LETTER TO THE EDITOR

A case report of an acquired inhibitor to coagulation factor V

H. SHANMUGAM, S. JAYARANEE and G. I. EOW
Division of Laboratory Medicine, Department of Pathology, University Malaya, Kuala Lumpur, Malaysia

Introduction

Acquired inhibitors to coagulation factors are a rare occurrence in clinical practice. When they occur, early diagnosis is of utmost importance. There are two major types of inhibitors: i) those that develop in individuals deficient in a specific factor after exposure to that exogenous factor and ii) those that develop because of some auto or allo-immune event. The first form is usually of low titre with simple kinetics whereas the second type that generally develops in elderly non-haemophiliacs because of a variety of causes is of higher titre with complex kinetics [1]. Acquired inhibitor to coagulation factor V (FV) is an even rarer event, usually seen in association with the use of topical bovine thrombin in surgical patients. These inhibitors can also manifest after surgical procedures (without thrombin use) or exposure to antibiotics (aminoglycosides and beta lactams), blood transfusion, bacterial infections or associated with autoimmune disorders, malignancy or pregnancy [2,3]. In some groups of patients there is no apparent cause. The clinical presentation is variable and ranges from a lack of clinical bleeding to severe haemorrhage. Seventy two per cent of the reported cases with spontaneous inhibitors suffered bleeding complications which can be fatal in up to 22% of patients [2].

As a result of the rarity of this condition, treatment of bleeding patients poses a challenge to clinicians. There are many documented treatment modalities for acquired FV inhibitors. Treatment options for bleeding patients include Fresh Frozen Plasma (FFP) transfusions, platelet transfusions, plasma exchange, intravenous immunoglobulins or bypassing agents such as prothrombin complex concentrates or recombinant Factor VIIa. A recent review [4] indicates that because of the small number of patients and non-uniformity of treatment dosages used thus far, a proper evidence-based treatment approach to control bleeding in these patients is not possible yet. Eradication of inhibitors with immunosuppressive therapy may also be considered. Asymptomatic patients generally require no therapy.

In this study, we report a case of an asymptomatic patient with acquired FV inhibitor that was detected when the patient had a progressively worsening coagulation profile after undergoing an emergency surgical procedure.

Case Report

A 69-year-old gentleman was referred to our hospital for management of Fournier’s gangrene, a necrotizing bacterial infection of the male genitalia. On admission, his haemoglobin level was 129 g L\(^{-1}\) (normal range: 130–180 g L\(^{-1}\)). The serum aspartate transaminase (AST) and alanine transaminase (ALT) were elevated at 93 IU L\(^{-1}\) (normal range: 15–37 IU L\(^{-1}\)) and 155 IU L\(^{-1}\) (normal range: 30–65 IU L\(^{-1}\)) respectively. Coagulation studies revealed an activated partial thromboplastin time (APTT) of 48.7 s (normal range: 26.0–38.9) and prothrombin ratio (PR) of 1.42 (normal range: 1.0–1.2). The platelet count was within the normal range. The patient was afebrile on admission but had been started on antibiotics at the referring hospital. There was no family history or past medical history of bleeding diathesis.

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At our centre, the patient underwent emergency wound debridement. During surgery he had a hypotensive episode which required inotropic support. He was transfused with four units of FFP intra-operatively in view of the prolonged APTT and PR, which were attributed to the underlying liver cirrhosis. The intra-operative blood loss was documented as 300 ml. However, the haemoglobin level had dropped from 129 g L\(^{-1}\) preoperatively to 88 g L\(^{-1}\) and the patient...
was further transfused with two units of FFP and packed red cells each. He developed a spike of temperature on the first postoperative day and an additional antibiotic was added. On the fourth postoperative day, *Escherichia coli* was isolated from the wound site. The APTT (Fig. 1) and PR increased progressively despite multiple FFP transfusions as well as intravenous Vitamin K injections. However, there was no excessive bleeding noted from the wound site.

