

# A Rare Seen Hemorrhage Disorder: Factor XI Deficiency Hemophilia C

## Nadir Görülen Bir Kanama Bozukluğu: Faktör XI Eksikliği Hemofili C

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### Abstract

Factor XI deficiency is a hemorrhage disorder which can be either autosomal recessive or/and autosomal codominant and effects both women and men. Factor XI deficiency is uncommon in non-Jewish general population and average frequency of disorder is 1/1 million. Clinical phenotype is nonhomogeneous and bleeding risk depends on individual's reaction against hemostatic variances. There is a poor relation between the Factor XI plasma level and bleeding tendency. In case of Factor XI deficiency, uncommon, unlike hemophilia A and B, spontaneous hemorrhage, surgical or trauma sequent are at risk. Hemarthrosis and intramuscular bleeding are common in hemophilia A and B but not typically seen in Factor XI deficiency disorders. Common symptoms are easy bruising and nosebleed. History of the disorder mostly indicates the findings about the difficulty in staunching. In this case, after detecting the activated partial thromboplastin time length before the operation due to build upon mandibula, management of patients, having Factor XI deficiency hemophilia C which is a cause of rare seen hemorrhage disorder, are presented in terms of bleeding diathesis.

### Öz

Faktör XI eksikliği kadınları ve erkekleri etkileyen otozomal resesif geçişli aynı zamanda otozomal dominant geçiş de gösterebilen bir kanama bozukluğudur. Yahudi olmayan genel popülasyonda Faktör XI eksikliği yaygın değildir ve yaklaşık görülme sıklığı 1/1 milyondur. Klinik fenotipi heterojendir ve kanama riski bireyin hemostatik değişikliklere verdiği cevaba göre değişmektedir. Faktör XI'in plazma düzeyi ile kanama eğilimi arasında zayıf bir ilişki vardır. Faktör XI eksikliğinde hasta hemofili A ve B'ye benzemeyen şekilde yaygın olmamakla birlikte spontan kanama ve cerrahi ya da travmayı takip eden kanamalar için risk altındadır. Hemartroz ve kas içi kanama hemofili A ve B'de yaygındır ancak Faktör XI eksikliği olanlarda tipik olarak görülmez. Yaygın görülen semptomlar kolay morarma ve burun kanamasıdır. Sıklıkla öyküde kanamanın zor durduğuna yönelik bulgular görülmektedir. Bu olguda mandibula üzerinde kitle nedeni ile operasyon öncesi incelemelerinde aktive parsiyel tromboplastin zamanı uzunluğu tespit edilerek nadir görülen bir kanama bozukluğu nedeni olan Faktör XI eksikliği hemofili C tanısı alan olgunun kanama diyatezi açısından yönetimi sunulmuştur.

## Introduction

Identification of patients with bleeding and coagulation disorders before life-threatening hemorrhage or major surgical interventions, and management of the disease have resulted in significantly improved survival for these patients (1,2). Bleeding disorders are examined in two categories as primary and secondary bleeding disorders. Those that are caused by deficiency of coagulation factors usually present as hemophilias. Bleeding due to factor deficiency may be caused by deficiencies of factors either in intrinsic or extrinsic pathways. Hemophilia C, which is caused by deficiency of Factor XI (FXI), is a rare coagulation disorder. It is different from the more frequently observed hemophilia A and hemophilia B in the way that it causes spontaneous hemarthrosis and intramuscular bleeding, and that it can be seen in both sexes as a result of autosomal recessive and rarely autosomal dominant inheritance. FXI deficiency is not very common in the non-Jewish general population. The prevalence of the disease is approximately 1 in 1 million (2-4). It shows heterogenous clinical phenotype, and the risk of bleeding varies depending on individual's response to hemostatic changes. There is no linear relationship between factor levels and bleeding tendency and incidence of spontaneous bleeding (4). Unlike patients with hemophilia A or B, patients with FXI deficiency are under risk for spontaneous bleeding following surgery or trauma. Although hemarthrosis and intramuscular bleeding are common in hemophilia A and B, they are typically absent in those with FXI deficiency. Commonly observed symptoms include easy bruising and epistaxis (1,5). In order to avoid risk of serious bleeding particularly in surgical interventions, it is important to diagnose these patients before surgery with regard to management of surgical intervention. The present case report presents management during diagnosis and operation of a 11-year-old patient who underwent mandibular surgery due to mass lesion on jaw and was detected to have elongated activated partial thromboplastin time (aPTT) during preoperative screening.

## Case Report

Eleven-year-old male patient presented to oral and maxillofacial surgery clinic with complaints of

swelling and pain at his jaw. According to his history, he did not have fever, night sweats, or itching. It was learned that he had prolonged bleeding following a tooth extraction two years ago, and a detailed anamnesis revealed that he had prolonged bleeding following circumcision, he got easily bruised, and bleeding after small cuts did not stop easily. There was no family member who had similar complaints. There was no known disease in his medical history. In physical examination, there was a painful mandibular mass with hard consistency, which had a size of 3x2 cm. Peripheral blood smear examination showed 55% neutrophils, 35% lymphocytes, 7% monocytes, 3% eosinophils, and clustered platelets, without presence of any atypical cells. Biochemical tests did not show any findings suggestive of a malignancy. Ultrasonographic examination of the area revealed solid mass of 26x21 mm size on the left mandible. Due to an initial diagnosis of odontoma, operation was planned. During preoperative preparations, aPTT value was found to be prolonged, and the patient was consulted to our clinic. Apart from the mass lesion on the jaw, the patient's anamnesis and physical examination did not have any feature. The patient was investigated for possibility of a bleeding disorder. His laboratory test results were; white blood cell:  $6.42 \times 10^3/\mu\text{L}$ , hemoglobin: 13.2 g/dL, hematocrit: 39.1%, platelet:  $375 \times 10^3/\mu\text{L}$ , aPTT: 91.3 sec., international normalized ratio 1.06, pentylentetrazol 11.7 sec., and a repeat aPTT test result was 90.1 sec. A secondary hemostasis disorder was considered in the patient, and factor levels were analyzed. Accordingly, factor activity levels were 74% for Factor VIII; 51% for Factor IX, 103% for Factor XII, and <1% for FXI. Based on these results, the patient was diagnosed with hemophilia C. Prior to the operation, 10 cc/kg fresh frozen plasma (FFP) was administered to the patient. aPTT measured 6 hours after administration of FFP was normal. The patient was operated successfully. No bleeding occurred during or after the operation. The pathological examination of the excised mass was reported as odontoma.

