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CASE REPORT

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Post-dental extraction bleeding: Emphasis on the diagnosis of rare coagulation disorders

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Abstract

Disorders of the fibrin stabilizing and fibrinolytic pathway should be considered in patients with excessive postsurgical bleeding with normal screening tests of hemostasis. History, clinical assessment of the timing and severity of bleeding along with utilization of advanced tests such as global hemostasis assays and appropriate coagulation factor assays (especially FXIII) will aid in the diagnosis.

KEYWORDS

factor XIII deficiency, postdental extraction bleeding, tranexamic acid

1 | INTRODUCTION

Blood clotting is a complex process involving the coordinated participation of cells and substances leading to a controlled sequence of events that usually end in a cross-linked fibrin mesh that aids to cess hemorrhage. Involvement of several cells, tissues, and chemicals has led to the identification of numerous disorders that may present due to abnormalities of one or several of these components. Several of these disorders are extremely rare and limited to sporadic reports in literature.[1] Oral cavity is a site where excessive bleeding can be detected in such disorders, both spontaneous and provoked secondary to minor or major trauma. If such bleeding disorders exist in patients seeking oral and maxillofacial surgical treatment, it is usually pre-diagnosed and patients present with relevant history of the disorder and its treatment.[2] In some instances, the minor oral and maxillofacial surgical trauma may be the driving force for the diagnosis of a coagulation disorder as seen in several cases of Mild hemophilia.[3,4] However, it is rare for an oral and maxillofacial surgeon to end up as the first healthcare contact to diagnose such a disorder due to manifestations in the oral cavity.

2 | CASE HISTORY AND EXAMINATION

A 35-year-old male patient was reported with bleeding from a Right II premolar extraction site. He underwent

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atraumatic intra-alveolar extraction of the grossly mutilated tooth 10 days earlier. Subsequently, every 48–72 h, he experienced three episodes of mild bleeding from the surgical site. Conventional conservative measures using pressure, figure-of-eight sutures, electrosurgery managed the issue temporarily during the first three episodes. Routine hematological and biochemical investigations carried out at several centers were reported to be within normal limits.

During the fourth episode, he was referred for maxillofacial surgical opinion. On eliciting history with leading questions, the parents and the elder sister were not alive (cause of death—unknown) precluding chances of knowing the events during his birth/childhood. He was born to a consanguineous marriage in a home-care setting, a common occurrence in a setting of rural India, 35 years earlier. He vaguely recalled his mother's account of excessive bleeding during delivery. He revealed recurrent minor bleeding from a minor injury during childhood and 15 years age typically occurring 48–72 h post-injury. However, several other injuries during his life healed uneventfully with no noticeable prolonged bleeding. There was no history of hemarthrosis, muscle hematomas, or easy bruising. There was negative history of any surgical procedures, hospitalization, blood transfusion, drug history, or allergy.

3 | EXAMINATION

No abnormality was detected on examination of all systems, particularly with no evidence of hepatosplenomegaly, purpura, ecchymosis, muscle hematomas, and hemarthrosis. On local examination of the extraction site, a mild ooze was found from the palatal aspect of the mucoperiosteal flap. The bleeding was clinically similar to that of a capillary ooze (Figure 1). The socket was found to be delayed, presumably due to the several procedures carried out earlier to aid in the cessation of the bleeding.

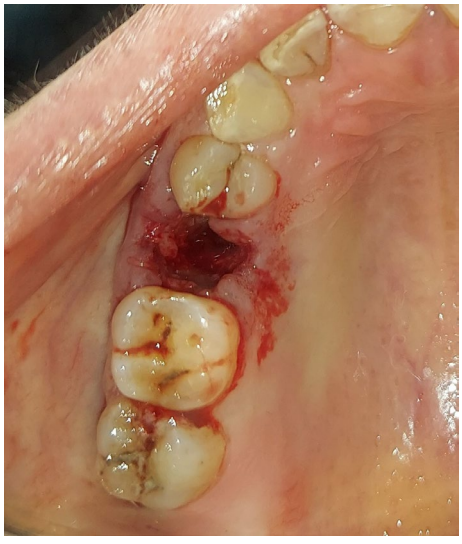

FIGURE 1 Appearance of the extraction socket 10 days post-extraction with continuous mild capillary ooze

4 | INVESTIGATIONS

Routine hematological and biochemical investigations were repeated, all of which were found to be well within normal limits, particularly, hemoglobin, platelet counts, peripheral blood smear (PBS), bleeding time (BT), whole blood clotting time (WBCT) international normalized ratio of prothrombin time (INR), activated partial thromboplastin time (aPTT), serum fibrinogen (SF), liver function tests (LFT), and renal function tests (RFT).

