

Hemophilia C: A Case Report With Updates on Diagnosis and Management of a Rare Bleeding Disorder

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Abstract

Hemophilia C or factor XI deficiency is a rare clotting disorder with prevalence of only 1 per 1 million. A 24-year-old male with multiple abdominal surgeries complicated by wound infections and poor healing was admitted to plastic surgery service for an elective abdominoplasty. Hematology was consulted for increased intraoperative and postoperative bleeding. Laboratory workup showed high-normal activated plasma thromboplastin time of 31 s (reference: 23 - 34 s), prothrombin time (PT) of 15 s (reference: 11.8 - 14.3 s) and internationalized normal ratio (INR) of 1.2. Patient had normal factors VIII, IX, XIII levels and normal von Willebrand's factor level. The factor XI level came back at 0.28 (0.44 - 1.43 U/mL) diagnostic for intermediate factor XI deficiency. Factor XI is responsible for thrombin generation after clotting is initiated as well as clot stabilization. The confirmatory test is factor XI assay. The management of factor-XI deficiency is based on history of bleeding and nature of the procedure.

Keywords: Factor XI deficiency; Hemophilia; Coagulation cascade; Coagulopathy; Clotting disorders

Introduction

Factor XI deficiency is also called hemophilia C and Rosenthal syndrome. It was first recognized in 1953 in patients who experienced severe bleeding after dental extractions [1]. Considered a rare disorder, the estimated prevalence is 1 in 1,000,000. In populations where consanguinity is common, higher prevalence has been reported (8% among Ashkenazi Jews of Israel). It is recognized that factor XI deficiency does not correlate very well with the degree of bleeding and is often a diagnosis made prospectively after excessive bleeding is encountered unexpectedly during procedures [2]. We present the case of

a patient who was diagnosed with factor XI deficiency during workup of increased perioperative bleeding.

Case Report

The patient is a 24-year-old male with past medical history significant for obesity, anxiety and chronic omphalitis. He developed omphalitis following an abdominoplasty for excess skin after weight loss. Therefore, he underwent wide excision of umbilical stalk, direct lipectomy and placement of wound VAC (vacuum-assisted closure). He continued to have poor healing at the site and tunneling of the wound edges. There was concern for ongoing wound infection at follow-up, and he received an antibiotic course followed by local wound care.

He presented to our hospital for complex abdominal wall closure. He underwent sinus tract excision, recreation of the umbilicus and layered closure of the fascia followed by skin closure with drains. Postoperatively patient was started on lovenox dose 30 mg twice a day (BID) for deep vein thrombosis (DVT) prophylaxis, with the first dose administered 3 h after the surgery. Patient developed hemorrhage at the surgical site and was taken back the next day for washout and closure. Approximately two units of blood clots were removed per operative notes. Patient was noted to have diffuse oozing rather than bleeding from a single or multiple vessels consistent with a clotting abnormality rather than an anatomic etiology. His hemoglobin did drop from 11 g/dL at midnight of surgery to 9 g/dL by the next morning.

Hematology was consulted due to concern for excessive bleeding. The patient reported that he had multiple surgeons who had told him in his lifetime that he had increased intra and postoperative bleeding but he had no workup done for the same. He denied any family history of bleeding disorders. He also denied any history of purpura, epistaxis, gum bleeding, or hemarthrosis. He did have dental extraction without any complications. Patient was a non-smoker and non-alcoholic.

Initial laboratory results were notable for chronic normocytic anemia with hemoglobin and hematocrit of 9 g/dL and 27% respectively. Prothrombin time (PT) was 15.1 s (reference: 11.8 - 14.3 s), internationalized normal ratio (INR) of 1.2, and plasma thromboplastin time was high normal at 31 s (reference: 23 - 34 s). Further workup showed normal factor VIII, IX, XIII activities and normal von-Willebrand's antigen and activity. Thromboelastography was normal except low R-time of 4.2. Closure time and thrombin time were noted to be normal.

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Finally, factor XI activity was noted to be low at 0.28 U/mL (reference: 0.44 - 1.43 U/mL). He didn't have any subsequent episodes of bleeding. He was educated on his increased risk of bleeding and potential need for fresh frozen plasma (FFP) infusions or factor XI infusions prior to future surgical procedures, and was asked to follow-up with the local hemophilia center to create a plan for any future surgeries that he may undergo.

