rounds [coagulation and hematology]

Acquired Factor V Inhibitor with Lupus-Like Features

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- Acquired factor V inhibitor
- Lupus-like features
- Laboratory tests
- Clinical manifestations
- First reported case without complications

Acquired factor V inhibitors are rare and have been associated with surgery, malignancy, blood transfusion, systemic infection, use of antibiotics, and exposure to bovine thrombin contaminated with bovine factor V. Three previous cases of factor V inhibitor with lupus-like features have been reported in literature.[1-3] All of them had either bleeding or thrombotic complications. We report an unusual case with a factor V inhibitor showing features of lupus anticoagulant without any coagulation complications.

Case History

Patient is a 68-year-old male who had femoral-popliteal bypass surgery due to peripheral vascular disease. Coagulation test results were normal before and after surgery. Patient developed infection of the groin and was admitted this time for intravenous antibiotic treatment (3 weeks after surgery). Patient had a history of coronary artery disease, hypertension, hyperlipidemia, and prostate adenocarcinoma. Patient had no history of liver disease and liver function tests were in normal range. His past medical history was also negative for any bleeding or thrombotic diathesis and systemic autoimmune disease. Coagulation tests on this admission showed prolonged prothrombin time (PT) and partial thromboplastin time (PTT). Subsequent laboratory studies revealed a factor V inhibitor with lupus-like features. Patient was treated for the groin infection during this hospitalization with no bleeding or thrombotic complications and was discharged 12 days after admission. Medical records of his clinic visits showed no clinical complications for 14 months after discharge.

Materials and Methods

Coagulation tests were performed with standard laboratory techniques.[4] Specific factor assays (factors II, V, and X) were performed with 1-stage assays based on PT. Standard curves were prepared from known dilutions of reconstituted lyophilized plasma mixed with specific factor-deficient plasmas. Calculations were based on linear regression of the log-log conversion of clotting time versus activity. Factor V inhibitor activity was determined using the Bethesda assay technique. The lupus anticoagulant activity was determined using dilute russell viper venom time (dRVVT) and Platelet Neutralization Procedure (PNP). All coagulation tests were performed on an Electra 1800C coagulometer (Beckman-Coulter **M**, Fullerton, CA) with reagents from Dade Behring **M** (Deerfield, IL).

Results

Coagulation studies on admission showed that PT was prolonged to 51 seconds (reference range 11 to 13 seconds) and PTT was >150 seconds (reference range 22 to 34 seconds). Prothrombin time and PTT were not corrected with a 1:1 mixing, which is indicative of a circulating anticoagulant. Subsequent tests were performed to rule out an inhibitor in the common pathway and also lupus anticoagulant. Fibrinogen was elevated at 5.61 g/L (reference range 1.7 to 4.1 g/L). Factor II (85%) and X (114%) were in normal ranges (reference ranges 83% to 117% and 45% to 155%, respectively). However, factor V was markedly decreased (<2%; reference range 50% to 150%), and factor V inhibitor was markedly increased (20 Bethesda Unit). Dilute russell viper venom time was prolonged and the PNP result was positive, consistent with a lupus-like inhibitor. Typically in the presence of a lupus-like inhibitor, factor assays carried out at the usual dilutions are falsely reduced. This effect can be overcome by carrying out the assays at high dilution in buffer. While the apparently reduced levels of factors II and X were readily corrected with dilution (up to 1:320 in this case), factor V level remained low. Other laboratory studies included normal liver function tests, hemoglobin of 107 g/L (reference range 140 to 180 g/L), white cell count of 7.9 x 10^{10}/L (reference range 4.8 to 10.8 x 10^{10}/L), and platelet count of 293 x 10^9/L (reference range 133 to 333 x 10^9/L). Over a period of 2 months after discharge, patient's PT, PTT, and factor V eventually returned to normal ranges while factor V inhibitor and lupus-like inhibitor became undetectable. No thrombotic or bleeding complications were found in the 14-month period of follow-up for this patient.