5 | TREATMENT

The bleeding was controlled by packing with Surgicel® (Ethicon LLC; Figure 2) and application of continuous pressure using an acrylic splint (Figure 3). Immediate intravenous infusion of tranexamic acid 10 mg/kg was carried out.

6 | DIAGNOSIS, TREATMENT, OUTCOME, AND FOLLOW-UP

Though advanced investigations to elicit platelet activity were not carried out, bleeding time was found to be well within normal limits. Combined with the fact that platelet counts were also within normal limits, the possibility of both a qualitative and quantitative platelet defect was ruled out.

Normal PT, INR, aPTT, and SF ruled out deficiencies in both the intrinsic pathway and extrinsic pathway (and common pathway) of the coagulation cascade. Excessive bleeding with no anatomic, hematological, and biochemical abnormalities along with typical presentation of bleeding after a particular time period (48 h in our case)[5] guided us to evaluate clot stability.[6] Clot solubility in 5 M Urea was negative after 24 h. Factor XIII (FXIII) is the only coagulation factor that does not get involved in the intrinsic and extrinsic pathway but only aids in clot stability. Therefore, a defect in the FXIII activity was explored. FXIII activity (Berichrom, Siemens) revealed a value of 40 IU/dl (Reference – 70–140 IU dl^{-1}), falling within the category of mild FXIII deficiency (FXIIID). A definitive diagnosis of post-extraction hemorrhage with mild FXIIID was confirmed after consulting with a hematologist. Mixing study

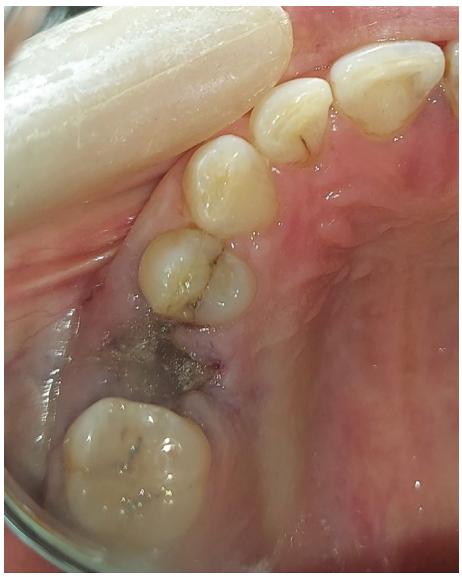

FIGURE 2 Surgicel® packed and cleansed extraction socket. The socket is slightly overfilled with Surgicel® so that the acrylic splint (see Figure 3) will apply continuous pressure

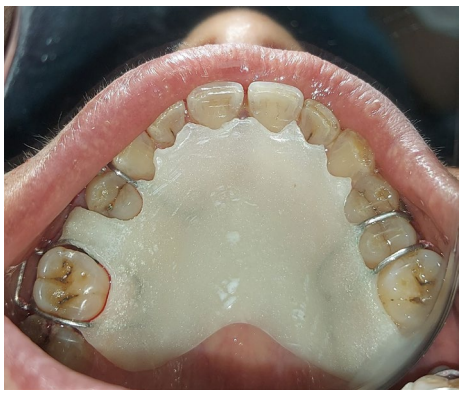

FIGURE 3 Acrylic splint in situ

with normal plasma and binding assays failed to reveal evidence of FXIII autoantibodies. The diagnosis was revised to post-extraction hemorrhage with mild congenital FXIIID.

Intravenous infusion of tranexamic acid 10 mg/kg was continued thrice daily for 4 days. The patient was discharged on the 5th day and was advised 10 ml of 4.8% Tranexamic mouthwash for 2 min, four times a day for the next 3 days with advice for an emergency visit in case of recurrent bleeding. No bleeding was observed, the patient was recalled after 7 days (3 days after discharge), and the splint was removed. Further follow-up to ascertain socket healing was carried out at 02 weeks, 01 month, and 03 months. Since it was only a mild deficiency, the patient was kept on observation. Further bleeding was not observed.

