CASE REPORT

Successful perioperative management in a patient with factor XI deficiency

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SUMMARY

Factor XI (FXI) deficiency is an autosomal disorder which manifests as bleeding of varying severity. While homozygotes typically experience more dramatic bleeding symptoms, heterozygotes may experience clinically significant bleeding following surgical procedures or trauma, and therefore the condition is not purely recessive. The clinical significance of FXI deficiency is complicated in that FXI levels do not correlate well with bleeding severity, and in fact the bleeding risk is variable even for an individual in response to different haemostatic challenges. We present the case of a 74-year-old man of Ashkenazi Jewish heritage with a family and personal history of bleeding during surgical procedures, who presented with excessive bleeding following total thyroidectomy. He was found to have a FXI level of 52% (low normal). Genetic testing revealed that he was heterozygous for the c.403G>T mutation. This case demonstrates successful work-up and perioperative management of a patient with FXI deficiency.

BACKGROUND

This report describes a classic presentation of mild factor XI (FXI) deficiency, consistent with a heterozygous genotype. The work-up and subsequent perioperative management of his condition is a model for appropriate management of suspected rare factor deficiencies. However, the case also highlights areas of necessary research to determine best management practices, to correlate genetic and laboratory profiles to bleeding risk and to qualify the risks of rare factor deficiencies in response to various haemostatic challenges.^{1,2}

CASE PRESENTATION

The patient is a 74-year-old Caucasian male of Ashkenazi Jewish heritage referred to haematology 6 weeks post-total thyroidectomy for multinodular goitre. The thyroidectomy was complicated by excessive bleeding requiring cauterisation 3 hours post-procedure as well as significant ecchymosis (see figure 1). The patient had experienced bleeding following prior surgical procedures, including epistaxis requiring cauterisation following a tear duct recanalisation, increased bleeding following mole excision and increased bleeding following wisdom tooth extraction. A prior wide local excision of a squamous cell carcinoma had been performed without any excessive bleeding documented. His maternal history was notable for severe

postpartum haemorrhage and excessive bleeding requiring transfusion following total abdominal hysterectomy. Following his thyroidectomy, the patient divulged that while his daughter had no personal history of excessive bleeding, she had been found on genetic testing to have heterozygous FXI deficiency.

The patient's physical examination 6 weeks post-thyroidectomy was notable for faint/resolving ecchymosis on the neck and upper chest. Laboratory studies revealed mild anaemia with a haemoglobin of 12.1 g/dL (normal range: 12.8–17.7 g/dL), normal platelet count of $224 \times 10^9/L$ (normal range: 162–427 $\times 10^9/L$), normal activated partial thromboplastin time (APTT) of 31.1 s (normal range: 11.8–35.5 s), normal prothrombin time of 13.7 s (normal range 11.8–14.6 s), normal fibrinogen of 335 mg/dL (normal range 207–454 mg/dL) and normal thrombin time of 14.8 s (normal range: 14–20 s). He had elevated factor VIII levels of 174% (normal range 50%–150%), elevated von Willebrand factor of 187% (normal range 50%–150%) and elevated ristocetin cofactor of 158% (normal range 50%–150%).

DIFFERENTIAL DIAGNOSIS

There is no specific diagnostic tool recommended for identifying heterozygous FXI deficiency. Severe (homozygous, compound heterozygote or dominant negative genotype) and heterozygous FXI deficiency cases often come to clinical attention following a bleeding complication. While the APTT is prolonged in severe FXI deficiency, the PT/APTT may be normal in heterozygous deficiency.^{3,4} In patients with bleeding abnormalities and the absence of classic disorders such as haemophilia A and B and von Willebrand's disease, mild factor deficiencies rise to the top of the differential. In this patient's case, the history of bleeding following surgical procedures, normal PT/APTT, normal platelet count, normal von Willebrand panel, his Ashkenazi Jewish heritage and revelation of his daughter's genetic testing made a strong case for FXI deficiency.

