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CASE REPORT

Acquired Factor XIII Deficiency with Multiple Hematoma

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SUMMARY

Background: **Acquired factor XIII (FXIII) deficiency is a rare but potentially life-threatening hemorrhagic disorder, most commonly observed in middle-aged and elderly individuals. Due to its normal routine coagulation profile, it is frequently misdiagnosed or diagnosed late, especially in patients presenting with unexplained bleeding or hematoma.**
Methods: **We report a case of acquired FXIII deficiency in a patient with recurrent, unexplained spontaneous hematomas and normal coagulation results. The diagnostic process includes a urea clot lysis test as an initial screen for FXIII deficiency, followed by specific tests, such as the chloroacetic acid lysis test, and assessment of residual FXIII activity. It is treated with infusion of cold precipitates and the use of immunosuppressive therapies, including corticosteroids and azathioprine.**
Results: **The patient showed poor response to conventional multidisciplinary management. Finally, the patient is automatically discharged to a higher-level hospital.**
Conclusions: **This case underscores the need to consider rare coagulation disorders like acquired FXIII deficiency in patients with unexplained hematomas and normal routine coagulation results. Early identification using targeted diagnostic tests can guide prompt and effective management. Treatment remains challenging in patients with poor response to cold precipitation, corticosteroids, and azathioprine.**
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KEYWORDS

Factor XIII deficiency, acquired, bleeding, hematoma, treatment

INTRODUCTION

The prevalence of congenital FXIII factor deficiency is approximately 1 in 2 million [1]. Although there is a lack of epidemiological data on the exact prevalence of acquired FXIII factor, it is still a relatively rare disease. Acquired FXIII deficiency may be associated with autoimmune mechanisms [2]. This case highlights the importance of considering acquired FXIII deficiency in patients with unexplained bleeding symptoms, especially if coagulation is normal. Early recognition and prompt treatment are essential to improve the prognosis

of these patients. However, the course of treatment for patients who fail to respond to infusion of cold precipitation and antibody therapy can be quite complex and challenging.

CASE PRESENTATION

On March 19, 2023, an 82-year-old male with a history of splenectomy denied thrombosis and had no history of bleeding or family history since childhood. Due to the discovery of "left hip swelling and pain accompanied by left lower limb bruising for more than 10 days, aggravated for 5 days", he was admitted to the intensive care unit of Jinhua Hospital affiliated with Zhejiang University (Jinhua, China). Upon admission, he experienced restlessness, profuse sweating, and an inability to lie flat.

At admission, his blood pressure was 105/53 mmHg, heart rate was 95 beats per minute, and oxygen saturation was 90%. The patient was conscious and sat in an upright posture. After physical examination, it was found that the patient had anemia, a catheter was inserted to determine urinary output, and the heart rhythm was normal. The breathing sounds in both lungs were coarse, and wheezing could be heard. The left lower limb had limited movement, and the lower limbs and scrotum were swollen.

Laboratory examination: Blood routine: Total white blood cell count 5.56 x 10^9/L, hemoglobin concentration 61 g/L, total platelet count 242 x 10^9/L. The coagulation function was normal. Rheumatism immunity was completely negative. Antiphospholipid antibodies were all negative. Coagulation factor activity assay: Coagulation factor V 166%, coagulation factor VII 309%, coagulation factor IX 158%, coagulation factor XII 55%; brain natriuretic peptide (BNP) was normal. Enhanced three-dimensional reconstruction of lower limb arteries (Figure 1): multiple sclerosis of lower limb arteries, high-density shadows of muscle clusters in the left hip and right anterior femur, with hematoma considered.

The patient's hospital screened for normal coagulation factors, multiple unexplained hematomas throughout the body, and later developed swelling and pain in the right thigh. B-ultrasound: Multiple liquid dark areas under the skin (at the root of the right thigh), with a large area of 54 mm x 25 mm x 37 mm (Figure 2).

We provided a comprehensive consultation for the entire hospital (including imaging, ultrasound, rheumatology and immunology, hematology, and vascular surgery). The discussion results first considered the deficiency of factor XIII or the formation of factor XIII inhibitors, which can be further examined and clarified. He was transferred to the Hematology Department on March 23, 2023.

Blood samples were collected for external examination and returned for urea lysis test: clot lysis at 24 hours. Clotting factor XIII activity was less than 2% as determined by the chlorohexanoic acid lysis test. Based on the patient's medical history and late onset age, the diagnosis was acquired factor XIII deficiency.

Treatment: dexamethasone injection was administered intravenously in combination with 50 mg azathioprine orally three times a day for immunosuppressive therapy. Multiple infusions of cryoprecipitate improved factor XIII activity; however, the activity of factor XIII was still less than 3%, and there was no significant change in hematoma. It was recommended to add rituximab, but the family refused and requested to go to a higher-level hospital.

DISCUSSION

Factor XIII (FXIII) is the final component of the coagulation cascade, primarily responsible for stabilizing blood clots by cross-linking fibrin [3]. Acquired FXIII deficiency may result from excessive consumption, reduced synthesis, and immune antibody-mediated interference. Among these, autoantibodies can disrupt fibrin cross-linking, impairing clot stability and significantly increasing bleeding risk.

Traditional coagulation function screening indicators such as PT and APTT may be normal, which makes diagnosis more difficult. If there is bleeding, it is considered to be coagulation factor deficiency bleeding, and vigilance needs to be raised. Therefore, specialized testing of FXIII activity is required to confirm the diagnosis.

