Acquired Factor V Inhibitor: A Case Report

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ACQUIRED FACTOR V INHIBITOR: A CASE REPORT

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SUMMARY – A 19-year-old asymptomatic man who was admitted to our hospital for investigation of prolonged screening coagulation assays, prothrombin time and activated partial thromboplastin time is presented. Further evaluation revealed factor V deficiency and the presence of specific factor V inhibitors. The appearance of these inhibitors may be associated with administration of some antibiotics, topical bovine thrombin preparations containing bovine factor V during surgical or dental procedures, after blood transfusions and in patients with malignancy or autoimmune diseases. Factor V inhibitors may also develop spontaneously in patients without any clearly identifiable cause. Our patient had no personal or family history of bleeding tendency or thromboembolic event. There is a general consensus that asymptomatic patients should not be treated regardless of their inhibitor titer and residual factor V levels.

Key words: *Blood coagulation factors – antagonists and inhibitors; Antibodies – immunology; Blood coagulation disorders – immunology; Factor V – immunology; Factor V – adverse effects; Case report*

Introduction

Factor V (FV) is a coagulation factor in the common pathway which also contributes to physiological anticoagulation. It is encoded by the F5 gene. Activated FV, factor Va, is a cofactor in the conversion of prothrombin to thrombin by factor Xa. Non-activated FV is a cofactor with protein S in the inactivation of factor VIIIa by activated protein C.

The coagulation protein FV is a high molecular weight (330 kDA) single-chain glycoprotein that circulates in human plasma at a level of ~7 μg/mL[1-3]. Platelets contain ~20% of the FV of human blood. FV inhibitors are antibodies that bind to FV and promote their degradation or block their participation in normal hemostasis[3].

The clinical features of patients with acquired FV inhibitors vary from asymptomatic laboratory abnormalities to mild or life-threatening bleeding. Many patients do not bleed. One reason may be that platelet FV residing inside the platelet α granule is protected from circulating antibodies. Occasionally, some patients, paradoxically, developed thrombotic complications[4,5]. However, most of these patients had additional risk factor for thrombosis which might have played a role[4].

The FV inhibitors initially are detected in routine laboratory evaluation by prolongation of both prothrombin time (PT) and activated partial thromboplastin time (aPTT), both of which fail to correct upon mixing with normal plasma. The definitive diagnosis of FV inhibitor requires specific factor inhibitor assessment using a standard Bethesda assay[6]. Because of the presence of the inhibitor, plasma FV levels are decreased. Individuals with reduced FV levels should also have a FVIII assay performed to exclude combined FV and FVIII deficiency. Acquired inhibitors to coagulation FV represent an uncommon coagulation disorder. The appearance of these inhibitors may be associated with a range of clinical conditions including operative exposure to bovine thrombin, surgery (without exposure to such proteins), drug exposure (β-lactam antibiotics, aminoglycosides), transfusion of blood components, recent bacterial infections, malignancy, autoimmune disorders,

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congenital homozygous FV deficiency, pregnancy, or idiopathic (in about 18% of cases)[7-10]. Bovine thrombin preparations are topical hemostatic agents that contain bovine FV. They are frequently used during cardiovascular, orthopedic, neurosurgical and dental procedures applied either directly to the bleeding site or as a component of fibrin glue[11]. Human antibodies to these hemostatic agents have been shown to cross-react with both human thrombin and human FV. The persistence of FV inhibitor has been reported over a range from <1 month to several years[12].

Case Report

Our patient was a 19-year-old man who was admitted to hematology department following the review of a routine laboratory investigation. The PT and aPTT showed significant prolongation. Additional testing was performed and factor assays showed decreased FV (20.8%; normal range 70%-120%). The Bethesda assay showed a FV inhibitor of 0.56 Bethesda units. Other coagulation factors were normal. The patient and his family had no history of bleeding diathesis or thrombotic events. He did not report recent surgery or dental procedure, and had not been exposed to bovine thrombin, fibrin glue or antibiotics. There was no evidence of malignancies, liver disease or connective tissue disease. We did not find any clearly identifiable precipitant and the patient was considered to have idiopathic FV inhibitor. Our patient did not receive any medication and ten weeks later the antibodies to FV disappeared spontaneously. The coagulation test showed normalization of PT, aPTT and FV activity.

