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/mL1,2. 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 hemostasis3.

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 complications4. However, most of these patients had additional risk factor for thrombosis which might have played a role4.

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 assay5. 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,
congenital homozygous FV deficiency, pregnancy, or idio-
topathic (in about 18% of cases)\textsuperscript{2-10}. Bovine thrombin
preparations are topical hemostatic agents that contain
bovine FV. They are frequently used during cardiovas-
cular, orthopedic, neurosurgical and dental procedures
applied either directly to the bleeding site or as a com-
ponent of fibrin glue\textsuperscript{11}. Human antibodies to these he-
mostatic 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\textsuperscript{12}.

Case Report

Our patient was a 19-year-old man who was admit-
ted 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
coaugulation factors were normal. The patient and his
family had no history of bleeding diathesis or thrombot-
ic 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 tis-
ue disease. We did not find any clearly identifiable pre-
cipitant and the patient was considered to have idio-
pathic 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 doc-
dumented 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 an-
tibodies often manifest a prolonged TT because of the
presence of antibodies against bovine thrombin, which
is used in TT test by many clinical laboratories\textsuperscript{8,13}. Lu-

References

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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 parcialnog 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, govedeg trombina koji sadrži govedi faktor V primijenjenih lokalno za vrijeme kirurških i zubnih zahvata, nakon transfuzije krvi i u bolesnika s malignim ili autoimmunim bolestima. Inhibitori faktora V mogu također nastati spontano u bolesnika bez jasno otkrivenog uzroka. Naš bolesnik i njegova obitelj nisu imali anamnestičkih podataka o sklonsosti krvarenju niti tromboemboliji. Općio je stanje da bolesnike bez simptoma nije potrebno liječiti, bez obzira na titer inhibitora i preostalo razinu faktora V.

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