TREATMENT

Careful evaluation of patients with severe FXI deficiency and meticulous planning for haemostasis during and after major surgery or trauma is necessary to prevent major bleeding events. Though literature suggests a minimum plasma level of FXI of 30%–40% to be necessary for surgery,⁵

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Figure 1 Resolving ecchymosis postoperative day 7 following thyroidectomy for multinodular goitre.

consideration of a history of bleeding is critical given the aforementioned lack of correlation between levels and clinical severity of bleeding. Treatment, usually with fresh frozen plasma (FFP), should be started prior to surgery and carefully monitored thereafter by assays of FXI level.^{6,7} One of the limitations of FFP is the large volume required to replace clotting factors. Additionally, in patients who develop FXI antibodies or have total IgA deficiency, the use of plasma is not an option and other strategies are needed.^{7,8}

Replacement of the missing FXI with one of two types of FXI concentrates has been successfully used.^{8,9} Due to a decreased risk of volume overload and infection transmission compared with FFP, this may be a preferred treatment in patients with known FXI deficiency, though it is not without risk. Several reports of arterial thrombosis or venous thromboembolism following FXI replacement have occurred, and some of these thrombotic events have been fatal. For this reason, the two FXI concentrates available globally (manufactured in Europe) are unavailable in US markets.^{9,10} The addition of heparin as part of the manufacturing process to the FXI concentrates has reduced—but not eliminated—the incidence of such events.^{6,9,11} Since many patients who developed clotting complications were elderly with pre-existing cardiovascular disease, FXI concentrates should only be used after careful consideration of risks in such patients weighed against alternative agents.^{9,12}

Antifibrinolytics have particular effectiveness in FXI deficiency. Minor procedures such as tooth extractions and skin biopsy can be successfully managed by administration of antifibrinolytics, such as tranexamic acid and aminocaproic acid, without the need for plasma.¹³ Other strategies to prevent or manage excessive bleeding include the use of desmopressin (DDAVP), factor eight inhibitor bypassing activity (FEIBA) and recombinant factor VIIa.^{7,14,15} A 2016 systematic review found thrombotic risk of FFP, FEIBA, DDAVP and tranexamic acid treatments to be lower than treatment with replacement FXI concentrates, as no patients for whom the former treatments were used experienced thrombosis in their review of 310 cases.¹⁴ Thrombotic complications of FXI concentrates have primarily been observed with the first generation concentrates or with administration of

higher dosages. Some advocate that when used in appropriate doses, FXI concentrates are no more thrombogenic than FEIBA or recombinant factor VIIa. Similarly, when using FXI concentrates, the potential thrombotic risk of antifibrinolytics should also be weighed carefully against the severity of the clinical picture, procedural risk of bleeding and history of successful bleeding management in the patient.

OUTCOME AND FOLLOW-UP

Given his genetic ancestry, family history of heterozygous FXI deficiency and history of bleeding complications, serum FXI levels were measured and found to be 52% or at the low end of the normal range as defined by our laboratory of 50%–150%. Subsequently, genetic testing was offered and performed. This testing revealed that he was heterozygous for the c.403G>T mutation (also referred to as p.Glu117X using legacy nomenclature), consistent with his genetic heritage. Following this work-up, the patient underwent a wide local excision of melanoma. Despite low-normal FXI levels, he received FFP in postoperative recovery due to his prior severe bleed and postoperative complications and experienced no clinically significant bleeding.

DISCUSSION

FXI deficiency (also known as Rosenthal syndrome or haemophilia C) is an autosomal bleeding disorder that equally affects men and women, with the highest prevalence observed in Ashkenazi Jews. The disorder characteristically presents with bleeding following surgery or traumatic injury without spontaneous bleeding.^{3,7,16}

At least 152 mutations causing FXI deficiency have been identified, including the p.Glu117X and Phe283Leu mutations that are prevalent in the Ashkenazi Jewish population. This population has a rate of heterozygous (partial) FXI deficiency of approximately 10%.^{8,16,17} The degree of deficiency appears to correlate with the number of affected alleles: homozygotes or compound heterozygotes have an FXI level of <15 U/dL (corresponding to severe functional deficit) and heterozygotes display levels of 25–70 U/dL or normal values.¹⁸ However, a dominant negative effect of some mutations has been described owing to the dimeric structure of FXI, leading to the phenotypic expression of severe deficiency even with a single affected allele.¹⁶ Even severe FXI deficiency rarely presents with spontaneous bleeding, though sometimes menorrhagia is observed. Bleeding is often observed following trauma or surgical procedures.^{7,8,16}

