


CASE REPORT

Case of concurrent factor VII and factor XI deficiencies manifesting as spontaneous lower extremity compartment syndrome

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Abstract

Factor VII and XI deficiencies are rare bleeding disorders typically associated with mild or provoked bleeding. This case report describes a patient with factor VII and XI deficiencies with an unprovoked episode of lower extremity hematoma causing compartment syndrome requiring multiple surgeries, extensive transfusion of blood products, and ultimately amputation.

KEYWORDS

bleeding disorder, clotting factor, coagulopathy, compartment syndrome, factor VII deficiency, factor XI deficiency, hematoma, hemophilia C, Rosenthal syndrome

1 | INTRODUCTION

Factor VII deficiency and factor XI deficiency (hemophilia C or Rosenthal syndrome) are rare bleeding disorders associated with variable phenotypes ranging from asymptomatic cases to severe bleeding.¹⁻⁶ Hemostasis starts with formation of the platelet plug, followed by the clotting factor cascade resulting in thrombin generation and fibrin clot formation. The extrinsic and intrinsic pathways work synergistically to generate factor X and thrombin.

Crucial to the extrinsic pathway, factor VII is synthesized in a vitamin K-dependent process in the liver, and after endothelial injury, it forms a complex with tissue factor (TF) to activate factor X. Factor XI is synthesized in the liver in a vitamin K-independent process,^{7,8} and thus, its levels are not affected by vitamin K levels or vitamin

K antagonists such as warfarin. Factor XI is activated by thrombin and activated factor XII (XIIa), as well as autoactivation by itself. Activated factor XI (XIa) activates factor IX which along with activated factor VIII (VIIIa) activates factor X. In contrast to factors VIII and IX of the intrinsic pathway, factor XI has been shown to be a more auxiliary contributor to hemostasis.^{9,10}

The prevalence of factor VII deficiency is estimated to be roughly 1 in 500,000, and the prevalence of factor XI deficiency is estimated to be 1 in 1 million.⁷ Factor XI deficiency is much more common in Ashkenazi Jewish populations with a heterozygosity rate of 5% and a homozygosity rate of 0.2%.¹¹ Factor 7 (F7) gene mutation is autosomal recessive; most factor 11 (F11) gene mutations are autosomal recessive; however, autosomal dominant inheritance patterns can be seen.⁷ Individuals with homozygous

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gene mutations tend to have lower factor levels <10%,^{1,9} yet heterozygous individuals with mild or moderate deficiency can still experience bleeding. The two genes are located on separate chromosomes (F7 gene on chromosome 13, F11 gene on chromosome 4), and hundreds of different mutations have been identified for each disorder.¹²⁻¹⁴ In addition to heritable factor deficiencies, acquired deficiencies can be seen in cases of liver disease, disseminated intravascular coagulation (DIC), and vitamin K deficiency or antagonism in the case of factor VII.^{8,14}

Both bleeding disorders can range from asymptomatic to severe bleeding. Roughly 30% of factor VII deficient individuals are asymptomatic.^{1,14} When symptomatic, factor VII deficiency typically presents with mild bleeding including epistaxis, gingival bleeding, and menorrhagia; however, severe bleeding including gastrointestinal (GI) and central nervous system (CNS) bleeds can occur.¹ In comparison with those with factor VII deficiency, a larger proportion of individuals with factor XI deficiency are asymptomatic,⁵ and the bleeding observed in these patients is often provoked by surgery or trauma.^{4,9,15,16} A perplexing issue encountered by clinicians in both disorders is the fact that genotype and factor activity levels do not correlate well with risk of bleeding.^{1,2,15} Herein, we present the case of a 44-year-old male patient diagnosed with spontaneous compartment syndrome found to have factor VII and factor XI deficiencies.

2 | CASE PRESENTATION

A 44-year-old male patient presented to the emergency department with right lower extremity pain, swelling, numbness, and loss of motor function. The pain and swelling began 4 months prior; however, progression of excruciating pain and new-onset numbness and loss of mobility of 2 days duration prompted the patient to come to the hospital. The patient had a past medical history of cirrhosis, type 2 diabetes, hyperlipidemia, and a recent multiphase computed tomography (CT) scan of the liver showing a 6 cm mass compatible with hepatocellular carcinoma (HCC). The patient tested negative for hepatitis B and hepatitis C.

