Factor V Inhibitor in a Liver Transplant Patient Associated with Porcine Xenoperfusion*

J. DAVID SMITH, M.D.,
RAKESH SINDHI, M.D.,
ROBY ROGERS, M.D.,
and JOHN LAZARCHICK, M.D.

Department of Pathology and Laboratory Medicine,
Department of Surgery,
Medical University of South Carolina,
Charleston, SC 29425

ABSTRACT

The development of a high-titer factor V inhibitor is described in a patient who underwent orthotopic liver transplantation followed by porcine xenoperfusion after an acute rejection episode. The inhibitor showed no cross-reactivity to either porcine or bovine factor V, nor was it accessible to human platelet factor V. The limitations of treatment modalities including intravenous immunoglobulin, steroids, cytotoxic therapy, intense plasmapheresis and platelet transfusions are discussed.

Introduction

Inhibitors of coagulation factors are immunoglobulins directed against specific coagulation factors that either neutralize their procoagulant activity or form a complex resulting in their accelerated clearance from the circulation.1,2,3 The first report of bleeding owing to circulating inhibitors of coagulation factors was in 1906 by Weil.4 While most inhibitors are directed at Factor VIII procoagulant activity, antibodies against VII, vWF, IX, V, XI, XIII and thrombin have been reported.1,3,5,6,7 Most commonly, coagulation inhibitors are associated with transfusions in a factor deficient patient, autoimmune diseases, or spontaneous development in an otherwise normal patient.8,9 The factor inhibitors are usually IgG, particularly subclass IgG4.9

Factor V (FV) is a cofactor in the prothrombinase complex which mediates prothrombin to thrombin and consists of Va/Xa/Ca++/phospholipid. Factor V is a 330 Kd single chain protein cleaved to FVa which is a 71 Kd light chain and a 105 Kd heavy chain noncovalently bound by calcium. Factor V is also found in the alpha granules of platelets. FVa increases the rate of conversion of prothrombin to thrombin by 4 to 5 orders of magnitude; therefore, FV is required for normal hemostasis.10 Factor V inhibitors are relatively rare, usually IgG and again of the subclass IgG4.10,11 They present clinically with variable severity ranging from minimal hemorrhagic complications to severe hemorrhagic diathesis.1,2,3,5,6,9,10,11 Fortunately, they are often transient and spontaneously disappear.2,6,9,10 Etiologic associations of FV inhibitors include major surgical procedures, exposure to topical thrombin, tuberculosis, exposure to aminoglycoside antibiotics, transfusions in patients with factor deficiency, and spontaneous develop-
Platelet FV is protected from anti-FV antibody and accounts for approximately 20 percent of circulating FV. 

Case Report

The patient was a 43-year-old white male with a history of hepatitis C and liver failure. His past medical history is significant for rheumatic fever in 1973, an upper gastrointestinal bleed in 1974, development of osteonecrosis after a motor vehicle accident in 1974, and surgical repair of a laceration in the right hand in 1976. There was no history of exposure to topical thrombin preparations. Physical examination was remarkable only for icteric sclerae and hepatomegaly. He was admitted to the Medical University of South Carolina on 10/11/96 and underwent his first orthotopic liver transplantation with primary graft failure necessitating removal of the donor liver. From 10/14 to 10/15, extracorporeal liver perfusion with a procine venograft was used as a bridge to a second transplant. During xenoperfusion, the patient and porcine liver circulations remained separate; a dialyzing membrane with exclusion limits of 20 Kd separated the two circulations.

On 10/16, a second orthotopic liver transplantation was performed. One day later, a right parietal infarct was identified by CT scan. During the next 6 weeks, the patient underwent hemodialysis, aggressive plasmapheresis, platelet transfusions, chemotherapy (cytoxan, vincristine), steroids, and Prosorba column therapy. On 12/8, his mental status changed abruptly and an extensive right parietooccipital hemorrhage was found on CT scan. Life support was removed according to the family’s wishes and he was pronounced dead on 12/8.

Discussion

Initial evaluation by our Hemostasis Laboratory revealed coagulation factors with normal or near normal values for II, VII, X, XI but an isolated FV deficiency was identified (table I). This suggested hepatic coagulation factor synthesis was occurring following the second orthotopic liver transplant. A mixing study with equal parts normal pooled plasma (NPP) and patient plasma showed no correction suggesting the presence of an inhibitor. Subsequent studies confirmed the presence of a FV inhibitor at an initial titer of 9.8 Bethesda units (Bu). The therapeutic modalities mentioned achieved a reduction in FV Inhibitor titer but could not eliminate the Ab titer completely (table II).

Assays for FV Ab were performed using porcine and bovine plasma. This was done similarly to the usual assay, but porcine and bovine plasma were diluted down to 100 percent FV activity. Porcine and bovine plasma were then separately incubated with the patient’s plasma as above. Recovery of FV activity was ~100 percent thus excluding cross-reactivity. The FV inhibitor levels were 5.5 Bu when the tests for porcine and bovine cross-reactivity were performed. Thus, no cross-reactivity of human anti-FV to porcine or bovine FV was identified.

Since platelet therapy has been shown to be a treatment modality in some patients, it was endeavored to determine whether or not platelet FV was accessible to anti-FV antibody. To perform the study, a platelet preparation of 1.4 x 10^6/uL was washed to rid the sample of plasma proteins. The sample was then mixed with patient plasma which had 6.4 Bu anti-FV, incubated for 30 minutes, centrifuged, and the supernatant was reassayed for residual FV inhibitor. Nitrophenylphosphate, which showed 100 percent FV activity was mixed with the patient’s plasma supernatant. The anti-FV antibody titer showed no change. If the platelet FV was accessible to the anti-FV antibody, then the anti-FV antibody should
have decreased. Therefore, since no antibody was bound by platelet FV, platelet FV appears to be inaccessible to the patient’s plasma anti-FV antibody.

Conclusions

Various therapies have been used with varying success for coagulation factor inhibitors and include intravenous IgG, steroids, cytotoxic therapy, plasmapheresis, and platelet transfusions. Many of these treatments were implemented with out patient. The patient developed a FV inhibitor with a titer up to 9.8 Bethesda units after an orthotopic liver transplant with porcine xenoperfusion. The FV Ab did not cross-react with porcine or bovine FV. Platelet therapy has been shown to be beneficial in some patients.6,8,11 Our patient’s platelet FV was inaccessible to the anti-FV antibody; he received massive amounts of platelets over the course of his hospitalization. Whether or not a therapeutic advantage was obtained by platelet therapy in the patient is uncertain, especially given the terminal hemorrhagic event. Aggressive plasmapheresis reduced but did not eliminate the anti-FV antibody titer. The etiologic mechanism behind the development of a FV inhibitor in this patient is unknown. Xenosensitization apparently played no role in the development of the FV inhibitor in this patient. However, with increasing use of xenoperfusion as a bridge to transplantation, an increase in apparent spontaneous development of coagulation inhibitors may occur and clinicians need to be aware of this possibility.

References