Discussion

Acquired FV deficiency caused by development of inhibitors to this coagulation protein is a rare finding. According to the Medline database, 155 cases were documented between 1955 and 2006. The diagnosis of FV inhibitor is established on the basis of prolonged PT and aPTT. FV levels are decreased and mixing studies or Bethesda method can confirm the presence of a FV inhibitor. Patients with spontaneous autoantibodies should not manifest a prolonged thrombin time (TT). In contrast, patients with bovine thrombin-induced antibodies often manifest a prolonged TT because of the presence of antibodies against bovine thrombin, which is used in TT test by many clinical laboratories[9,13]. Lupus anticoagulant assays as the platelet neutralization procedure, which was not performed in our case, may be positive in patients with FV inhibitors because of the presence of FV in platelet α granules[14,15].

Many of the early reported cases of FV inhibitors developed spontaneously in patients without any clearly identifiable precipitant, as it was the case in our patient. In the last 10 years most cases of the presence of FV inhibitors were due to exposure to bovine thrombin preparations, topical hemostatic agents used during surgical and dental procedures. In patients with no identified cause, FV inhibitors disappeared in about 62% of cases after a mean of 23 weeks[8]. However, it may take up to one year or even longer for this to occur[7,8,10].

The clinical manifestations associated with FV antibodies range from asymptomatic laboratory abnormalities to mild or fatal bleeding. Although patients with spontaneous inhibitors have a more pronounced bleeding tendency, our patient was asymptomatic. Some authors report on the absence of any significant differences in FV activity and inhibitor titer between asymptomatic and symptomatic patients[7].

Therapeutic intervention depends on the predominant clinical manifestations. For asymptomatic patients, no specific treatment other than careful monitoring appears to be necessary. In patients with hemorrhagic symptoms the mainstay of therapy is immunosuppression. Corticosteroids (prednisone, dexamethasone), cyclophosphamide, azathioprine or cyclosporine have been used successfully to reduce autoantibody production[7,9]. Intravenous immunoglobulin has also proved quite effective[16-18]. Plasmapheresis and immunoadsorption can rapidly reduce antibody titers[19,20]. These patients can also be managed with fresh frozen plasma or platelet transfusion[21,22]. Platelet transfusion appears to be a highly useful mode of "bypassing" the inhibitor since platelet FV does not become accessible to the inhibitor until platelets are activated. Patients with severe or life-threatening bleeding should receive multimodal therapy.

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Sažetak

STEČENI INHIBITOR FAKTORA V: PRIKAZ SLUČAJA

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Prikazan je slučaj 19-godišnjeg bolesnika bez simptoma, koji je upućen u našu bolnicu zbog ispitivanja uzroka produljenih probnih testova zgrušavanja, protrombinskog vremena i aktiviranog parcijalnog tromboplastinskog vremena. Daljnje istraživanje ukazalo je na nedostatak faktora V i prisutnost specifičnog inhibitora faktora V. Prisutnost ovih inhibitora može biti povezana s primjenom antibiotika, goveđeg trombina koji sadrži goveđi faktor V primijenjenih lokalno za vrijeme kirurških i zubnih zahvata, nakon transfuzije krvi i u bolesnika s malignim ili autoimunim bolestima. Inhibitori faktora V mogu također nastati spontano u bolesnika bez jasno otkrivenog uzroka. Naš bolesnik i njegova obitelj nisu imali anamnestičkih podataka o sklonosti krvarenju niti tromboemboliji. Opći je stav da bolesnike bez simptoma nije potrebno liječiti, bez obzira na titar inhibitora i preostalu razinu faktora V.

Ključne riječi: *Faktori zgrušavanja krvi – antagonisti i inhibitori; Protutijela – imunologija; Bolesti zgrušavanja krvi – imunologija; Faktor V – imunologija; -Faktor V – štetni učinci; Prikaz slučaja*