At presentation, the patient had the following vital signs: heart rate 108, respiratory rate 25, blood pressure 158/99, temperature 37.2 °C, and sO₂ 99% on room air. On examination, the patient had a right posterior lower thigh hematoma extending to the posterior knee (Figure 1). His right leg was diffusely edematous, tense, and erythematous from knee to ankle with tenderness to palpation and decreased sensation. Range of motion testing of the right knee, ankle, and foot was limited due to pain. Distal pulses were detectable by palpation and biphasic on Doppler



FIGURE 1 Computed tomography angiography (CTA) images of the patient's right lower extremity in the sagittal (A), coronal (B), and axial (C) views revealed a 25.4 × 7.9 × 4.4 cm hypodense collection within the adductor musculature, a fluid collection versus hemorrhage in the posterior popliteal joint space, and diffuse swelling of anterior, lateral, and posterior compartments of the calf without evidence of acute limb ischemia or active contrast extravasation

ultrasound. Compartment pressures were elevated in the anterior and posterior compartments below the knee, and the patient was taken to the operating room for emergent fasciotomy.

At presentation, the patient had severe macrocytic anemia (hemoglobin 6.0 g/dl, mean corpuscular volume 109.8 fl) and a low platelet count of 79,000 per μ l. He had prolonged PT (25.7 s, normal = 11.8–14.4 s), international normalized ratio (INR 2.36, normal = 0.87–1.13), and PTT (56.2 s, normal = 24.4–36.6 s).

Four compartment fasciotomy revealed extensive tissue necrosis and a 500 ml hematoma in the posterior compartment, which was evacuated. Three days later, a second surgery was performed with evacuation of a second posterior compartment hematoma and further debridement of necrotic tissue. A day later as the patient was having ongoing transfusion requirements due to lower extremity bleeding, decision was made to proceed with above-knee amputation as he had no function below the knee and no viable muscle tissue on inspection. After the amputation, the patient required four additional surgeries for hematoma evacuation and surgical

hemostasis. Over his 6-week hospitalization, the patient required 52 units of packed red blood cells (pRBC), 41 units of fresh frozen plasma (FFP), 5 units of platelets, and 5 units of cryoprecipitate.

Coagulopathy work-up was initiated after 34 units of FFP had been infused, which raises the possibility that true factor activity levels at presentation were less than the laboratory values reported. PT and PTT remained prolonged, and mixing studies were normal without evidence of inhibitor or circulating anticoagulant, suggestive of a true factor deficiency. For each of the factor deficiencies, the normal range is 60%–150% with 40%–60%, 20%–40%, and <20% representing mild, moderate, and severe deficiency, respectively. The following factor activity levels were reported: FVII 23%; FVIII 199%; FIX 62%; and FXI 16%. Von Willebrand factor (vWF) antigen and activity levels were elevated, and thromboelastography was normal except for a prolonged R time. Thus, it was suspected that the patient's severe bleeding was related to severe factor XI deficiency and moderate factor VII deficiency.

Upon further investigation by the hematology team, it was discovered that the patient had a history of bleeding (hematoma, ear bleeding, ecchymoses, and hemoptysis) and a history of prolonged PTT dating back to 2015. This further supports the diagnosis of factor XI deficiency.

In an effort to treat the patient's persistent acute bleeding, extensive volumes of FFP, recombinant factor VIIa (rFVIIa), and tranexamic acid were utilized throughout the patient's hospitalization. He was eventually stabilized, but due to the new diagnosis of Child–Pugh Class C hepatocellular carcinoma, in the setting of his comorbidities and functional status, the patient elected for hospice care. Two months after discharge, the patient passed away.

3 | DISCUSSION

To our knowledge, this is the first reported case of compartment syndrome in a patient with factor XI deficiency. Only one other case of compartment syndrome has been reported in an individual with factor VII deficiency, and the patient's compartment syndrome was associated with a large iliofemoral deep vein thrombosis (DVT).¹⁷ The patient in the present case report had no family history of bleeding disorders, but he did have a personal history of ear bleeding, hemoptysis, ecchymoses, and hematoma in the setting of a prolonged PTT that was suggestive of a coagulopathy. Of note, this episode of hematoma and compartment syndrome was unprovoked, while most bleeding seen in factor XI deficiency is provoked by surgery or injury.^{4,9,15,16} Despite early intervention and

extensive treatment with blood products, the patient had a suboptimal outcome illustrating the severe and potentially life-threatening bleeding that can be seen in these rare bleeding disorders. This clinical presentation is particularly relevant in the setting of the recent development of anti-FXI drugs for DVT prophylaxis after orthopedic surgery.¹⁸

In this case, the patient had both prolonged PT and prolonged PTT and was found to have intermediate factor VII deficiency and severe factor XI deficiency. Since these measurements were performed after the bleeding episodes and extensive FFP infusions, it is probable that the factor levels preceding hematoma formation were actually much lower and both in the severe range. The half-life of factor VII is roughly 1–4 h,^{19–21} and the half-life of factor XI is around 12 h.²² Thus, the reported factor levels (FVII 23%, FXI 16%) likely represent a partial repletion from rFVIIa and FFP in the setting of a persistent defect in synthesis.

