant was negative. Factors I, V, VII, VIII, IX, X, XI, XII ranged between 60-240%. Factor II level was 11%. The patient's PT and APTT were corrected to 13.6 and 43.8 seconds upon mixing with equal volume of normal plasma. Factor II activity post-mixing was 42%.

The patient received vitamin K supplement and six units of fresh frozen plasma. PT and APTT immediately after the transfusions were 19.3 and 58.5 seconds, respectively, but rapidly returned to pre-transfusion levels 8 hours later.

He was given prothrombin concentrate therapy using Promthrombinex-HT[®]. Despite treatment with 2200 IU of factor II every 8 hours, bleeding persisted with the development of a left iliac hematoma and femoral neuropathy. There was only transient improvement of clotting profile after factor II infusion lasting for less than six hours, suggesting an accelerated clearance of prothrombin from the circulation. He was given intravenous normal human immunoglobulin (Intragam[®]), 0.4g per kg per day for 5 days. He responded promptly with normalization of PT and APTT in five days without Prothrombinex-HT[®]. He has remained in remission for 18 months since treatment. Subsequent investigations showed no apparent cause of the hypoprothrombinemia.

Detection of anti-prothrombin antibodies. Antiprothrombin antibodies was detected by ELISA using microtiter plate (Maxisorp, Nunc Denmark) coated with 80 uL/well of human prothrombin (Diagnostica Stago, Asnieres France).³ We also used an indirect method to document accelerated clearance of prothrombin. An aliquot of 0.25 mL of patient's serum were mixed with 0.25 mL of normal plasma. After incubation at 37° C for one hour, 0.125 mL of 50% polyethylene glycol (PEG) were added to a final concentration of 10% to precipitate any immune complex. After centrifugation, PT was performed on the supernatant (Experiment A). The above experiment was repeated with normal serum in place of patient's serum (Experiment B) and normal saline in place of PEG (Experiment C). The PT of the normal plasma sample was 10.4 seconds. The PT of the supernatant from experiments A, B and C were 33.2 seconds, 9.95 seconds, and 9.25 seconds respectively.

Bajaj *et al.* demonstrated the presence of non-neutralizing anti-prothrombin antibodies in two patients with acquired hypoprothrombinemia using double immunodiffusion and binding experiments utilizing ¹²⁵I-prothrombin.² In the lupus anticoagulant-acquired hypoprothrombinemia syndrome, the antibodies were directed against the COOH-segment of prothrombin, while in the acquired hypoprothrombinemia without lupus anti-coag-

ulant, the antibodies were directed against the NH₂ segment which is not essential for the procoagulant activity of prothrombin.⁴ The deficiency is secondary to rapid clearing of prothrombin/anti-prothrombin complexes from the circulation.² The detection of anti-prothrombin antibodies by ELISA and the PEG precipitation test results provided indirect evidence of a similar mechanism in our patient. PEG, in various concentrations (3.5-13%), has been used to precipitate immune complexes.⁵ We chose a final concentration of 10%. Some patients with lupus anticoagulant-acquired hypoprothrombinemia syndrome responded well to corticosteroid.⁶ Danazol⁷ and intravenous immunoglobulins were successful in other cases.⁸ However, there is no recommended treatment for acquired hypoprothrombinemia without associated lupus anticoagulant. Our case suggests that intravenous immunoglobulin might be useful in this setting.

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