CASE REPORTS

Differential diagnosis and therapeutic limitations in a rare case of acquired factor X deficiency

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Abstract

Acquired Factor X deficiency is a rare coagulation disorder, which predominantly presents with mucocutaneous bleeding, and is associated with systemic amyloid light-chain (AL) amyloidosis in the vast majority of cases. There are, however, rare case reports of its occurrence in the context of acute respiratory infection, various malignancies, and following exposure to certain medications. We report a case of an 82-year-old man who presented with a Non-ST segment elevation myocardial infarction, decompensated biventricular failure, Respiratory Syncytial Virus (RSV) pneumonia, active haemoptysis, and a profound coagulopathy. Initial laboratory studies were consistent with acquired isolated Factor X deficiency (prolonged Prothrombin Time and Activated Partial Thromboplastin Time, correction with mixing studies, factor X level < 3%), however Congo red staining for AL amyloidosis on abdominal fat biopsy was negative. The patient was acutely managed with prothrombinex therapy with partial but temporary reversal of their coagulopathy and resolution of their bleeding. Unfortunately, solid organ biopsy was deemed unsafe and the patient passed away from recurrent sepsis before a formal diagnosis of the underlying aetiology could be made. This article describes a diagnostic approach to coagulation factor deficiencies and AL amyloidosis, and their limitations in the coagulopathic patient. It further reviews the correlation between severity of bleeding complications and Factor X coagulant activity. Lastly, it outlines potential treatment options for acquired Factor X deficiency; such as coagulation factor replacement, plasma exchange, and targeted amyloidosis therapies.

Keywords

1 Introduction

Factor X is a vitamin-K dependent zymogen produced in the liver, and plays a pivotal role in coagulation by facilitating activation of prothrombin to thrombin. Factor X deficiencies are amongst the rarest coagulation disorders, and can be inherited or acquired. The inherited form is autosomal recessive, whereas acquired, isolated factor X deficiency is associated with systemic amyloid light-chain (AL) amyloidosis in the vast majority of cases.

2 Case presentation

An 82-year-old man presented with central chest pain, dyspnoea, mucopurulent sputum and two months of intermittent haemoptysis; on a background of type 2 diabetes mellitus with nephropathy, ischaemic heart disease and non-compliance to all medical therapy for several years. On presentation he had decompensated biventricular heart failure, and his electrocardiogram (ECG) demonstrated atrial fibrillation with rapid ventricular response and anterior-lead ST segment depression. Serial high-sensitivity Troponin Ts were 220 and 1,191 ng/L respectively. A transthoracic echocardiogram demonstrated mild left ventricular hypertrophy with an anterior regional wall motion abnormality, and a diagnosis of non-ST segment elevation myocardial infarction (NSTEMI) was made. Furthermore, a chest X-ray confirmed a concurrent right middle lobe pneumonia, with Respiratory syncytial virus (RSV) subsequently identified on respiratory viral swab.

The patient was initially managed with intravenous loop diuretic (frusemide) therapy, intravenous cephalosporin antibiotics, aspirin and non-invasive ventilation; with rapid improvement in his clinical condition. A urinary catheter was inserted and heavy frank persistent haematuria followed.

Initial blood tests revealed renal impairment (Urea 9.4 mmol/L, Creatinine 135 mmol/L), abnormal liver function tests (Bilirubin 41 umol/L, Alkaline Phosphatase 412 U/L, Gamma-glutamyl transpeptidase 371 U/L, Alanine transaminase 66 U/L, Aspartate transaminase 103 U/L), and a markedly abnormal coagulation profile (Prothrombin time [PT] 38.7 seconds, Activated Partial Thromboplastin Time [APTT] 59.9 seconds, International Normalised Ratio [INR] 4.5). An initial Full Blood Count showed mild anaemia (Haemoglobin [Hb] 125 g/L), normal white cell count (10.63×10^9/L) and normal platelet count (285×10^9/L). Disseminated Intravascular Coagulation was not present with a normal fibrinogen (4.1 g/L) and a slightly elevated D-dimer (0.83 µg/ml). An abdominal ultrasound demonstrated borderline hepatomegaly with normal echotexture and a normal spleen; and viral and autoimmune liver screen was unremarkable. Haematology were consulted after an initial treatment with intravenous Vitamin K and 2 Units of Fresh Frozen Plasma (FFP) failed to correct his coagulopathy which was contributing to heavy haematuria after insertion of a urinary catheter, with a Hb drop from 125 g/L to 99 g/L.

Mixing studies with 50% normal pooled plasma demonstrated complete correction of PT and APTT. Common pathway coagulation factors, *i.e.* Factors II, V, X, were assayed with levels of 76.0%, 101.0%, and < 3% respectively. A progressive inhibitor was not identified based on 2 hour incubation using a PT assay. A diagnosis of acquired isolated factor X deficiency was subsequently made. In the context of ongoing active bleeding (haemoptysis and frank haematuria), and given that the patient's cardiac presentation was thought to be primarily due to a "Type 2" myocardial infarction [1] rather than acute coronary plaque rupture, with a greater risk of further myocardial injury with worsening anaemia and resulting hypoperfusion, the patient was administered three factor prothrombinex (50 U/kg) with resultant moderate sustained improvement in PT (see Table 1). Thereafter, he was given 25 U/kg prothrombinex twice daily until his bleeding resolved over five days. Given his profound coagulopathy aspirin was ceased. Due to the significant risk of complications with an arterial puncture, and the clinical suspicion of a "Type 2" myocardial infarction [1], a coronary angiogram was not performed.

