Case Report

Acquired factor V inhibitor secondary to an autoimmune disease : a case report.

Inhibiteur acquis anti Facteur V secondaire à une maladie auto-immune: à propos d'un cas.

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Abstract

Acquired anti-Factor V antibodies (AFVI) deficiency is uncommon. The clinical features vary from asymptomatic to severe hemorrhagic tendency. We report a case of a 77-year-old woman suffering from rheumatoid arthritis. She developed AFVI, discovered during a preoperative check-up without bleeding symptoms. Clinicians and surgeons should be aware of this rare, but potentially life-threatening complication.

Keywords: Acquired factor V deficiency, Inhibitor, autoimmune disease, complications

Résumé

Le déficit acquis enfacteur V (FV) est rare. Les caractéristiques cliniques varient d'une forme asymptomatique à une tendance hémorragique sévère. Nous rapportons ici le cas d'une femme de 77 ans souffrant d'une polyarthrite rhumatoïde qui a développé un inhibiteur acquis du FV découvert lors d'un bilan préopératoire sans symptômes hémorragiques. Les cliniciens et les chirurgiens doivent être conscients de cette complication rare, mais potentiellement fatale.

Mots-clés: inhibiteur acquis anti-facteur V, maladie auto-immune, complication

INTRODUCTION

FV functional disorders can cause hemorrhagic or thrombotic events (1,2). Developing AFVI is a rare hemostatic disorder and its clinical manifestations are multifarious, from no bleeding manifestations to fatal hemorrhagic or thromboembolic events. The cases of FV autoantibodies reported in the literature have been frequently related to the use of topical bovine thrombin during surgical procedures, antibiotic administration, blood transfusions, cancers, and autoimmune disorders (3). We, herein, report an asymptomatic patient who developed AFVI potentially secondary to an autoimmune disease.

Case report

A 77-year-old female was admitted to the hospital for tumefaction with pain and stiffness of her right elbow. Her medical history included rheumatoid arthritis; and two elbow arthritis surgeries. She had no history of significant coagulation disorders with prior surgical procedures or other family bleeding history. The clinical examination objectified a fistulated hygroma of the right elbow and a fever. Thus, a surgical procedure was indicated. The coagulation profile revealed both prolonged Prothrombin Time (PT) of 48 seconds (11.7-14.5 seconds) and Activated Partial Thromboplastin Time (APTT) of 122 seconds (26.5- 40 seconds). Upon laboratory examination, her hemoglobin level was 100 g/L, her white blood cell count was $5{,}810^9$/L, her platelet count was 30410^9/L. The blood chemistry revealed no liver dysfunction (Table 1). Therefore, the patient received an infusion of 6 units of fresh frozen plasma, vitamin K and 400 units of prothrombin complex concentrate without correction of her coagulation parameters. Clotting screen tests showed significantly prolonged PT and APTT and a marked reduction of FV activity which was <1%, while the other coagulation factors' levels including fibrinogen, prothrombin, and factor X were within reference ranges. A mixing test with an equal volume of normal plasma failed to correct prolonged PT or reduced FV activity but the APTT was corrected (Table 2). The overall results indicated the presence of antibodies against factor V. Subsequently, a standard Bethesda assay confirmed the presence of FV inhibitor with a low level of 1.8 Bethesda Unit (BU). The patient received 0.5 mg/kg of prednisone. Based on the laboratory results, the operation was cancelled and our patient was treated only with antibiotics and antiseptics. Four months later, the biological assessment showed a PT of 48 s, an APTT of 125 seconds, and a FV <1% with an inhibitor titer of 1.5BU without bleeding episodes.

Table 1: Blood chemistry

Laboratory *data*	Patient's results (normal values)
ALT	8 (9- 40 IU/L)
AST	17 (15- 40 IU/L)
Total Bilirubin	17 (3-20 µmol/L)
GGT	22 (0- 40 IU/L)
Na	139 (137- 147 mmol/L)
K	3.8 (3.5- 5.3 mmol/L)
Cl	109 (99- 110 mmol/L)
Ca	2.17 (2.2- 2.6 mmol/L)
P	0.96 (0.8- 1.5 mmol/L)
Ur	8.9 (2.6 – 7.2 mmol/L)
Cr	57 (39- 89 mmol/L)
CRP	64 (<5 mg/L)

ALT: alanine aminotransferase; AST: aspartate transaminase; GGT: Gamma-glutamyl transferase; P: phosphorus; Ur: urea; Cr: creatinine; CRP: C reactive protein

