CASE REPORT

Bleeding associated with acquired factor V inhibitor in a patient on warfarin treated successfully with prednisolone

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SUMMARY

An 85-year-old man on warfarin for atrial fibrillation presented with skin bleeding. International normalised ratio (INR) and activated partial thromboplastin time (APTT) were elevated and did not correct even after warfarin reversal with vitamin K, prothrombin complex concentrate (PCC) and fresh frozen plasma. Mixing coagulation studies with normal plasma suggested the presence of an inhibitor rather than the multiple coagulation factor deficiencies expected with warfarin. Assays of the common-pathway coagulation factors revealed factor V concentration <2% with inhibitor level elevated to 11 Bethesda units. The bleeding resolved following a course of corticosteroids. Coagulation studies and factor V level returned to normal along with resolution of the inhibitor. We report the case of the diagnostic dilemma posed and successful therapy implemented despite the limited evidence-based data being available for the treatment of this rare condition.

BACKGROUND

Acquired factor inhibitors comprise a group of rare coagulation disorders and the most common of these, acquired factor VIII inhibitor, occurs in approximately 1.5 cases/million population/year.¹ Acquired factor V (FV) inhibitor is a rare haematological disorder with a recent systematic review recording only 159 case reports.²

A recent Australian study examined the frequency of FV inhibitors over a 5-year period and extrapolated the results based on the frequency for the Australian population to establish an incidence of 0.29 cases/million.³

Presentation of an acquired FV inhibitor can vary widely, with bleeding being a common presentation in 70% of cases.⁴ Patients can be asymptomatic, with a prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT) or with a varied degree of bleeding, ranging from mucosal bleeding, intracranial bleeding to widespread haemorrhage.^{1–4} The risk of spontaneous bleeding has been demonstrated to be linked to the residual FV activity in some cases of an acquired inhibitor.⁵

The cause of acquired FV inhibitors is varied, with autoimmune disorders, malignancy, medications and blood transfusions considered as common risk factors.¹ Previously, the most common cause of acquired FV inhibitors was exposure to bovine thrombin used in surgical procedures.⁶ Documented cases of acquired FV inhibitors in autoimmune conditions have been

established in Sjogren's syndrome, systemic lupus erythematosus (SLE) and in anti-neutrophil cytoplasmic antibody (ANCA) vasculitis.^{7–9} The medications implicated in acquired FV inhibitors include β -lactam antibiotics, fluoroquinolones and aminoglycosides.¹ While malignancy is a known risk factor, there is no specific malignancy identified as being more commonly associated with acquired FV inhibitors.¹

CASE PRESENTATION

We report a 85-year-old Caucasian man who presented to his local general practitioner for a routine checkup of his international normalised ratio (INR). He was started on warfarin in the year 2000 due to atrial fibrillation (AF) after failing to maintain sinus rhythm with amiodarone. He had been otherwise well prior to presentation with only a history of cellulitis necessitating β -lactam antibiotic therapy. Clinical examination showed an extensive skin bruise over the abdomen and an irregular pulse rate (82/min). His medical history was significant for gout, osteoarthritis, left total knee replacement in 1996, rate-controlled AF, congestive cardiac failure (on diuretics), aortic stenosis and hypertension. His medication included allopurinol, diltiazem, enalapril, furosemide, spironolactone, pravastatin, panadeine forte, fish oil, glucosamine and hydrocortisone-based creams. His blood group was B positive with no antibodies detected.

His previous INR had been therapeutic between 2 and 3. His INR on 27 December 2012 was 7.7. He reported no history of epistaxis, gingival bleeding, gastrointestinal blood loss or haematuria but did note easy bruising with skin ecchymosis. Warfarin was stopped on that day.

He returned for a repeat INR on 3 January 2013, 7 days after ceasing warfarin and was found to have an INR of 10.0. He denied any further warfarin consumption and had not been started on any other medications during that time. He reported skin bleeding mainly on the abdomen. He was admitted to the local hospital and started on intravenous vitamin K at 10 mg daily. His INR failed to correct despite daily vitamin K with an INR persistently above 10.0. At this point, he was transferred to our tertiary institution on 8 January 2013.

After transfer to the Launceston General Hospital, on 9 January 2013 he was started on 2000 IU of prothrombin complex concentrate (PCC). Further testing was performed to detect the warfarin drug level in blood and was undetectable.

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Following PCC, the patient's INR remained >10.0 and APTT significantly increased to 107 s. His full blood count showed stable normocytic anaemia with a haemoglobin count 98 g/L. By this stage, he had begun to develop ecchymoses at cannulation and venepuncture sites.