Thromboelastography (TEG) was carried out to estimate the potential risk of hemorrhage (carried out on the suggestion of an anonymous reviewer). The curve revealed a normal coagulation/reaction time (R = 6 min; normal = 2–8 min), a mild increase in the clot formation time (k = 3.5 min; Normal = 1–3 min), a normal angle but on the higher side (α = 75°; normal=55–78°), a borderline decrease in maximum attainable clot strength (MA = 48 mm; N = 51–69 mm), and a borderline percentage of clot lysis at 30 min (LY30 = 9%; N = 0%–8%). TEG curve further justified no active prophylaxis with FXIII infusion.

7 | DISCUSSION

Hemostasis is a complex process involving a delicate balance between thrombotic and anti-thrombotic pathways. Numerous bleeding diathesis has been identified with a wide range of etiological factors that ultimately manifests clinically as excessive bleeding either spontaneously or in response to trauma. The initial screening tests for the identification of these disorders include platelet count, PT (INR), aPTT, SF, and Platelet function tests. These tests will enable the clinician to focus the deficit toward the primary hemostatic mechanism or the coagulation pathway (and further into the extrinsic, intrinsic, or the common pathway). Due to the inherent disadvantages in these non-specialized tests, many disorders like those with only a minor deficiency in the amount of coagulation factors may be missed. Being less expensive and widely available, these tests are still the gold-standard tests for the diagnosis of bleeding diathesis in developing countries. Several disorders manifest with an abnormal clinical hemorrhage but do not provide pathological screening tests. These disorders generally include those but not limited to those associated with fibrin stabilizing and fibrinolytic pathways. These include FXIIID, α_2-antiplasmin deficiency, Quebec platelet disorder, and plasminogen activator inhibitor-1 deficiency.[7] Mild deficiency of coagulation factors like mild hemophilia A may not reflect accurately on the screening tests. Withstanding these screening tests, FXIIID and the other disorders mentioned above are generally diagnoses of exclusion.[6]

Factor XIII is a zymogen involved in the stabilization of blood clot by covalent cross-linking of fibrin, the end product of hemostasis. In addition to hemostasis, it contributes to several functions like phagocytosis of bacteria, wound healing, bone and cartilage growth, and embryo implantation. It is a heterotetramer composed of two each of subunits A and B. The chemical reaction involved in the hemostatic function also requires thrombin and calcium.

Congenital Factor XIII deficiency (CFXIIID) is a very rare coagulation disorder. Subunit A deficiency may be quantitative (Type I) or qualitative (Type II) in nature. Subunit B deficiency is even more rare and has a clinically milder phenotype.[8] The levels of severity may vary according to the activity of FXIII, producing features of varying intensity. Acquired FXIII deficiency (AFXIIID) can also be precipitated due to immune or non-immune mediated mechanisms. This instance was the first time that professional support was required by the patient due to excessive bleeding, the history of recurrent minor bleeding, probable family history, history of excessive bleeding during birth (probably a delayed umbilical cord bleeding), and negative drug history rules out the possibility of an AFXIIID. The most common cause for AFXIIID is an autoimmune reaction associated with several diseases such as systemic lupus erythematosus, rheumatoid arthritis, solid neoplasms, lympho/myeloproliferative neoplasms, monoclonal gammopathy or drugs such as isoniazid, procainamide, amiodarone, penicillin, ciprofloxacin, toclizumab, and valproate. Non-immune AFXIIID may be precipitated by decreased production in liver diseases, increased consumption due to disseminated intravascular coagulation, stroke, inflammatory bowel disease, sepsis, pulmonary embolism, Henoch-Schönlein purpura, and major surgical procedures including neurosurgery, orthopedic surgery, gastric cancer surgery, and cardiovascular surgeries.[9]

This instance was the first time that professional support was required by the patient due to excessive bleeding, the history of recurrent minor bleeding, probable family history, history of excessive bleeding during birth (probably a delayed umbilical cord bleeding), negative drug history rules out the possibility of an AFXIIID. Based on the facts of exclusion based on the diagnostic criteria,[10] our patient was classified as congenital FXIIID. Most of the patients reported in the world are usually grouped in country-based cohorts with specific genetic mutations and a high prevalence of consanguineous marriage.[11] No such cohort has been reported in India. However, our patient had a history of parental consanguinity. The death of the patient's sibling and parents precluded the chances of proving any familial association by performing a FXIII assay. However, the account of the mother regarding excessive bleeding during parturition may be an insight to a probable excessive umbilical cord bleeding, the most pathognomonic feature of FXIIID.[11]