Table 2: Results of clotting screen

Laboratory test	Patient's results (normal values)
PT(s)	48 (11.7- 14.5 s)
PT(s) (mixing test)	15.8 (11.7- 14.5 s)
APTT (s)	122 (26,5- 40 s)
APTT(s) (mixing test)	34..6 (26.5- 40 s)
Factor V (%)	<1 (70- 120%)
Factor V(%) (mixing test)	30 (70- 120%)
Factor X (%)	94 (70- 120%)
Factor II(%)	129 (70- 120%)
Factor VII(%)	97 (55- 170%)
Factor VIII(%)	155 (60- 150%)
Factor IX(%)	128 (60- 150%)
Fibrinogen (g/L)	5.05 (2- 4 g/L)
Platelet count (/L)	304 $x10^9$
Lupus anticoagulant	Negative

APTT: activated partial thromboplastin time; PT: Prothrombin Time

DISCUSSION

FV is a coagulation protein that is synthesized by the liver and possibly by megakaryocytes. It plays a pivotal role in hemostasis: it participates in procoagulation because it is an essential cofactor of coagulation factor X in the common pathway (4) and its inactivated form participates in the inactivation of factor VIII *via* activated protein C (APC). FV deficiency is rare among bleeding disorders, although it can ensue from an inhibitor antibody. AFVI prevalence is very low (0.09/100,000,000–0.29/1,000,000 per year) but it could be underestimated due to the absence of symptoms or missed diagnosis (3,5). In fact , 94 cases of AFVI were documented in the literature (6).

Various conditions have been mostly associated with the presence of FV inhibitors, including bovine thrombin during surgical procedures, antibiotics (cephalosporins, amino-glucosides, and penicillins), infections, surgery, malignancies and autoimmune disorders. The limited utilization of topical bovine thrombin has reduced its role in causing AVFI to arise. No predisposing factor was found in a considerable number of cases.

In a review, patients affected by AFVI were over 65 years (the median age at presentation was 69 years, range 3–91 years) with men having a higher incidence (52 cases) than women (26 cases) (3), as our observation. The clinical features of acquired Factor V deficiency vary from asymptomatic to severe hemorrhagic tendency, bleeding was present in 63 of 78 patients (81%) at the diagnosis (3). As for AFVI symptoms, bleeding from gastric, urinary, and respiratory mucosa was most frequently found. A large percentage of AVFI patients (32%) showed hematuria(3). Post-surgery bleeding (16%) and hematoma (11%) are additional symptoms in AVFI patients. Less frequent symptoms are intracranial (8%) and retroperitoneal bleeding (5%) (3). However, patients with intracranial hemorrhage had a poor prognosis (7). The mortality rate from bleeding was 12% (1). The discovery of F V inhibitor usually occurs in association with prolonged PT and APTT and an isolated FV

deficiency in patients with negative personal and familial bleeding histories, as the case of our patient (8). The inhibitor was confirmed by using the traditional Bethesda method. In the literature, in contrast with the titers of other coagulation factor inhibitors, the titer of FV inhibitor does not always correlate with the bleeding risk and the same true for factor V activity (9). In fact, the median inhibitor titers in both bleeders and non-bleeders was19 BU (3). The purpose of the treatment is both to control bleeding disorders and to eradicate the inhibitor. Although treatment is unnecessary for asymptomatic patients, a number of therapeutic options have been used in symptomatic patients. In a systematic review, 71% had a satisfactory clinical response to the transfusion of platelet concentrates which protect FV from inhibitors at least until platelet activation and degranulation (3). In the same review, immunosuppressive regimens with corticosteroids alone or in association with cyclophosphamide or other immunosuppressants had been used successfully to suppress inhibitor production in 63% with remission in 76% (3). The poor response to fresh frozen plasma in this case was due to its low concentration of Factor V, which could be easily inactivated by circulating inhibitors (2). In cases of severe bleeding, platelet transfusion/ plasma exchange or intravenous immunoglobulins and chemotherapy were used as recommended (2, 10). Nevertheless, for unclear reasons, recombinant FVIIa seems to aid in hemostasis despite its dependence on FV for its mechanism of action. It is possible that FVIIa utilizes platelet FV and may be used as an adjuvant to platelet transfusions (6).

CONCLUSION

Despite the presence of an FV inhibitor, the patient showed no bleeding symptoms. Various treatments have been attempted but a standardized management of patients when the inhibitors are not associated with significant bleeding is still lacking. The presence of life-threatening FV inhibitor cases underscores the need for prompt diagnosis and treatment. Thus, further investigation is mandatory to clarify the long-term prognosis and optimal management of this disease.

Disclosure of interest:
The authors declare that they have no competing interest.

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