Recurrent Bleeding after Head Trauma Caused by Acquired Factor XIII Deficiency

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Summary: Factor XIII (FXIII) is the final factor in the coagulation cascade. FXIII plays a critical role in clot stabilization by cross-linking fibrin and making the clot denser and stiffer. FXIII plays crucial roles in platelet clot retraction, wound healing, and tissue repair. When FXIII is deficient, unusual bleeding that persists for several days, delayed healing, and morbid granulation may occur. We present a case of acquired FXIII deficiency presenting as recurrent bleeding after head trauma. A 66-year-old man fell from a ladder and sustained a head injury. The patient had a history of postremission acute myeloid leukemia and Stanford type B aortic dissection and was on three antihypertensives but no antiplatelets or anticoagulants. Approximately 1 month postinjury, the patient suddenly experienced repeated bleeding and hematoma. Routine coagulation tests were normal; therefore, we suspected another type of coagulation disorder. Low FXIII activity was identified 39 days postinjury. We immediately administered concentrated human coagulation FXIII (Fibrogammin P). The patient’s head contusion was completely healed by day 55 postinjury. Acquired FXIII deficiency should be considered when routine coagulation test results are normal. Plastic surgeons who treat injuries routinely must be cognizant of FXIII deficiency because the condition can be life-threatening and early detection is important. Whenever the process of wound healing is unusual or hematoma and bleeding recur unexpectedly with no clear explanation—despite suitable treatments—FXIII deficiency should be suspected and, if present, must be appropriately treated without delay. (Plast Reconstr Surg Glob Open 2022;10:e4109; doi: 10.1097/GOX.0000000000004109; Published online 15 February 2022.)

CASE PRESENTATION

A 66-year-old man fell approximately 3 m from a ladder and sustained an injury to the back of his head. The wound was sutured by a local doctor on the same day. The following day, there was an oozing hemorrhage from the wound. He visited the nearby department of neurosurgery, and computed tomography revealed traumatic subarachnoid hemorrhage and cerebral contusion. He was admitted to our hospital and administered antihypertensive and hemostatic agents.

Four days postinjury, expansion of the hematoma at the cerebral contusion stopped, but re-bleeding from the wound occurred, and he was referred to our department (Fig. 1). The patient had a history of postremission acute myeloid leukemia and Stanford type B aortic dissection and was on three antihypertensives but without antiplatelets or anticoagulants. Results of routine coagulation tests were normal; therefore, we suspected another type of coagulation disorder. Low FXIII activity was identified 39 days postinjury. We immediately administered concentrated human coagulation FXIII (Fibrogammin P). The patient’s head contusion was completely healed by day 55 postinjury. Acquired FXIII deficiency should be considered when routine coagulation test results are normal. Plastic surgeons who treat injuries routinely must be cognizant of FXIII deficiency because the condition can be life-threatening and early detection is important. Whenever the process of wound healing is unusual or hematoma and bleeding recur unexpectedly with no clear explanation—despite suitable treatments—FXIII deficiency should be suspected and, if present, must be appropriately treated without delay.
the bleeding using bipolar forceps and tried compression hemostasis. Despite our efforts, bloody exudate persisted. Due to the unusual recurrent bleeding, we consulted a hematology specialist at our hospital. Due to the clinical course, we suspected acquired factor XIII (FXIII) deficiency. Thirty-nine days postinjury, further investigation revealed reduced FXIII activity (19%; normal range: 60%–120%). We administered concentrated human coagulation FXIII (Fibrogammin P, 240 units/vial; CSL Behring, King of Prussia, Pa.). After 2 days of administration, the FXIII activity increased to 46%, and bloody exudate markedly decreased. Fifty-five days postinjury, the wound was completely healed (Fig. 3). The patient is currently being followed up at the outpatient department; no bleeding from the wound has recurred.