The initial formation of thrombin via the extrinsic coagulation pathway activates FXI, which continues to generate thrombin via the intrinsic pathway. Thrombin is necessary for fibrin formation and also activation of thrombin activable fibrinolysis inhibitor, which protects the fibrin clot against lysis.^{19,20} The role of FXI in haemostasis thus can be viewed as providing a combination of procoagulant and antifibrinolytic activity. This association helps explain the particular risk of bleeding in FXI deficiency with surgeries involving tissues with high fibrinolytic activity such as the nasal cavity, nasopharynx, oropharynx and urinary tract.^{11,21} Patients with severe (homozygote or compound heterozygote) or one of the dominant negative mutations may manifest bleeding complications more obviously or severely than their heterozygote or 'mild' counterparts.¹⁰ In mild cases, or presumed pure heterozygotes, bleeding events are more rare, with

wide-ranging estimates of injury-related bleeding from <10% to 60% following trauma.¹⁸

At this time, genetic testing for FXI deficiency can only indicate the presence or absence of a mutation or variation. Inference of bleeding risk from genetic or laboratory profile is not yet well characterised by the literature. Bleeding risk does not correlate well to serum FXI levels or activity. Even a single individual may manifest bleeding of variable severity when faced with different haemostatic challenges or with similar haemostatic challenges over time.^{16 18} Yet measurement of FXI expression by phenotypic assay is an important benchmark of expression of the FXI genes and mutation burden or lack thereof. Furthermore, genetic testing may allow clinicians to additionally characterise concomitant genetic changes which might further compromise haemostasis. Global coagulation assays such as thromboelastography/thromboelastometry and thrombin generation testing may be clinically useful in evaluating phenotypic bleeding risk as well as response to treatment.^{22–24}

The patient described in this report represents the classic presentation of mild FXI deficiency, consistent with a heterozygous genotype. His APTT value was not elevated and FXI levels measured a low normal value of 52% (normal 50%–100%). He had a medical history of excessive bleeding following tear duct surgery, thyroidectomy, mole excision and tooth extraction. This patient's prior episodes including tooth extraction and skin biopsy not requiring intervention are consistent with the variability of bleeding risk in patients with this bleeding disorder. The patient's ancestry and family history of FXI deficiency focused our suspicion for this rare bleeding disorder. However, rare factor deficiency should be on the differential for any individual presenting with history of abnormal bleeding but is not found to have more common bleeding disorders such as haemophilia A and B or von Willebrand's disease. Clinical history taking is critically important,

and providers should consider a bleeding diathesis such as FXI deficiency in patients who present with excessive bleeding following trauma or surgery, especially bleeding in tissues with high fibrinolysis.

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Learning points

- Clinical history significant for risk factors—Ashkenazi Jewish heritage and a history of abnormal bleeding—suggest the possibility of FXI deficiency even in the setting of normal haematological labs.
- The importance of a detailed personal and family bleeding history obtained prior to invasive procedures cannot be understated. Bleeding following prior trauma or invasive procedures may be the only clues in the patient's history in more mild forms of haemophilia, von Willebrand disease and other less common factor deficiencies such as FXI deficiency.
- Recognising that heterozygous FXI deficiency may have a normal APTT and low-normal FXI levels, it is appropriate to consider confirmatory genetic testing.
- Thromboelastography/thromboelastometry or thrombin generation testing may be clinically useful in evaluating bleeding risk as well as response to treatment in Factor XI deficiency.
- Genetic screening for rare bleeding disorders can be considered based on several factors, including: (1) severity of past bleeding events; (2) planned future procedures; (3) ancestry and (4) family history of excessive bleeding or known mutation.

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