In view of the persistent deranged coagulation profile, the patient was referred to a haematologist for further management. A mixing study with an equal volume of normal pooled plasma was carried out and showed partial correction of the APTT and PR, suggesting the presence of a common pathway coagulation factor inhibitor. A repeat mixing test showed similar results. Specific factor testing was done and revealed undetectable FV activity (<1.0%). Inhibitor assay using the Bethesda method confirmed the presence of a high titre FV antibody [17.6 Bethesda units (Bu)]. Factor VII, factor VIII (FVIII) and factor IX activities were found to be decreased at 3.5%, 17% and 2.3% respectively. A repeat FVIII and FIX (FIX) assays using serial dilutions of patient plasma showed activities of 53% and 72% respectively. Lupus anticoagulant assay was unfortunately not included in the laboratory investigations.

The patient had wound dehiscence and was planned for wound closure under general anaesthesia. On advice of the haematologist, this was temporarily deferred. The patient was discharged home 59 days after the surgery. The APTT was near normal at 41.9 s, PR was normal (1.2) and FV activity was 120% at the time of discharge. He did not receive any treatment for the acquired inhibitor during his stay in hospital. The patient was readmitted 1 month later for wound excision and closure. On this admission, the APTT was still mildly prolonged at 41.0 s and PT ratio was normal at 1.17. The surgery was uneventful with no excessive bleeding noted intra-operatively. He was discharged well with no further intervention.

**Discussion**

FV inhibitors are antibodies that bind to FV and promote its degradation and/or prevent it from participating in normal coagulation. In our patient, we postulated that the development of the inhibitor was most likely as a result of Fournier’s gangrene. The patient was given aminoglycosides and transfused with blood components. He had also undergone a major surgical procedure. However, his coagulation profile was already deranged at the time of admission and therefore it is unlikely that these factors could have been responsible for the development of the inhibitor.

Coagulation factor inhibitors are suspected when there are abnormalities in routine coagulation screening tests. Mixing studies will usually show partial or no correction of the APTT or PR. Confirmation of the presence of inhibitors is by specific factor assays and inhibitor assays. In our patient, the mildly prolonged APTT and PR at presentation were attributed to abnormal liver function and liver cirrhosis. However, the progressive prolongation of APTT and PR despite multiple FFP transfusions and Vitamin K injections led to further investigations. The diagnosis was confirmed with a FV assay and inhibitor assay. FVIII and FIX levels were initially found to be low. Serial dilutions of the patient’s plasma followed by factor level quantification revealed normal FVIII and FIX levels. It was concluded that the presence of a potent FV inhibitor interfered with the other factor assays and yielded falsely low factor levels.

Patients with acquired FV inhibitors have variable presentations that include no bleeding to life threatening haemorrhages as compared with patients with FVIII inhibitors who frequently present with bleeding diathesis. It is postulated that this more variable presentation could be because of some FV storage in platelet alpha granules, which renders it inaccessible to degradation by inhibitors [5]. Patients with lower FV levels (<1%) as well as longer prothrombin times and APTTs should be closely observed for bleeding tendencies [4]. The common bleeding sites appear to be the mucous membranes of the gastrointestinal and genitourinary tracts as well as postsurgical wounds [4]. In our patient, the only evidence of probable excessive bleeding was during the initial surgery when there was a significant drop in the haemoglobin
level although the FV levels were <1% and he was at high risk to haemorrhage.

From a therapeutic point of view, there is a general consensus that asymptomatic patients should not be treated regardless of their inhibitor titre and residual FV plasma level [2,3]. Our patient did not receive any therapy as he displayed no bleeding manifestations after the surgery. The overall probability of disappearance of FV inhibitors are 88.3% in a median time of 9.7 weeks [3]. In our patient, the coagulation profile returned to baseline levels after approximately 55 days of hospital stay and at discharge, FV level was normal at 120% and FV inhibitor was undetectable. As a precautionary measure, wound closure was deferred for another month.

Delay in arriving at the diagnosis resulted in transfusion of unwarranted amounts of FFP during and after surgery. Once the cause of the deranged coagulation parameters was established, the patient was monitored closely for bleeding and further FFP transfusions were withheld. In conclusion, this case-study highlights the importance of a differential analysis that considers the presence of clotting factor inhibitors in susceptible patients and early diagnosis for appropriate management.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

References