It is difficult to estimate the relative contribution of each factor deficiency in the clinical presentation; however, it may be reasonable to predict that both deficiencies played a role. While there is a weak correlation between factor levels and clinical phenotype, individuals with factor VII level >5% usually do not experience severe bleeding.^{1,7} The association between factor XI level and bleeding risk is also weak; however, some studies have shown a higher risk of bleeding in patients with factor XI level <20%.⁹ Nevertheless, in both disorders, bleeding can be seen in individuals with mild or moderate factor deficiency.

It is unusual to observe unprovoked bleeding in factor XI deficiency (hemophilia C),^{9,16} and it is exceptionally rare for life-threatening bleeding to occur as was seen in this case. In contrast to hemophilia A and hemophilia B which can cause spontaneous hemarthrosis or hematomas, hemophilia C often involves oral, nasal, or genitourinary bleeding after surgery or trauma.¹⁶ This may support the more complementary role of factor XI in the intrinsic pathway relative to factors VIII and IX. Factor VII deficiency is classically associated with menorrhagia, epistaxis, and gingival bleeding; however, rare life-threatening GI and CNS bleeds have been described.¹ Hematomas have been reported in 20% of individuals with factor VII deficiency,¹⁴ but progression to compartment syndrome is exceedingly rare. Considering the severe factor deficiencies and the fact that neither disorder is normally associated with compartment syndrome, it is plausible to assume that both factor deficiencies contributed to the patient's presentation.

Genetic testing was not performed for this patient; therefore, it cannot be ascertained whether the patient's factor deficiencies were congenital or acquired. It is

important to note that factor VII and XI deficiencies can be seen in patients with liver disease^{7,8,14} such as the patient in this case with cirrhosis and HCC.

Peri-operatively and post-operatively, the patient required extensive transfusion of pRBC, FFP, platelets, and cryoprecipitate as well as rFVIIa and tranexamic acid. In patients with factor VII or XI deficiency experiencing an acute bleeding episode, treatment options include FFP, recombinant factor XI, rFVIIa, and antifibrinolytic agents (tranexamic acid and 6-aminocaproic acid). Recombinant factor XI is not available in the United States, so FFP and antifibrinolytics are typically used.⁷ Recombinant factor XI can be associated with an increased risk of thrombosis, while potential adverse effects of FFP include volume overload, transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), allergic reaction, and anaphylaxis.¹⁵ These risks can be more pronounced in individuals with heart failure or renal failure, and large volumes of FFP must be given to reach physiologic factor XI levels due to the low concentration of factor XI in FFP.¹⁵ Antifibrinolytics are relatively well-tolerated and effective. All of the aforementioned treatment strategies lack robust evidence, and randomized controlled trials are limited.

In addition to treatment of acute bleeding, blood products and pharmacotherapy can be used for peri-procedural prophylaxis in patients undergoing surgery. FFP, recombinant factor XI, rFVIIa, and antifibrinolytic agents are used; however, selection of patients for prophylaxis can be difficult as there is a paucity of evidence. Factor levels can be helpful, yet factor VII and XI levels are weakly correlated with bleeding risk.^{1,2,15}

Other blood products including pRBC and platelets are often given to patients with factor deficiencies for peri-procedural prophylaxis and treatment of acute bleeding. In patients with factor VII or factor XI deficiency, transfusion of pRBC and platelets should be guided by normal transfusion goals. While pRBC and platelets can help acutely bleeding and surgical patients with tissue perfusion and coagulation, respectively, there are risks associated with transfusions including acute hemolysis, anaphylaxis, TRALI, TACO, sepsis, febrile non-hemolytic reaction, and allergic transfusion reaction.²³

When predicting bleeding risk, clinicians should consider factor levels, the site and type of surgery, previous bleeding episodes, and combined hemostatic defects. Unfortunately, there are no standardized scores or algorithms to guide physicians. Further research is needed to elucidate optimal treatment of acute bleeding and peri-procedural management of surgical patients with factor VII and factor XI deficiencies. Ongoing research regarding

bleeding risk stratification tools may prove valuable to assist in clinical decision-making.

4 | CONCLUSION

This case is meant to illustrate a spontaneous, life-threatening bleeding episode in a patient with severe factor XI deficiency and moderate factor VII deficiency. Further research is needed to stratify bleeding risk based on factor activity levels and other patient characteristics; additionally, randomized controlled trials regarding peri-procedural prophylaxis and management of acute bleeding may be valuable.

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CONFLICT OF INTEREST

No conflict of interest are present for the authors of this paper.

AUTHOR CONTRIBUTIONS

Joseph P. Marshalek was involved in literature review, writing, editing, and final approval. David Yashar was involved in literature review, writing, editing, and final approval. Karen Huynh was involved in patient's care, writing, editing, and final approval. Sarah Tomassetti was involved in patient's care, writing, editing, and final approval.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

Data for the use of this case report were obtained from the electronic health record and can be obtained upon request from the corresponding author.

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