Over the next 5 days, the patient was progressively given a total of 4000 IU of PCC and 8 units of fresh frozen plasma (FFP). Despite this intervention and daily vitamin K orally he continued to have an INR >10.0 and an APTT >100 s. His skin bleeding, however, was resolved and showed no signs of further active bleeding. On mixing the patient's plasma with normal plasma in a ratio of 1:1, the PT and APTT were not changed immediately and after 2 h incubation, a pattern suggesting the presence of inhibitor(s), either to multiple factors or to a common pathway factor. Therefore, an assay of the common coagulation factor pathway was conducted and revealed very low FV ($<2\%$) using PT-based clotting, one-stage assay with an inhibitor level of 11 BU/mL. The FV Inhibitor assay was based on the PT-based FV assay. The method principle uses the Nijmegen modified Bethesda assay, as for an FVIII inhibitor, but with FV-deficient plasma to dilute the sample and an FV assay. The fibrinogen and factor II levels were normal. Factor X was slightly low without a clinical significance (table 1). Lupus anti-coagulant assay was negative by dilute Russell viper venom test (DRVVT). Immune markers with antinuclear antibody (ANA), ANCA, rheumatoid factor (RhF) and anticardiolipin antibody with ELISA technique were negative. Serum protein electrophoresis showed a small IgG κ band of 6 g/L, which is most likely consistent with monoclonal gammopathy of unknown significance. Serum-free light chains (SFLC) were normal.

The patient was started on prednisolone orally at a dose of 1 mg/kg body weight, which was tapered gradually over 6 weeks. Both PT/INR and APTT responded well to the steroids with a decline of inhibitor level (figure 1).

The patient was discharged in good health, without bleeding and presented as an outpatient for further follow-up with the haematologist.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis on presentation was broad, covering coagulation factor inhibitors and deficiencies involving the common pathway. The following is a summary of our differential list prior to obtaining further diagnostic tests beyond the prolonged APTT and PT (table 1).

- ▶ Prothrombin inhibitor: Occasionally seen in antiphospholipid syndrome with lupus anticoagulant positive. Both anticardiolipin antibodies and lupus anticoagulant were negative.
- ▶ Thrombin inhibitor: Associated with systemic lupus erythematosus, rheumatoid arthritis and monoclonal gammopathy.

Table 1 Initial coagulation factors assay using one-stage prothrombin time (PT)-based clotting assay.

Coagulation factor	Level (IU/dL)	Normal range
Factor II	91	70–120
Factor V	<2	70–120
Factor VII	67	70–130
Factor IX	102	60–160
Factor X	54	70–120
Factor XI	75	60–160
Factor XII	111	50–170

Figure 1 Different coagulation studies in response to the treatment.

Both ANA and RhF levels were normal with normal thrombin level.

- ▶ FV inhibitor: Associated with systemic lupus erythematosus, ANCA vasculitis, primary Sjogren's syndrome. ANCA was negative. FV inhibitor was evident and seems to be idiopathic in nature.
- ▶ Factor X inhibitor: Associated with amyloid light-chain amyloidosis (due to amyloid fibrils cross-linking with factor X). There was no clinical evidence for amyloidosis. SFLC was normal. Factor X was slightly low.
- ▶ Fibrinogen inhibitor: Associated with SLE, ulcerative colitis and multiple myeloma. Fibrinogen level was normal.
- ▶ Disseminated intravascular coagulation (DIC): D-dimer assay and fibrinogen were within normal limits. The blood film also did not show any evidence of DIC with a normal platelet count of 169/nL.
- ▶ Severe vitamin K deficiency or vitamin K malabsorption: The patient had received daily intravenous vitamin K injection without any response.
- ▶ Liver disease with compromise of synthetic function: Liver function enzyme, albumin and bilirubin were within normal limits.

Figure 2 The patient presented with skin bruises including a large ecchymosis on the abdomen extending to the pelvis as shown.

Table 2 Different coagulation studies in response to the treatment.

Date	Prothrombin time (N 11–13 s)	Activated partial thromboplastin time (N 23–35 s)	Factor V level (N 70–120 IU/dL)	FV inhibitor (Bethesda units/mL)
16/01/13	99	107	2	11
28/01/13	91	78	–	–
1/02/13	65.2	62	–	–
6/02/13	23.2	36	17	0.5
19/02/13	17.2	31	66	0.0

TREATMENT

Initial treatment at our institution encompassed measures to stop bleeding with FFP and PCC. The patient had received 4000 units of prothrombinex at our institution with a failure to correct the INR or APTT and therefore, we subsequently attempted reversal of the coagulopathy with FFP. Following 8 units, the INR remained elevated. The presence of a clotting factor inhibitor became increasingly likely.

Specific treatment for the inhibitor was commenced with immunosuppressive therapy, oral prednisolone at 100 mg daily with gradual tapering of the dose. He remained on a maintenance dose of 12.5 mg oral prednisolone at discharge.

