Editorial Comment: Factor XIII: One More Critical Factor for Hemostasis

Factor XIII (FXIII) is an important clotting factor that clinicians may not be familiar with. FXIII circulates in an inactive form as a heterotetramer made up of 2 type-A and 2 type-B subunits held together by noncovalent bonds. FXIII is activated to FXIIIa via thrombin-mediated proteolytic cleavage during the final steps in the hemostatic cascade.[1,2] FXIIIa is an enzymatic transglutaminase that cross-links fibrin monomers to create a more stable clot structure that resists biochemical dissolution (fibrinolysis) and mechanical disruption.[1] Recently, Aleman et al.[3] have also determined that FXIII activity is critical for red blood cell retention within clots and directly affects the size of venous thrombi.

FXIII deficiency is a rare clinical problem that is difficult to recognize. Congenital FXIII deficiency results from reduced FXIII levels and/or activity. In these patients, diagnosis may follow prolonged umbilical stump bleeding, poor wound healing, spontaneous intracranial hemorrhages, or protracted bleeding after major surgical interventions or trauma.[1] Acquired FXIII deficiency can develop after massive hemorrhage and/or dilutional changes associated with trauma or surgery or can occur with liver disease, disseminated intravascular coagulation, sepsis, or other disease states. These patients may or may not present with clinical bleeding due to either the level of FXIII and/or the degree of traumatic or surgical injury.[1] Development of FXIII inhibitory autoantibodies is extremely rare and in most cases is idiopathic. In either situation, suspected FXIII deficiency is confirmed by assays that quantify either the patient's transglutaminase activity or specific protein and subunit levels.

Management of FXIII deficiency involves replacement therapy, and 2 FXIII concentrates are currently available. In 2011, a purified FXIII concentrate, Corifact® (also called Fibrogammin, CSL Behring, King of Prussia, PA) was approved to prevent bleeding in patients with congenital FXIII deficiency. The Food and Drug Administration later expanded its use to include perioperative management of surgical bleeding in adults and children. Corifact is isolated from the pooled plasma of healthy donors and undergoes extensive purification. In 2013, recombinant FXIII A-subunit Tretten® (Novo Nordisk, Bagsvaerd, Denmark) was approved for routine prophylaxis with congenital FXIII A-subunit deficiency. Notably, 95% of patients with FXIII deficiency have the A-subunit deficiency. We have studied recombinant FXIII for repletion in patients undergoing cardiac surgery because FXIII levels are significantly decreased after cardiopulmonary bypass.[4,5] Alternately, because cryoprecipitate contains significant amounts of FXIII, cryoprecipitate may be a potential alternative in this setting in emergencies where when FXIII concentrate is not available.[6]

In this issue of *A&A Case Reports*, Tone et al.[7] report a case of a patient with airway compromise arising from a spontaneously occurring sublingual hematoma resulting in turn from acquired FXIII inhibitor. The patient's surgical and dental histories were negative, but she reported a history of large hematomas which had not previously been attributed to a bleeding disorder. Although standard screening tests were normal, the patient's FXIII activity was low (0.08 U/mL with a normal range of 0.75–1.50 based on a Siemens Berichrom FXIII unit level). Interestingly, a mixing assay indicated the presence of a high-titer FXIII inhibitor. Subsequent treatment included immunosuppressive therapy to reduce the inhibitor titer and plasma-derived FXIII concentrate (3500 units [50 units/kg] every 8 hours) to improve clot quality and prevent airway obstruction.

What are the important take-home messages for clinicians? As noted by the authors, the most common bleeding disorders observed in patients with normal routine coagulation tests are von Willebrand disease and platelet function disorders. Acquired bleeding disorders are also likely to be due to use of new oral anticoagulation drugs, such as apixiban, dabigatran, edoxaban, and rivaroxaban, or antiplatelet drugs, such as clopidogrel, prasugrel, and ticagrelor, and may be far more common.[8,9] The authors suggest that FXIII deficiency should also be included on this list. This position is supported by a recent analysis of hospitalized patients revealing that 21% of adults and 52% of children had FXIII levels <50 U/dL, suggesting that acquired FXIII deficiency is relatively common in patients after surgery and in the intensive care unit.[10] In these patients, FXIII deficiency may easily be missed, even with a hematology consult. In the current case, although previous IM hematomas may have been an early clue to the disorder, the patient's current complaint was specific to airway bleeding, an unusual presentation of FXIII deficiency. Thus, this case was a particularly challenging example of FXIII deficiency and diagnosis.

Fibrinogen is a critical component of clot formation and an important target for monitoring and treating in bleeding patients.[11] In a life-threatening hemorrhage, clinicians should consider the use of cryoprecipitate, because it provides fibrinogen, as well as significant amounts of FXIII, von Willebrand factor, and other constituents critical for clot formation.[6,12] If a patient develops a severe hemorrhage, then a massive transfusion protocol that includes cryoprecipitate plus fresh-frozen plasma with all coagulation factors should be considered. Accordingly, in the current case report, the patient received cryoprecipitate and frozen plasma even before the diagnosis of a FXIII deficiency was made. Notably, however, FXIII activity remained low in spite of the addition of cryoprecipitate, likely due to the presence of the FXIII inhibitor. Ultimately, a multimodal approach using plasmapheresis plus high levels of FXIII concentrate was required to reduce inhibitor levels and maintain FXIII levels >0.5 U/mL. Of note, the authors also empirically used an antifibrinolytic, tranexamic acid, in our view a useful drug for multiple reasons. Fibrinolysis is a critical component of bleeding, and plasmin contributes to coagulopathy through multiple mechanisms.[13]

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In summary, bleeding and its complications can occur due to multiple occult causes that in the "heat of battle" may be difficult to diagnose and treat. Prompt identification of the source of bleeding is critical; the investigation should evaluate both genetic and acquired origins, including von Willebrand disease, platelet disorders, recent prior anticoagulation therapy, and more insidious causes such as FXIII deficiency. If FXIII deficiency is present, specific concentrates should be used if available.[14] If not, physicians should consider both fresh-frozen plasma and cryoprecipitate. During life-threatening hemorrhage, a massive transfusion protocol with adjunct use of tranexamic acid should be considered.[13,15]

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