There is currently no unified treatment for acquired factor XIII deficiency, and further exploration is needed [2, 4]. Typical treatments include cold precipitates, fresh frozen plasma, or recombinant factor XIII [5,6]. These treatments offer only temporary benefits as they do not eliminate autoantibody production [4].

Autoimmune FXIII deficiency treatment involves achieving hemostasis while also targeting the elimination of autoantibodies through immunosuppressive therapy [4,7]. In a scope review, it was proposed that corticosteroids, cytotoxic drugs such as cyclophosphamide, cyclosporine, intravenous immunoglobulin, rituximab, plasma exchange (TPE), etc. may have therapeutic effects, with cyclophosphamide and rituximab being the most common additives [8].

Some cases also report benefits from plasma exchange (TPE) and immunoadsorption, though effects are not durable [9]. Nonetheless, there exists pertinent literature indicating that TPE may, in fact, be an unrecognized contributor to the development of acquired FXIII deficiency [10]. Rituximab, a monoclonal anti-CD20 antibody, is a promising option, especially when autoimmune mechanisms are suspected [11,12]. Yet more data are needed before it can be considered a first-line treatment.

Tone et al. [13] reported that 72% of the 55 patients who underwent eradication therapy attained either complete or partial remission of antibodies. But the effect of our case was not satisfactory. Therefore, exploring the

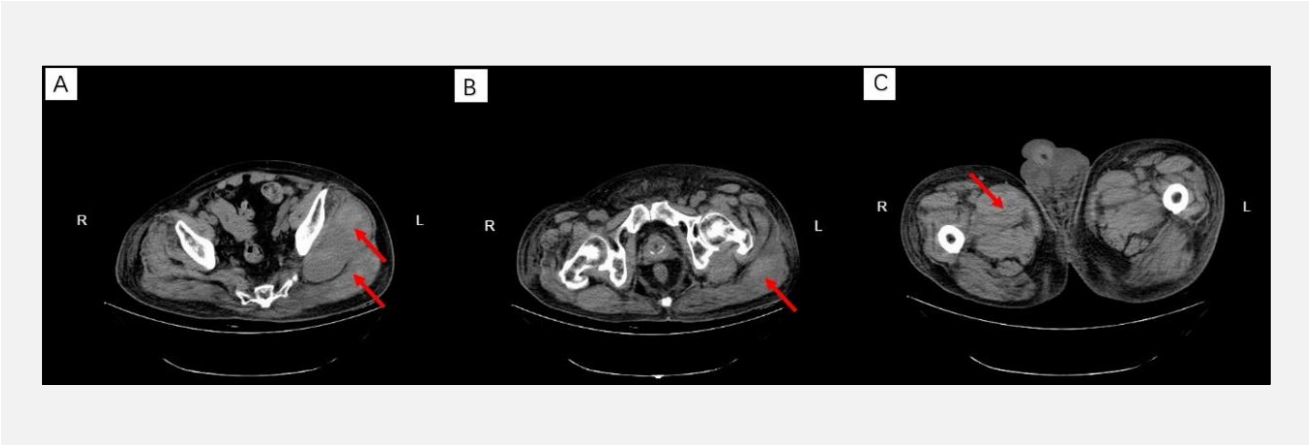

Figure 1. Enhanced three-dimensional reconstruction of lower limb arteries shows involvement of thigh muscles in the following locations: A) Left gluteus medius and gluteus maximus, B) Left gluteus maximus, C) Right anterior femur.

The exact location is marked with an arrow in the figure.

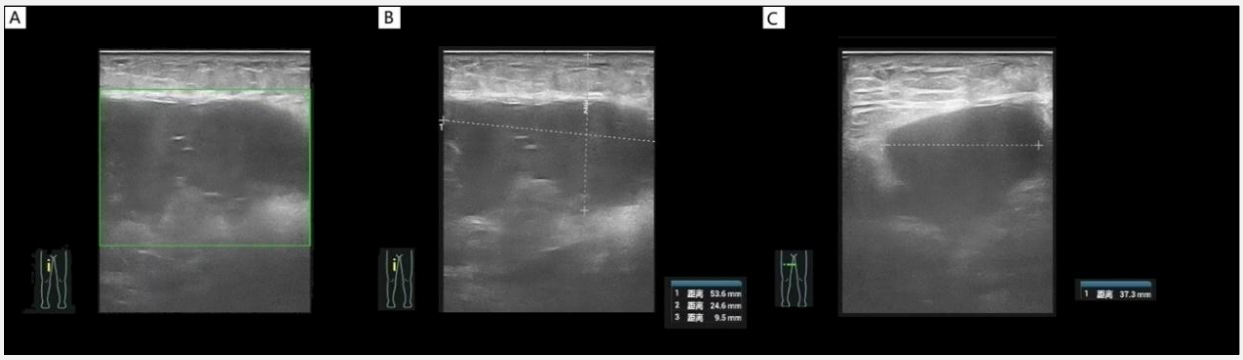

Figure 2. B-ultrasonic of the mass on the right thigh shows the size of the hematoma.

A) Multiple liquid dark areas under the skin, with no obvious blood flow signal observed, B) Hematoma length diameter x hematoma width diameter: 54 mm x 25 mm. Distance of hematoma from skin surface 9.5 mm, C) The height of the hematoma is 37 mm.

application of other immunomodulators in the treatment of patients with low antibody clearance rates using steroids combined with azathioprine remains an area worthy of research.

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Consent Statement:
Written informed consent was obtained from the patient to publish this report in accordance with the Journal's patient consent policy.

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Declaration of Interest:
There is no declaration of interest by any of the authors.

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