Case Report

Massive Delayed Bleeding after Breast Reconstruction Caused by Acquired Factor XIII Deficiency

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ABSTRACT

Factor XIII, also called the fibrin-stabilizing factor, is the last clotting factor in the second stage of coagulation. Postoperative hemorrhage caused by factor XIII deficiency occurs with a delay of a few days and may be lethal, depending on the intensity of bleeding. Prompt diagnosis and treatment interventions are critical for preventing fatal outcomes. There are two types of factor XIII deficiency: congenital and acquired. While the congenital type is usually diagnosed early in relation to bleeding from the umbilical cord, the acquired type manifests during adulthood and may be caused by various factors. One is the increased consumption of factor XIII during trauma and surgery. All routine preoperative coagulation tests are normal in this condition, causing its diagnosis before an operation difficult.

We report a case of acquired factor XIII deficiency that manifested as massive hemorrhage on the first postoperative day after breast reconstruction with a deep inferior epigastric perforator flap. This paper aims to alert plastic surgeons on the condition, since awareness is critical to initiate immediate and effective treatment. We suggest that if surgeons encounter incomprehensible postoperative delayed hemorrhage, verification of factor XIII activity must be promptly done to diagnose factor XIII deficiency and avoid lethal hemorrhage.

Key words: factor XIII deficiency, hypovolemic shock, perioperative care, postoperative hemorrhage

Case presentation

A 48-year-old woman was diagnosed with left-sided breast cancer. The initial operation entailed left mastectomy, sentinel lymph node biopsy, and tissue expander (TE) insertion. On postoperative day 1 (POD1), bloody discharge from the chest drain was observed and it continuously reduced under compression. However, between POD13 and POD14, the amount of discharge increased (Fig. 1). A computed tomography scan of the chest revealed a hematoma underneath the left pectoralis major muscle (Fig. 2). The next day, POD14, 250 mL of hematoma was removed. No further bleeding occurred, and the patient was discharged on POD20 (Fig. 3).

Ten months later, breast reconstruction was performed using a deep inferior epigastric perforator (DIEP) flap. Intraoperatively, no obvious hemorrhage was observed. On the day of the operation, all indicators, including drain amount and color, were unremarkable; while vital signs were stable. However, in the afternoon of POD1, intense bleeding from the chest drain was observed, blood pressure and heart rate indicated a state of shock, then the patient briefly lost consciousness. The patient recovered from the shock upon administration of six units of red cell concentrate. Then, emergency hematoma evacuation was performed. Intraoperatively, we found diffuse oozing hemorrhage across the entire surgical field but could not identify bleeding from an individual vessel. A total of 900 mL of hematoma was removed. Further investigations confirmed normal preoperative blood coagulation tests and no family or personal history of bleeding. The patient was a nullipara and had no previous surgeries, despite having gynecological diseases such as uterine myoma,
Due to concerns about the unusual repeated delayed hemorrhage postoperatively, we consulted the Department of Hematology at our institution. A bleeding disorder was suspected and further investigations revealed factor XIII activity of 48% (normal range 60–120%). Concentrated human coagulation factor XIII (Fibrogammin® P, 240 units/vial; CSL Behring, King of Prussia, PA, USA) was administered to the patient. An hour later, factor XIII activity increased to 78%. Under this therapy, no further bleeding occurred, and the patient was discharged on POD10 (Fig. 4). She is currently being followed up monthly in the outpatient department, and no additional bleeding has occurred since then.

Discussion

Factor XIII is a tetramer, which consists of an active A-subunit and a B-subunit that function as carrier proteins. The A-subunit is synthesized in leukocytes, such as megakaryocytes and monocytes/macrophages; whereas the B-subunit is produced in the liver. They bind together to form the A2B2 tetramer. Factor XIII is activated by thrombin and consequently cross-links fibrin. Finally, it forms a fibrin clot that is resistant
to shear stress and fibrinolysis. Thus, factor XIII is called the fibrin-stabilizing factor.

