Case report

Recurrent venous thrombosis in a patient with chronic lymphocytic leukemia and acquired protein S deficiency

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Abstract—A patient with chronic lymphocytic leukemia and an undetectable plasma level of protein S (PS), associated with recurrent venous thrombosis, is described. The laboratory investigation revealed the concomitant presence of an inhibitor directed to PS and a monoclonal protein in the patient’s plasma. After treatment with prednisone and cyclophosphamide both the inhibitor to PS and the monoclonal component disappeared.

Key words: Protein S inhibitor; venous thrombosis; chronic lymphocytic leukemia.

INTRODUCTION

Protein S is a component of the natural anticoagulant system and acts as a co-factor of activated protein C in the inactivation of coagulation factors Va and VIIIa [1]. For this reason, patients with either hereditary or acquired PS deficiency are predisposed to recurrent thrombotic manifestations [2]. Acquired PS deficiency can occur in a variety of clinical conditions [3], but protein S deficiency due to a specific circulating inhibitor directed to PS is extremely rare and has been reported in only a few cases so far. To the best of our knowledge the association of inhibitor to PS and recurrent venous thrombosis in patients with chronic lymphocytic leukemia has not yet been reported.

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CASE REPORT

A 60-year-old male presented with blood lymphocytosis in April 1986 when he was diagnosed as having chronic lymphocytic leukemia (CLL). At the beginning of 1988 treatment with cyclophosphamide and prednisone was initiated because of the occurrence of hemolytic anemia and lymph node enlargement. In March 1991 he suffered deep vein thrombosis of the right leg and was treated with intravenous heparin followed by acenocoumarol (Sintrom). Two months later he developed re-thrombosis in the same area despite the correct anticoagulant therapy. Acenocoumarol was continued for the following six months. In March 1993 the patient was admitted to our hospital following a sudden onset of pain and swelling of the complete left leg. Doppler-ultrasonographic examination showed massive left iliaco-femoral vein thrombosis which completely obstructed the venous lumen. His hemoglobin was 110 g/l, platelets $32 \times 10^9$/l and leukocytes $37 \times 10^9$/l. The differential white cell count was consistent with the diagnosis of CLL. Biochemical tests revealed elevated levels of serum alkaline phosphatase (285 U/l; normal, 30–90 U/l), aspartate aminotransferase (AST) (44 U/l; normal, <27 U/l) and alanine aminotransferase (ALT) (69 U/l; normal, <30 U/l). Blood tests for antibodies to hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) and hepatitis A virus (HAV) of the IgM class were negative. Hypoalbuminemia (29 g/l) was also disclosed, indicating the presence of a mild liver disease of unclear origin. Serum protein immunoelectrophoresis revealed the presence of a monoclonal IgG component in a concentration of 7 g/l. Continuous intravenous heparin was administered initially, in addition to antibiotics and erythrocyte concentrates.

Twenty-five days after admission the patient’s general condition improved significantly and unfractionated heparin was substituted with low molecular weight (LMW) heparin (Fragmin, 5000 U, twice a day, s.c.). In the blood sample taken 7 days after the introduction of LMW heparin complete absence of total PS:Ag and PS activity was found (Table 1). By mixing studies — using equal volumes of the patient’s plasma and normal plasma — the presence of an inhibitor directed to PS was established. After 2 hours of incubation the residual total PS:Ag (determined by Laurell rocket immunoelectrophoresis) and PS activity (clotting method) in the mixture were only 39% and 41%, respectively, of values found in the control mixture of normal plasma and imidazole buffer. Despite transfusion of 15 ml/kg fresh frozen plasma, PS activity remained undetectable in the patient’s blood taken one hour after treatment. The levels of antithrombin III (AT III), protein C and plasminogen (measured by chromogenic substrates) were moderately decreased while fibrin(ogen) degradation products (FDP) were elevated. The mixing experiments were also performed in the measurements of AT III and protein C but the presence of inhibitors to these anticoagulants was not detected. Cyclophosphamide and prednisone therapy were introduced and two months later the inhibitor to PS could no longer be detected in the patient’s plasma, while PS:Ag and PS activity increased gradually up to 40% and 49%, respectively. At the same time, disappearance of the monoclonal protein along with a drop in FDP values and a slight increase in the