**DISCUSSION**

FXIII—the final factor in the coagulation cascade—plays a critical role in clot stabilization by cross-linking fibrin and making the clot denser and stiffer. FXIII also mediates platelet clot retraction, wound healing, and tissue repair. Unusual bleeding for several days, delayed healing, or morbid granulation occur when FXIII is deficient. Congenital FXIII deficiency is a rare bleeding disorder (1: 2,000,000) inherited as an autosomal recessive trait, with higher frequency in countries with consanguineous marriages. Severe inherited FXIII deficiency is characterized by delayed umbilical cord bleeding. Autoimmune FXIII deficiency due to autoantibodies against FXIII subunits can be secondary to autoimmune conditions like systemic lupus erythematosus, rheumatoid arthritis, and malignancy. Nonimmune causes include increased FXIII consumption (eg, due to massive surgical bleeding, disseminated intravascular consumption, or thrombosis) or decreased FXIII synthesis (eg, in liver disease or leukemia).

Diagnosis and treatment of acquired FXIII deficiency begins with heightened suspicion of the disease when traditional routine coagulation tests, such as prothrombin time, activated partial thromboplastin time, and international normalized ratio, are normal. It is necessary to measure FXIII activity using a functional quantitative assay; determination of FXIII antigens might also be informative. Measurement of FXIII activity is generally outsourced, and the results may be delayed (at our institution, we received the results after a week). Other conditions, such as thrombasthenia and fibrinolysis inhibitor deficiencies, including alpha-2 plasmin inhibitor deficiency or plasminogen activator inhibitor-1 deficiency, may also exhibit normal routine coagulation tests. For repeated bleeding, as in our case, it was necessary to determine platelet function or fibrinolysis inhibitor levels for accurate diagnosis.

Treatment of acquired FXIII deficiency secondary to autoantibodies includes autoantibody eradication by immunosuppressive therapy or removal by plasma exchange with immunoadsorption. Options for FXIII replacement include highly purified plasma-derived FXIII concentrate (Corifab/Fibrogammin P) and...
recombinant FXIII-A2 concentrate (Tretten). If FXIII concentrates are not readily available, cryoprecipitate and frozen plasma may be used. Cryoprecipitate is produced from frozen plasma and contains a higher concentration of FXIII (~3 IU mL$^{-1}$) compared with that of frozen plasma (1 IU mL$^{-1}$).

Neither the patient nor his family had a history of increased bleeding. In fact, patients with acquired FXIII deficiency rarely experience bleeding symptoms. We presumed that the cause of acquired FXIII deficiency was hyper-consumption because of his history of dissecting aortic aneurysm. In the aneurysm, local disseminated intravascular consumption occurred by coagulation activation associated with blood turbulence in the aneurysm and fibrinolytic activation in the aortic aneurysm wall. It is believed that chronic consumption in the aneurysm is within compensation. We suspected he chronically lacked FXIII, but his FXIII requirement increased because of the cerebral contusion and head trauma, and FXIII became depleted. He had a history of acute myeloid leukemia, and although it was postremission, it was possible that the synthesis of FXIII was below that of healthy individuals.

Paradoxically, in our case, the intracerebral hematoma expansion ceased, whereas bleeding from the wound continued. The stiff clot was comparatively easier to form at intracranial bleeding points than at the scalp. Additionally, the wound was more likely to be rubbed against bedding because of its location. As it was challenging to stabilize the clot, we could have used a fibrin sealant alone or in combination with concentrated human coagulation FXIII to reduce the risk of re-bleeding in patients with acquired FXIII deficiency. In previous reports, most bleeding occurred within a few days of the event that triggered bleeding (eg, surgery). Fibrin stabilization is inadequate in patients with FXIII deficiency; therefore, clinicians should carefully check for any bleeding at least a week after the event. In our case, repeated bleeding and hematoma occurred approximately 1 month postinjury. Unlike previously reported cases, our patient had chronic FXIII deficiency. Extra care was required until the wound was completely healed.

**CONCLUSIONS**

When the process of wound healing is unusual or hematoma and bleeding unexpectedly recur despite appropriate treatments, FXIII deficiency should be suspected. In such cases, we would like to encourage consulting a hematologist for thorough evaluation and management.

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