Most of the patients with FXIIID present with other symptoms such as subcutaneous, intramuscular, or mucosal bleed. Our patient remained asymptomatic throughout because of mild deficiency of FXIII. Studies have revealed that patients with FXIII level of more than 30 IU dl^{-1} remain mostly asymptomatic (43%),[12,13] a small subset of them showing bleeding after surgery/trauma/drugs that alter platelet function or coagulation.[1] In patients with mild deficiency, the diagnosis is reached usually after a non-major bleeding episode (as in our case) or after screening as a relative of a known patient with FXIIID. FXIII level of 40 IU dl^{-1} ensured sufficient activity leading to no life-threatening complications similar to those seen in severe deficiency. The minimum activity of FXIII for patients to remain asymptomatic has been found to be 30 IU dl^{-1}.[13]

For the same reason, clot solubility test was found to be negative in our patient. Clot solubility tests are not considered to be the first-line screening investigation due to its low sensitivity (FXIII activity of 5% is enough to render the clot stable) and reliability.[14] FXIII activity tests (using ammonia release or amine incorporation) or antigen assays are sensitive investigations for accurate estimation of FXIIID that guides classification and prophylactic treatment. Identification of the genetic mutation by gene sequencing is confirmatory.[14] But in a regular set-up, these advanced tests may not be always possible as the first-line investigation due to less availability, time-consuming nature, and increased cost. However, since autoantibodies were not detected by mixing study or binding assays, CFXIIID was confirmed.[10]

With a baseline FXIII of more than the threshold of 30 IU dl^{-1} and borderline normal TEG, no regular prophylactic transfusions were considered by the hematologist since the risk of developing major complications are nonexistent.[12] A simple mechanism to maintain pressure on the wound and maintaining clot integrity was enough to ensure hemostasis. Infusion of tranexamic acid aided in better clot stability by inhibiting the conversion of plasminogen to plasmin.

Factor XIII deficiency is considered to be underestimated disorder due to the drawbacks in the laboratory estimation of FXIII.[14] It is important that in view of limited literature in the Indian scenario (no reported cohorts) along with limited availability of advanced laboratory investigations, this disorder needs to be considered in situations of excessive bleeding, especially when regular coagulation studies were standard.

It is improbable that a dental surgeon will be the first point of contact to diagnose this disease, since patients with severe deficiency manifest life-threatening complications such as intracranial and gastrointestinal hemorrhage. However, mild deficiency cases (with FXIII level greater than 30 IU dl^{-1}) may present with maiden bleeding episode postdental management. This situation gets more complicated when combined with inadequate family history as evidenced in our case. Therefore, they should be aware of those bleeding diatheses that present with normal coagulation, so that, the diagnostic approach

can be stepped up and modified. This report happens to be one of its kind diagnosing this rare disorder in a patient presenting with post-extraction bleeding.

In diagnosing these disorders with normal coagulation studies, several diagnostic algorithms are in vogue. The screening coagulation studies are far from being physiological and are carried out to report the status of coagulation in artificially created segments or pathways. They do not take into consideration the interplay of several biochemical pathways that lead to the ultimate formation of a stable fibrin clot. For the conduction of these laboratory screening tests of hemostasis in a more physiological manner and to ensure correlation of the laboratory results with clinical risk of bleeding, global hemostasis assays are being carried out in several regions of the world. These tests reflect the clinical scenario better than the screening tests and coagulation factor assays. However, they are not thoroughly standardized and several pre-analytical, analytical variables remain to be addressed for accurate validation of these tests. They include thrombin generation time, TEG, and aPTT wave form analysis, among which TEG is of particular importance in FXIIID.[15] It studies clot formation from initiation to breakdown, by virtue of which it can practically detect disorders of primary hemostasis, coagulation pathway and fibrinolytic pathway. A pathological TEG combined with normal screening tests as mentioned above will accurately reflect FXIIID, however minor the deficiency may be.[16] However, FXIII activity will still be required to quantify the deficiency. We have followed an alternate algorithm for the diagnosis of FXIIID in our case without involving TEG (Figure 4). However, post-diagnosis TEG for the purposes of correlation of the magnitude of FXIIID with clinical risk of bleeding reveals features typical of Mild FXIIID in our case.[17]