Table 1. Coagulation study results pre- and post-Prothrombinex administration

Time post Prothrombinex Administration (50U/kg)	PT (seconds) (Normal range 12.0-15.0)	INR (Normal range 0.8-1.1)	APTT (seconds) (Normal range 25.0-37.0)
Pre-administration	43.2	5.2	58.0
15 minutes	23.3	2.3	51.9
4 hours	29.1	3.1	57.4
8 hours	32.9	3.6	61.4

The patient had no detectable paraprotein and minimal urinary light chains detectable with < 0.1 g/24 hrs free kappa light chains. An elevated serum free kappa/lambda ratio (7.33) using a Freelite assay is highly suspicious in this clinical context for systemic AL amyloidosis. Congo red staining on abdominal fat biopsy was negative, however, and the patient was deemed unsafe for bone marrow, renal, liver or cardiac biopsies. The patient was discharged for further outpatient follow-up, but represented 18 days later with severe sepsis and coagulopathy, and rapidly passed away.

3 Discussion

Acquired factor X deficiency is associated with systemic AL amyloidosis in the vast majority of cases, and is reported in 6.3%-14% of cases of AL amyloidosis [2-3]. The mechanism of the factor deficiency in AL amyloidosis is direct irreversible binding of the factor to amyloid fibrils in the spleen (predominantly), vasculature, and liver, resulting in a substantially shortened circulating half-life and hence rapid clearance from the plasma [2-5]. There are very few cases in the literature of acquired Factor X deficiency occurring in the absence of AL amyloidosis, although a 2012 review [3] did identify 34 cases occurring in association with respiratory viral infections, mycoplasma pneumonial infection, various malignancies, inflammatory bowel disease, leprosy, and exposure to sodium valproate, amsacrine, and fungicides. Since this review, there have been two further cases occurring in association with respiratory tract infections [6, 7].

Isolated factor X deficiency with no inhibitor is diagnosed by prolonged PT and APTT with correction with mixing studies (1:1 normal plasma), followed by performing serial dilutions with factor X deficient plasma to quantify factor X functional activity [2, 5]. The severity of the deficiency is based on measured plasma levels of Factor X coagulant activity (FX:C). FX:C levels of < 1%, 1%-5%, and 6%-10% constitute severe, moderate, and mild deficiencies respectively [2]. The most frequent clinical presentation is mucocutaneous bleeding; in particular epistaxis, easy bruising, and menorrhagia. There is no definite correlation between bleeding severity and FX:C levels as patients often have multiple haemostatic defects such as vascular fragility due to amyloid infiltration, other coagulation factor deficiencies, abnormal fibrin polymerization, and abnormal platelet aggregation [5]. In our case, the patient demonstrated a relatively moderate bleeding phenotype (*e.g.* mild haemoptysis and haematuria only when provoked by catheter insertion) given the severity of deficiency (< 3%).

Diagnosis of AL amyloidosis is based on demonstration of apple green birefringence under fluorescent microscopy after Congo red staining of tissue. The highest yield is with biopsy of an involved organ, but bone marrow, rectal, and abdominal fat pad can also be performed. Aspiration of abdominal fat tissue is considered a simple and safe diagnostic method, with a specificity approaching 100% and sensitivity ranging from 52%-88% reported in the literature [8, 9]. In this case, despite the negative fat biopsy, we believe that amyloidosis was the most likely underlying condition; with the main differential being associated with his RSV infection which is even rarer. This highlights the limitations of this diagnostic technique and the clinical obstacles to diagnosis in a coagulopathic patient.

Furthermore, only 33%-50% of patients with AL amyloidosis have cardiac manifestations [10]. Of these, at least two-thirds have echocardiographic abnormalities such as abnormal global or regional myocardial relaxation (early stage), thickened ventricular walls, abnormal myocardial texture (granular sparkling), atrial dilation, valvular thickening or regurgitation, pericardial effusion, and a restrictive pattern (late stage) with elevated filling pressures [11].

Therapeutic options for acquired Factor X deficiency are limited with varying levels of success, and depend on the severity of bleeding complications. In most cases, administration of Vitamin K provides no therapeutic benefit. Although FFP, plasma exchange, and prothrombin complex concentrates (PCCs; *e.g.* Prothrombinex-VF) provide factor X replacement, their effect is only transient [3, 10]. Furthermore, the use of PCCs involves a significant risk of thromboembolic complications [5, 10]. Activated recombinant factor VII has been reported to be effective in promoting haemostasis [4, 10], and a very recent publication [11] has also described the successful use of a high-purity plasma-derived Factor X concentrate in two patients.

Splenectomy is highly effective for amyloid-associated factor X deficiency due to removal of factor X-binding splenic amyloid deposits [12, 13]. Achieving adequate haemostasis to safely control peri-operative bleeding, however, is a significant challenge. Other therapeutic options, specific to AL amyloidosis, include melphalan chemotherapy combined with corticosteroids or combined with autologous stem cell transplantation [14, 15]. Unfortunately in this case diagnostic issues and patient frailty prohibited institution of any of these therapeutic options.

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