Discussion

Factor V is a single chain plasma coagulation protein, which is activated by thrombin to form a 2-chain product, factor V_a. Factor V_a is an essential cofactor in the prothrombinase complex and mediates activation of prothrombin by factor X_a in the presence of a phospholipid surface and calcium ions. Factor V inhibitors are typically

Comparison of Coagulation Test Results and Clinical Complications Between the Current Case and the Previously Published Cases

T1

	PT (s)	PTT (s)	Plt (10^9/L)	F-V (%)	F-V-I (BU)	Complications
Current case	51	>150	293	<2	20	no
Case 1[1]	44	75	85	3	8	bleeding
Case 2[2]	41	57	129	<1	N/A*	thrombosis
Case 3[3]	55	155	355	<3	61	thrombosis

Plt: platelet; F-V: factor V; F-V-I: factor V inhibitor; BU: Bethesda unit.
**: data not available.*

autoantibodies. These acquired factor V inhibitors have been associated with surgery, malignancy, blood transfusion, systemic infection, use of aminoglycoside antibiotics, and exposure to bovine thrombin (used as fibrin glue in surgery) contaminated with bovine factor V. Factor V inhibitor in this patient was most likely associated with recent surgery and exposure to bovine thrombin, even though a definitive etiology could not be identified. Most of the factor V inhibitors, which have been characterized, are IgG antibodies, although IgM antibodies have also been reported. They inhibit the procoagulant activity of factor V and are associated with bleeding manifestations.[5,6]

Acquired inhibitors of factor V are relatively uncommon, and only 105 such cases have been reported in literature.[5] Acquired factor V inhibitors with features of lupus anticoagulant are extremely rare; only 3 cases have previously been reported.[1-3] Contrary to factor V inhibitor with bleeding manifestation, a thrombotic tendency in association with lupus-like inhibitor has been well-recognized.[7] It is clinically important to explore any coagulation complications caused by the combination of 2 such different entities: factor V inhibitor with a bleeding tendency and lupus-like inhibitor with a thrombotic tendency. Brandt and colleagues reported a case of factor V inhibitor with lupus-like features.[1] The patient, a 75-year-old woman with no prior history of bleeding, presented with hematemesis and hematuria. She was treated successfully with platelets and immunosuppression. Laboratory evidence of the inhibitor disappeared in 2 months, and the patient remained in remission for 8 months after discharge. Kapru and colleagues described a 68-year-old woman who presented with major thrombotic disease resulting in a sudden onset of limb gangrene.[2] A factor V inhibitor showing laboratory features of lupus anticoagulant was identified in this patient's plasma. Patient required limb amputation 2 weeks after admission. Six months after discharge, her coagulation parameters were normal, although her factor V level was still at a low level. More recently, Kamphuisen and colleagues reported a 71-year-old man who presented with deep-vein thrombosis after surgery.[3] Patient also developed skin necrosis after oral anticoagulant therapy was started. An inhibitor to factor V with lupus-like feature was found in this patient. Patient died a few days after admission.

In the current case, the patient had the combination of a prolonged PT and PTT, and failure to correct PT and PTT after 1:1 mixing with normal plasma. The decreased factor V level and increased factor V inhibitor level confirmed the presence of a factor V inhibitor. Further testing showed that dRVVT was prolonged and PNP result was positive, which was consistent with a lupus-like inhibitor with phospholipid dependency. It is not known for certain whether this patient had a factor V inhibitor with lupus-like features or coexistence of 2 separate inhibitors. Given the clinical course of this patient, it was unlikely that 2 separate antibodies (factor V inhibitor and lupus-like inhibitor) developed at the same time, as no coagulation abnormalities had been found 3 weeks prior to this admission. Therefore, this patient most likely had 1 inhibitor with both anti-factor V and lupus-like features. In contrast to the 3 previously reported cases which had either bleeding or thrombotic complications, the patient in our report showed no evidence of hemostatic complications. Comparison between the current case and the 3 previously published cases is shown in T1.

Conclusion

Acquired factor V inhibitor with lupus-like features may exhibit various clinical manifestations. Bleeding and thrombotic complications have been described in 3 previously reported cases. To our knowledge, this is the first reported case of lupus-like factor V inhibitor in a patient without any hemostatic complications.

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