## Discussion

FXI deficiency was first described in 1953 by Rosenthal. It is a rare bleeding disorder that manifests with different bleeding findings. It is named as "hemophilia C" or "Rosenthal disease" (6). Although

the prevalence of FXI deficiency is one in a million, In Ashkenazi Jews, the frequency of heterozygous disease and homozygous disease are 8% and 0.22%, respectively. FXI is localized to the 4<sup>th</sup> chromosome (4q35). Until today, more than 200 mutations have been identified in patients with FXI deficiency (2,7). Those with homozygous or compound heterozygous disease display more serious clinical course, while those with heterozygous disease have milder clinical findings (5). FXI is a plasma glycoprotein that is activated in the intrinsic coagulation pathway. The normal blood range of FXI is 70-150 U/dL. Heterozygous cases show partial deficiency and the blood level is 30-60 U/dL. Those with homozygous or compound heterozygous disease display severe FXI deficiency, and blood levels are below 20 U/dL. Spontaneous bleeding is quite rare in these cases, and clinically bleedings usually occur after a trauma or a surgical procedure (1). Unlike other hemophilia types, the bleeding tendency in hemophilia C patients is independent of the level of factor deficiency. There is no linear relationship between factor level and intensity of bleeding or spontaneous bleeding (4). Our case had prolonged aPTT in his preoperative screening tests, and his FXI activity level was <1%. The case did not experience any incidence of spontaneous bleeding before. After surgery or trauma, these patients bleed more than expected only if adequate treatment is not administered (1). Spontaneous bleeding in FXI deficiency is rare, but when it occurs, it has usually mild-moderate severity, and often stops without requiring any treatment. Current treatment modalities for FXI deficiency include administration of FFP, replacement therapy with FXI concentrates, antifibrinolytic medication support, fibrin glue application, and although less common, desmopressin treatment. If specific factors are not available, FFP is preferred in the first place. The most important drawbacks of FFP administration are possible requirement of high volumes, allergic reactions, and the possibility of transmission of infectious agents (2,3). Our patient was treated using FFP, and no side effect or transmission of an infectious disease was observed. Patients with FXI deficiency usually bleed after tooth extraction, tonsillectomy, adenoidectomy, nasal surgery and prostate surgery. In his history, our case also had an occasion of difficulty in stopping bleeding after tooth extraction.

These patients see great benefit from antifibrinolytic treatment. Therefore, tranexamic acid is the most commonly used agent. In addition to the ease of oral administration, it can also be used via intravenous route (3,8). In FXI deficient patients, tranexamic acid may be used alone or in combination with topical fibrin glue during tooth extraction procedures. For nasal surgery and tonsillectomy, parenteral tranexamic acid administration is recommended in addition to factor replacement. (1,3,8). If FFP will be used, the volume load and possible risk of thrombosis after use of FXI concentrate should be monitored closely. Before surgery, it should be ensured that patients have normal prothrombin time (PT) and platelet count (9). History of previous bleeding and interventions should be obtained in detail, and the treatment should be planned accordingly. Our case had prolonged bleeding after circumcision, and experienced abundant bleeding after tooth extraction two years ago. Bleeding control could be achieved with administration of FFP both prior to and during his operation. When using FFP, the risk of allergic reaction and volume load should be considered. In case of severe deficiency, FFP may not provide adequate correction of plasma factor levels. After infusion of FXI concentrate, factor levels are adequately corrected in 90% of the patients. The half-life of plasma-derived FXI has been measured as 46-52 hours. There have been reports of development of thrombosis after administration of FXI concentrate. Treatment-associated thrombosis risk is 10% (1,9). Therefore, there has been some changes to the content of FXI concentrate, and a guideline has been prepared to aid in determining the upper dose limit and for identification of high risk patients for thromboembolism. One study that examined the 5-year data after practicing the guideline has reported that there was no thrombosis development due to administration of FXI concentrate (10). There is considerable difference between centers regarding approach to patients with moderate FXI deficiency. The pathological diagnosis of the excised mass in our case was odontoma. Our case was diagnosed with hemophilia C prior to operation, and we administered FFP to prevent possible intraoperative bleeding. The operation was successfully completed without any complications, owing to the measures taken, and interdisciplinary planning. Primary evaluation of patients with history of symptoms that are suggestive

of bleeding diathesis must include PT and aPTT measurement. Isolated aPTT prolongation should prompt hemophilia A, B and C, and their presence should be investigated with analysis of coagulation factor levels.

### Ethics

**Informed Consent:** It was not taken.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: S.Ö., N.Ö.K., E.S., Concept: S.Ö., N.Ö.K., Design: E.S., Ş.Ü., Data Collection or Processing: Ş.Ü., N.A., Analysis or Interpretation: S.Ö., Literature Search: S.Ö., N.Ö.K., Writing: S.Ö.

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