Discussion

Factor XI deficiency, also called hemophilia C or Rosenthal syndrome was first described in 1953 in patients who experienced severe bleeding after dental extractions [1, 3]. The estimated prevalence is about 1 in 1 million with increased prevalence among certain populations such as Ashkenazi Jews (8-9%) due to consanguinity [1, 4]. Interestingly, studies have suggested 2 - 20 times more prevalence than the traditional estimates likely owing to the wide variation in the bleeding risk associated with factor XI deficiency and possible under recognition [4, 5]. In addition, the bleeding risk does not necessarily correlate with factor XI levels or clotting studies [6-8]. Most patients are diagnosed following increased bleeding during or after procedures such as our case. Although severe spontaneous bleeding is rare, menorrhagia and epistaxis have been reported in these patients [3].

The disorder is a result of mutations in the factor XI gene (f11) on chromosome 4 which consists of 15 exons spanning a genomic region of 23 kb. Approximately 253 mutations have been described in literature [9]. The role of factor XI in coagulation is thought to involve amplification of thrombin generation via positive feedback and stabilization of new clots by inhibiting fibrinolysis. Additional pathways such as thrombin independent thrombin-activatable fibrinolysis inhibitor pathway has also been proposed to explain the variability in bleeding, and might be clinically useful in helping identify patients with increased bleeding risk [10]. Bleeding in individuals with factor XI deficiency usually happens at areas of high fibrinolytic activity such oral cavity, pharynx, genitourinary tract usually in conjunction with surgical procedures [11]. It is less commonly associated with spontaneous bleeds such as hemarthrosis, but may occur in the setting of repetitive trauma such as in individuals engaged in sports [12].

Initial investigation panel for clotting abnormalities are composed of platelet count, bleeding time or closure time, platelet function tests, and PT and activated partial thromboplastin time (aPTT) tests. Factor XI assay helps confirm the diagnosis. Factor XI deficiency may prolong the aPTT, though a normal aPTT does not exclude mild deficiency and can result in false negative results [13]. Typically, the aPTT becomes prolonged when the factor XI level is significantly reduced to the range of < 15%. Novel plasma clotting and fibrinolysis assays are being investigated to better identify patients with factor XI deficiency and increased bleeding tendency [11, 13]. For instance Gidley et al identified that combining aPTT with rate of clot formation and area under curve in fibrinolysis helped identify factor XI deficient patients with increased bleeding tendency. When plasma from these patients was treated with

corn trypsin inhibitor (CTI), there was significantly reduced clot formation and increased susceptibility to fibrinolysis when compared to factor XI deficient patients without bleeding tendency or normal controls [11].

There is significant variability reported in the severity of bleeds even between individuals with similar genotype and making the phenotypic classification into bleeder vs. non-bleeder more useful in managing these patients [11]. Although the factor XI levels do not necessarily correlate with bleeding, patients are generally classified into three categories based on the levels: severe (< 15-20% of normal), intermediate (20-40%) and mild (> 40%) [3].

Patients with factor XI deficiency diagnosis will need careful preprocedural planning. In addition to bleeding history and factor levels, the type of procedure (major or minor) as well as site of surgery should be taken into consideration during preprocedural planning, as sites such as pharynx and urinary tract has higher fibrinolytic activity and are more prone to bleed [3]. For major procedures in individuals with severe factor XI deficiency or significant bleeding history, monitoring of factor XI activity in the perioperative period with replenishment using factor XI concentrates or FFP is recommended [14-21]. Two plasma-derived factor XI concentrates namely Hemoleven (a high purity product from LFB Biomedicaments, Les Ulis, France) and factor XI concentrate (a partially purified product from Bioproducts Laboratory, Elstree, UK) have shown efficacy, but have yet to be widely used due to unavailability in many parts of the world including USA. Therefore FFP is the primary modality for replacing factor XI [3, 22]. It is important to note that factor XI is not present in cryoprecipitate and large volume of FFP may be required that could lead to volume overload-related complications [1].