Hemostasis occurs in two stages. In the first stage, platelets adhere to a damaged area and aggregate to form a platelet plug. In the second stage, fibrin monomers cross-link into insoluble strands then stabilize the platelet clot into a thrombus. Fibrin stabilization is insufficient in patients with factor XIII deficiency. Thus, delayed postoperative bleeding may occur a few days after the operation.

**Factor XIII deficiency types and symptoms**

Factor XIII deficiency is classified as congenital, acquired, or autoimmune. The congenital type is very rare, affects approximately one in 1–5 million people, and is said to be related to consanguineous marriages. Major symptoms include repeated miscarriages in women, delayed wound healing, and delayed bleeding, which may be lethal. The most severe form starts to manifest early in life with bleeding from the umbilical cord, and 30% of these patients die from intracranial bleeding.

In contrast, the acquired forms of factor XIII deficiency are relatively frequent. A study reported that factor XIII activity levels were below 21% in hospitalized patients and 52% of children in intensive care units. Not all patients present with bleeding; in fact, almost all patients are asymptomatic. These features make the true morbidity of acquired forms of factor XIII deficiency difficult to grasp. These forms may be caused by aggressive consumption of factor XIII, reduced production, aggressive loss, or dilution after blood administration.

Aggressive consumption may result from disseminated intravascular coagulation, invasive operations, trauma, and chronic inflammatory bowel disease. Reduced production is seen in blood diseases such as leukemia, myelodysplastic syndrome, and liver disease. Aggressive loss is associated with dialysis and double filtration plasmapheresis, while dilution may be caused by blood transfusion. Clinicians should aim to identify the etiology of secondary bleeding.

In the autoimmune type, factor XIII antibodies are produced after birth. Autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, solid tumors, spreading leukocyte disease, lymphoid hyperplasia, and chronic use of medications, such as penicillin, antituberculosis, and antipsychotics, are related to this type, where half of the patients have a basal disease. The autoimmune type is rare and usually observed after minor trauma or without an identifiable cause in older adults.

Hematomas and bleeding may occur in any part of the body and could have critical consequences based on location; such as in cases of cardiac tamponade, intracranial bleeding, retroperitoneal hematoma, cervical hematoma, and thoracic hematoma. Prompt treatment is necessary to prevent lethal outcomes. Since bleeding may start several days after the first stage of hemostasis, clinicians should carefully monitor patients for any bleeding at least one week.

**Diagnosis and treatment**

Since all types of factor XIII deficiency present with normal...
routine coagulation test results, including prothrombin time (PT), activated partial thromboplastin time (APPT), fibrin degradation products, d-dimer test, and platelet count, preoperative diagnosis may be challenging. The diagnostic criteria for factor XIII deficiency in a surgical setting are 1) Normal ranges and values for PT, APTT, platelet count, and coagulation time, 2) Low levels of factor XIII activity (under 70%; mean range, 70–140%), 3) Postoperative bleeding several days to one week after. If all criteria are met, factor XIII deficiency is diagnosed. Treatment includes administration of concentrated factor XIII (Fibrogamin P®, 240 units/vial; CSL Behring, King of Prussia, Pennsylvania, United States) at an average dose of 40 units per kilogram. There is no certain rules about infusion rate and dosage per hour. Despite certain evidence isn’t confirmed besides attached physiological saline solution, specifically, an example, using 4 ml attached physiological saline solution and dissolve powdery formula, adding another physiological saline solution to make total amount 20 ml. Thereafter dripping that solution slowly taking 3-5 minutes, as a intravenous administration. Acidic solution, less than ph 6.0, like glucose solution is not recommended since when the two is mixed up, it may get mudded. However, exact protocols that correlate a specific dose with a corresponding increase in factor activity are yet to be established. If factor XIII is not readily available, fresh frozen plasma (2–3 mL/kg) or cryoprecipitate (1 bag/10 kg) may be used alternatively. However, the factor XIII content of 1 mL cryoprecipitate is too low to prevent bleeding. A study reported the presence of α-subunit mutation and congenital factor XIII activity of 48%, and the absence of a personal history of repeated miscarriage and family history of congenital factor XIII deficiency.