Platelet function tests (PFT) were not considered in the diagnosis as per the algorithm[6] due to the fact that primary hemostasis was clinically normal. BT or Platelet Function Assay-100 (PFA-100) can be used as screening tests to evaluate primary hemostasis. Platelet aggregometry and flow cytometry of the platelet receptors are time consuming and require fresh platelets. These advanced tests may be considered if the screening tests (BT, PFA-100) are abnormal or the history/clinical picture is strongly suggestive of a defect in the primary hemostasis despite normal screening tests. Bleeding time was found to be well within normal limits and combined with the fact that platelet counts were also within normal limits, the possibility of both a qualitative and quantitative platelet defect was ruled out. In addition, any platelet disorder or Von-Willebrand disease are more likely to cause immediate post-surgical bleeding unlike the delayed bleeding seen in our case. However, PFT is considered to be an initial screening test in characterizing patients with hemorrhagic tendency.[6]

Unlike other bleeding disorders, the level of FXIII correlates very well with that of bleeding tendency,[1] thus making prompt diagnosis very important; however, mild it may be, so the hematologist can institute appropriate management, when required. Though no prophylactic management is required at a FXIII level of more than

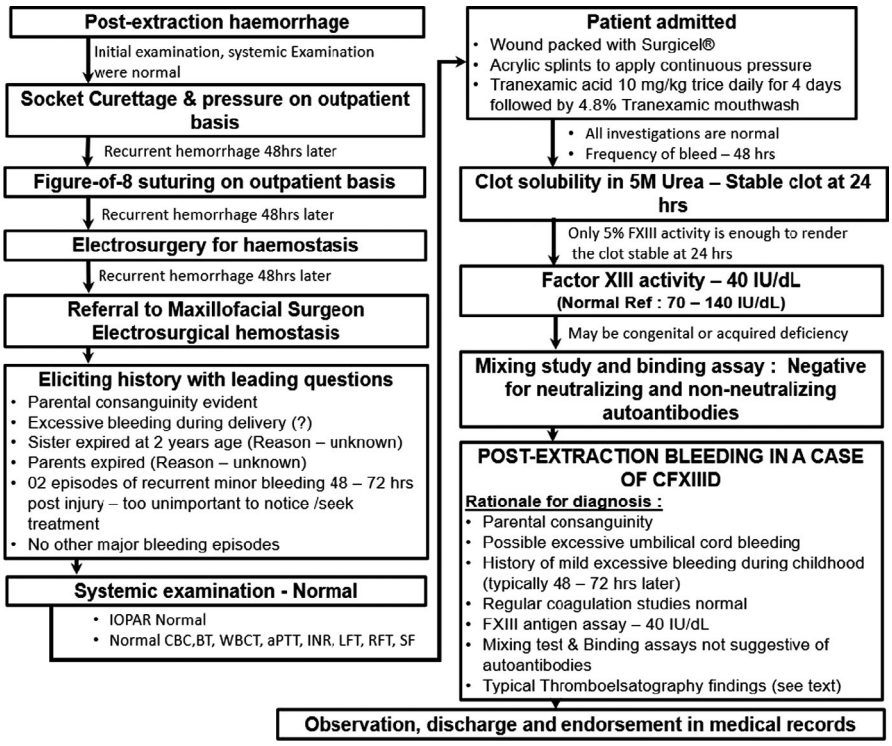

FIGURE 4 Flow Chart describing the management of the case (IOPAR, Intraoral periapical radiograph; CBC, Complete blood count; BT, bleeding time; WBCT, Whole Blood clotting time; PT, Prothrombin time; aPTT, activated partial thromboplastin time; INR, International normalized ratio of PT; LFT, Liver function tests; RFT, Renal function tests; SF, Serum Fibrinogen; hrs, hours; 5 M, 5 Molar; mg, milligram; kg, kilogram; IU, International unit; dl, deciliter; FXIII, Factor XIII; CFXIIID, Congenital FXIII deficiency)

30 IU dl^{-1}, perioperative maintenance at 60 IU dl^{-1} is recommended to prevent hemorrhagic complications.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Arunkumar Shadamarshan R: Contributed by provided the clinical material, working up the case and arriving at the final diagnosis. He was also involved in revising the manuscript critically for important intellectual content. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Rohit Sharma: Contributed in part by working up the case and arriving at the final diagnosis and gave the final approval of the version to be published. Ishan Pradhan: Contributed in drafting the manuscript, appropriate literature review and interpretation to be included in the manuscript. Pramod Kumar: Contributed in appropriate literature review and interpretation of available to be included in the manuscript.

ETHICAL APPROVAL

Necessary Ethics committee approval and informed patient consent have been obtained for the case study.