In case of concern for volume overload from simple infusion, therapeutic plasma exchange (TPE) can be considered [23]. TPE is a viable option for management of patients with acquired deficiency in the presence of inhibitor as well. Plasma exchange in these cases can help raise factor XI level while removing any potential non-neutralizing inhibitor in an isovolumetric fashion [24]. With careful attention to these factors, major surgeries can be performed in these patients [14-21]. The same principles also apply in the management of patients with bleeding complications such as subdural hemorrhage [19]. In a study by Alsammak et al 60% of a cohort of 28 patients with factor XI deficiency underwent surgical procedures without perioperative hemostatic intervention. They also demonstrated successful therapeutic plasma exchange for four procedures [25]. Topical preparations of anti-fibrinolytics such as ϵ -amino caproic acid or tranexamic acid can also be used and avoids the systemic side effects such as thromboembolism [3].

Females with factor XI deficiency suffer from menorrhagia as well as increased postpartum hemorrhage but no risk of abortions have been demonstrated [26]. The general consensus is that a multidisciplinary team should be involved in the care of pregnant patient with factor XI deficiency, and the treatment should be individualized based on patient's bleeding phenotype. Factor XI monitoring may not be as accurate or reliable as the bleeding history itself. While some experts have recommended using tranexamic acid, caution has been advised due to risk for thrombosis [27, 28]. Neuraxial anesthesia can

be considered after discussions of risks and benefits in patients with a non-bleeding phenotype [28]. Recombinant factor VII has also been successfully used in these cases [29]. Role of additional testing such as rotational thromboelastography to identify patients with increased bleeding risk has also been investigated and shown to be useful in a single study [30].

Due to the role of factor XI in thrombogenesis and inflammation, the deficiency has been proposed to offer protective role for cardiovascular events and venous thromboembolism (VTE) [31]. The study by Preis et al showed adjusted hazard ratio (HR) for cardiovascular events at 0.52 (95% confidence interval (CI), 0.31 - 0.87) in those with mild deficiency and 0.57 (95% CI, 0.35 - 0.93) in those with moderate-severe factor XI deficiency. The adjusted HR were 0.26 (95% CI, 0.08 - 0.84) for VTE [32]. In this study, groups were heterogenous with control group with less comorbidities and younger age which makes the protective effect potentially stronger. The decreased clotting associated with factor XI deficiency has been explored for postoperative venous thromboembolism prophylaxis [33]. However, there were concerns that factor XI knockout may result in poor outcome in the setting of infections such as pneumonia [34]. The present case also raises concern about the association of factor XI deficiency with poor wound healing and recurrent infections. However, a large scale retrospective study has demonstrated lack of association of partial and severe factor XI deficiency with incidence and mortality with pneumonia [34].

Factor XI activity is positioned at the intersection of thrombin generation in the coagulation cascade and contact activation mechanisms for inflammatory response [35]. Therefore factor XI deficiency may alter the inflammatory response in the human [4, 35]. This may have been responsible for the wound healing complications and recurrent infections in the current case. Whether this could be targeted in a beneficial way in the management of sepsis or other illnesses is unknown at this time. Similarly, role of factor XI in allergic response and the effects of its modulation on asthma are being studied [36].

As discussed earlier, there is also concern that factor XI deficiency may be more prevalent than traditional estimates. This should be kept in mind if and when factor XI targeted anticoagulants were to become more commonly used [4]. It is important to also note that at least in one study there was no increased risk of bleeding in factor XI deficient patients receiving standard anticoagulants when compared to general population [37].

In conclusion, although factor XI deficiency is an under-recognized entity, it remains a rare bleeding disorder with poor correlation with bleeding studies and wide variability in clinical presentation. Factor XI concentrates, FFP and TPE are the main modalities for managing patients with factor XI deficiency undergoing procedures or labor, and treatment should be individualized on a case by case basis. The role of factor XI in coagulation and inflammation is an ongoing area of research with potential impact on thromboprophylaxis and sepsis.

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Conflict of Interest

There is no conflict of interest.

Informed Consent

Not applicable.

Author Contributions

The author contributed towards conceiving and generating the case report.

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