In our patient’s case, we diagnosed acquired factor XIII deficiency based on normal preoperative coagulation tests, factor XIII activity of 48%, and the absence of a personal history of repeated miscarriage and family history of congenital factor XIII deficiency.

There was no evidence of liver disease (normal liver function tests), leukemia, or bone marrow disease. Thus, her coagulation factor productivity was suspected to be normal. She did not have any bleeding tendencies during her childhood, autoimmune disease, or long-term medications such as penicillin, antituberculosis, or antipsychotics. It appeared that she did not have a predisposition to bleeding.

In a two-term operation similar to that in this case, we can avoid lethal hemorrhage if we are able to diagnose factor XIII deficiency after the first operation. In addition, we can start preoperative remedy by preventive administration of concentrated factor XIII. Therefore, if surgeons encounter incomprehensible postoperative and delayed hemorrhage, verification of factor XIII activity is recommended.

In Japan, the National Health Insurance covers the administration of 1,440 units of concentrated human coagulation factor XIII per day, for five days. A study reported that patients with acquired and secondary types achieved better outcomes even with a single administration of factor XIII. Thus, supplemental treatment was adapted in our patient. After which, factor XIII activity remained sufficiently high, with no additional bleeding and no autoantibodies detected.

On the contrary, recombinant factor XIII (NovoThirteen®) is not covered by the Japan National Health Insurance for treatment of acquired and secondary types. Since this may cause the deactivation of factor XIII biological activity of the acquired type, it is only allowed for the congenital type.

We assume that the reason for the reduction of factor XIII in our patient was the increased consumption caused by the DIEP flap operation. However, considering that the intraoperative bleeding volume was only 250 mL and the operation time was 13 hours and 28 minutes, blood dilution caused by mass infusion and long-term surgical invasion are also suspected reasons.

**Perioperative management**

In the perioperative management of patients, where factor XIII activity of over 100% is required for invasive operations, the administration of supplemental factor XIII has been shown to be effective. However, as mentioned, deficiency is difficult to diagnose pre-operatively, and so is the prevention of bleeding without a pertinent history. If surgeons encounter delayed postoperative bleeding, factor XIII activity should be measured together with routine coagulation tests.

**Differential diagnosis**

In the scenario of delayed postoperative bleeding described above, we had to rule out alpha 2-antiplasmin inhibitor (a2-PI) deficiency and plasminogen activator inhibitor-1(PA-1) deficiency, which may also present with normal coagulation tests and postoperative bleeding. It is possible that a2-PI deficiency will present the same symptoms as factor XIII deficiency. We diagnose a2-PI deficiency when factor XIII activity is normal; however, plasma a2-PI density (mean level 6–7/dL) and activity (mean ratio 83–115%) are low.

PA-1 deficiency does not have a poorer prognosis than a2-PI deficiency. Bleeding caused by PA-1 deficiency occurs after trauma, surgery, and tooth extraction. We should suspect PA-1 deficiency when the patient presents low levels of PA-1 (mean level 20 ng/mL), with normal factor XII activity and a2-PI levels.

**Conclusion**

Even though so far only one case report exists for a latissimus dorsi flap, plastic and reconstructive surgery patients may
present with postoperative bleeding caused by factor XIII deficiency. Depending on the extent of bleeding, it may be lethal and would require prompt treatment. As plastic surgeons, we should be aware of the possibility of factor XIII deficiency when we encounter postoperative delayed and repeated bleeding. More detailed evidence-based data on the use of factor XIII supplementation is necessary. While there are several reports on factor XIII deficiency, for example, related to intracranial bleeding and severe bleeding after delivery and abdominal and orthopedic operations, there are limited case reports on the same in plastic and reconstructive surgery.

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COI statement

The authors have no conflict of interest to declare.

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