Outcome and follow-up

After the start of the corticosteroids, the PT and APTT improved slowly. Two weeks after the start, repeat FV level and inhibitor assay were performed. The inhibitor had decreased significantly to 0.5 Bethesda units/mL and the FV level had increased to 17 IU/dL. The patient continues on a maintenance dose of 12.5 mg prednisolone and the last FV level had increased to 66 IU/dL with unrecordable inhibitor level 2 months following the onset of the acquired FV inhibitor (table 2). PT returned to 17.2 s with an INR of 1.5.

Throughout the inpatient stay and the period of follow-up, the only complications secondary to the acquired inhibitor were the presence of skin ecchymoses over the abdomen and arms at the venepuncture and cannula sites.

Currently, the patient remains on regular outpatient review with his haematologist. The patient is being monitored for the future development of an oligosecretory myeloma/primary amyloidosis by SFLC assays or immunofixation. Although the FV inhibitor has resolved, anticoagulation in the setting of permanent AF remains controversial given the previous coagulopathy.

DISCUSSION

This case provided an interesting diagnostic dilemma. The presence of warfarin therapy initially created a confusing scenario, where the rising INR had suggested excessive anticoagulation. It was not until failure of the INR to reverse with cessation of warfarin and vitamin K therapy that further investigation was initiated. The presence of the deranged APTT also created further suspicion of an underlying coagulopathy. The initial treatment with intravenous vitamin K excluded the possibility of malabsorption, and with the failure to correct with PCC and FFP, further suspicion of an inhibitor eventuated. This case highlights a situation where standard therapy is ineffective and further investigations should be performed to confirm the proper diagnosis, which in this case was not excessive warfarinisation.

The next concern was that the failure to correct the PT/INR and APTT left the patient significantly coagulopathic and with a high risk of haemorrhage. We ensured that DIC and liver disease were not present. We opted to start empirical therapy after the mixing study supported the presence of an inhibitor. Empirical therapy involved immunosuppression with corticosteroids, as the majority of acquired inhibitors are associated with autoimmune conditions. Suppressing the immune production of this inhibitor was the only option to maintain haemostasis. The acute toxicity of corticosteroids is limited and hence provided a reasonably safe option while diagnostic tests were pending.

From the coagulation factor studies, we were able to confirm the presence of an acquired FV inhibitor. The autoimmune screen had returned a negative result, and while there was a presence of monoclonal gammopathy with a paraprotein of 6.0 g/L, there were no other diagnostic criteria suggestive of myeloma disease. Therefore, this remained as a monoclonal gammopathy of unknown significance. There was also no evidence of other haematological or solid organ malignancy in keeping with the idiopathic FV inhibitor. The only other association applicable in this patient was the recent exposure to β -lactam antibiotics for cellulitis 3 weeks prior to the development of the inhibitor.

Our treatment with corticosteroids resulted in a resolution of the acquired inhibitor. This treatment was supported by previous case reports showing benefit from corticosteroid therapy.¹ The additional option of cyclophosphamide has been suggested by some case reports, however, often in the setting of patients with a severe episode of bleeding.¹ Owing to a risk of bleeding and with an outcome difficult to predict, immunosuppressive treatment should theoretically accelerate the clearance of the inhibitor.

Fortunately, in our case the patient did not encounter life-threatening bleeding, but in this setting, treatment with platelet transfusion, plasmapheresis and intravenous immunoglobulin is recommended.^{1 4–5} Concurrently, immunosuppression should be considered.^{1 10} Some refractory cases have shown benefit with rituximab therapy.¹⁰ While the evidence remains supported only by case reports, the low number of cases makes large volume trials difficult to conduct in a reasonable time frame.

The co-occurrence of FV inhibitor with warfarin therapy in our case was likely just a coincidence. The oral vitamin K antagonist, however, possibly enhanced the haemorrhagic tendency due to the inhibitory antibody against FV, resulting in clinically evident bleeding. The separate dilemma of providing adequate thromboprophylaxis in a patient with a haemorrhagic tendency is a vexatious problem that requires tailor-made approaches for individual patients, yet often remains unresolved.

Learning points

- ▶ A rare acquired common-pathway coagulation factor inhibitor with bleeding complications was treated successfully with immunosuppressive therapy.
- ▶ High international normalised ratio (INR)/prothrombin time (PT) was misleading, as the patient was on warfarin. Therefore, a warfarin level should be sought in such cases, with mixing coagulation studies with normal plasma, in order to exclude presence of an inhibitor.
- ▶ Initial measures to control bleeding with FFP and prothrombin complex concentrate (PCC) may be only partially effective or even ineffective in the presence of an inhibitory antibody.
- ▶ Successful management of inhibitors requires accurate laboratory recognition. A preliminary mixing study interpreted in light of the clinical background is invaluable for diagnosis.
- ▶ Inhibitors have many causes, and thorough clinical workup and extensive investigations to exclude an underlying illness are required before concluding that the antibody is idiopathic.

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