PATIENT CONSENT STATEMENT

Informed patient consent has been duly obtained during the procedure and for the publication of photographs.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Peyvandi F, Palla R, Menegatti M, et al. Coagulation factor activity and clinical bleeding severity in rare bleeding disorders: results from the European network of rare bleeding disorders. *J Thromb Haemost*. 2012;10(4):615-621. https://doi.org/10.1111/j.1538-7836.2012.04653.x
2. Suzuki H, Kaneda T. Tooth extraction in two patients who had a congenital deficiency of factor XIII. *J Oral Maxillofac Surg*. 1985;43(3):221-224. https://doi.org/10.1016/0278-2391(85)90165-X
3. Martínez-Rider R, Garrocho-Rangel A, Márquez-Preciado R, Bolaños-Carmona MV, Islas-Ruiz S, Pozos-Guillén A. Dental management of a child with incidentally detected hemophilia: report of a clinical case. Torrés-Lagares D, ed. *Case Rep Dent*. 2017;2017:7429738. https://doi.org/10.1155/2017/7429738
4. Dhawan A, Sandhu S, Kaur T, Kapila S. Hemophilia A-an incidental finding in a patient with facial trauma. *Indian J Compr Dent Care*. 2011;1(1):43–46.
5. Shusterman SMC, et al. Transfusion of the patient with congenital coagulation defects. In: Hillyer CD, ed. *Blood Banking and Transfusion Medicine; Basic Principles and Practice*, 2nd edn. Churchill Livingstone Elsevier; 2007:467-481.
6. Karimi M, Peyvandi F, Naderi M, Shapiro A. Factor XIII deficiency diagnosis: challenges and tools. *Int J Lab Hematol*. 2018;40(1):3-11. https://doi.org/10.1111/ijlh.12756
7. Jain S, Acharya SS. Inherited disorders of the fibrinolytic pathway. *Transfus Apher Sci*. 2019;58(5):572-577. https://doi.org/10.1016/j.transci.2019.08.007
8. Kohler HP, Ichinose A, Seitz R, et al. Official communication of the SSC: diagnosis and classification of factor XIII deficiencies. *J Thromb Haemost*. 2011;9:1404-1406. https://doi.org/10.1111/j.1538-7836.2011.04315.x
9. Tak MTS, Rydz N, Goodyear D, Sholzberg M. Acquired factor XIII deficiency: A review. *Transfus Apher Sci*. 2018;57(6):724–730. https://doi.org/10.1016/j.transci.2018.10.013
10. Ichinose A, Kohler HP, Philippou H. Recommendation for ISTH/SSC criterion 2015 for autoimmune acquired factor XIII/13 deficiency. *Thromb Haemost*. 2016;116(4):772-774. https://doi.org/10.1160/TH16-05-0362
11. Scully M. Factor XIII deficiency, a primer for anesthesiologist. *Rev Mex Anestesiol*. 2016;39(Supl 2):S309-S312.
12. Menegatti M, Palla R, Boscarino M, et al. Minimal factor XIII activity level to prevent major spontaneous bleeds. *J Thromb Haemost*. 2017;15(9):1728-1736. https://doi.org/10.1111/jth.13772
13. Tahlan A, Ahluwalia J. Factor XIII: congenital deficiency factor XIII, acquired deficiency, factor XIII A-subunit, and factor XIII B-subunit. *Arch Pathol Lab Med*. 2014;138(2):278-281. https://doi.org/10.5858/arpa.2012-0639-RS
14. Dorgalaleh A, Tabibian S, Hosseini S, Shamsizadeh M. Guidelines for laboratory diagnosis of factor XIII deficiency. *Blood Coagul Fibrinolysis*. 2016;27(4):361-364. https://doi.org/10.1097/MBC.0000000000000459
15. Nair SC, Dargaud Y, Chitlur M, Srivastava A. Tests of global haemostasis and their applications in bleeding disorders. *Haemophilia*. 2010;16(Suppl 5):85-92. https://doi.org/10.1111/j.1365-2516.2010.02304.x
16. Bose E, Hravnak M. Thromboelastography: a practice summary for nurse practitioners treating hemorrhage. *J*

Nurse Pract. 2015;11(7):702-709. https://doi.org/10.1016/j.nurpra.2015.05.006

17. Martinuzzo M, Barrera L, Altuna D, et al. Effects of factor XIII deficiency on thromboelastography. Thromboelastography with calcium and streptokinase addition is more sensitive than solubility tests. *Mediterr J Hematol Infect Dis*. 2016;8(1):e2016037–e2016037. https://doi.org/10.4084/MJHID.2016.037

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