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A case of acquired coagulation factor XIII deficiency induced by inhibitor

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Abstract

Factor XIII (FXIII) is a plasma proenzym, which stabilizers fibrin clots and plays key role in hemostasis. Here we report a case of acquired FXIII deficiency caused by FXIII inhibitor, which is rare and pathogenisis is still unknown. Experience of treatment is limited to data from case reports. Immunosuppressive drugs may be used to reduce the inhibitors and may have been of benefit in this patient.

Keywords: Acquired factor XIII deficiency; Rituximab; Hemorrhagic disorder.

Introduction

Coagulation factor XIII (FXIII) is a plasma proenzyme that is activated by the coagulation cascade. FXIII is the final factor in the coagulation cascade and is the necessary for normal clotting process. FXIII plays a very important role in the formation of a stable fibrin clot by cross-linking fibrin, so it is also called fibrin stabilizer [1]. When FXIII is deficient, massive hemorrhage occurred in clinical. FXIII deficiency is a rare coagulation disorder clinically, which can be divided into two types: hereditary FXIII deficiency and acquired FXIII deficiency. Genetic FXIIII deficiency is a rare hereditary autosomal recessive disease in the clinic, with an incidence of about one in 2 million individuals. Acquired FXIII deficiency can be categorized as autoimmune and non-autoimmune. Autoimmune induced FXIII deficiency is extremely rare [2]. There are only more than 70 cases have been reported in the official literature in the world. Autoimmune induced FXIII deficiency has severe bleeding symptoms, may have repeated spontaneous bleeding, difficulties in treatment, and the mortality rate is close to 50%. Here, we present a case of autoimmune acquired FXIII deficiency presenting as left lower leg hematoma.

Case report

A 70s women patient with one-month history of the left lower leg hematoma was admitted our hospital. She had liver cirrhosis. She had no medical history of spontaneous and persistent bleeding after injury. The patient denied having personal or family history of blood disorder, bleeding and allergy. She had not fever on admission and she had no history of surgery recently. Other family members had not experience such hemorrhage. After admission, blood routine examination showed the white blood cell of 2.11×10^9/L, hemoglobin of 65 g/L, and platelet count of 228×10^9/L, coagulation tests showed the PT was 12s, APTT was 33s and TT was 16s, D-Dimer was 1283.07 ug/L and fibrinogen was 2.1 g/L. Routine biochemical examination including liver function and kidney function was normal. Immune function tests found IgG 1.97 g/L, IgA 0.65 g/L, IgM 0.048 g/L, C3 0.87 g/L and C4 0.26 g/L. ANA titer of 1:100 was with homogeneous patterns, while tests of anti-dsDNA, vWF is normal. We suspected that she suffered coagulation abnormality, thus,we performed the urea lysis test to examine FXIII activity, clots showed obvious signs of dissolution within 1h and urea

lysis was partially corrected by 1:1 mixing with normal plasma that implied the patient was FXIII deficiency due to the presence of inhibitor. PET-CT showed abnormal uptake of inguinal lymph nodes biopsy of inguinal lymph nodes is reactive hyperplasia.

Treatment: Patients was treated with cyclophosphamide (200 mg/d) and methylprednisolone (40 mg/d) and Considering the possible shortage of FXIII, cryoprecipitate was transfused. Following treatment, the hemorrhage stopped and hematoma began to mitigate gradually, FXIII activity returned to normal. Five months after initiating the treatment, we stopped the immunosuppressive treatment. Unfortunately, after one month of follow-up, the patient presented the left lower leg massive purpura. Antigen FXIII is 44.8%. The activity of FXIII is low, cyclophosphamide (200 mg/d) and methylprednisolone (80 mg/d) as immunosuppressive were given. Purpura gradually disappear. We reduced the cyclophosphamide and methylprednisolone to stop, and the patient's condition did not worse. After 3 months, the patient occurred re-bleeding with a seven-day history of hematuresiscr and required further haemostatic therapy. Antigen FXIII is 80.5% (normal range 75.02%-154.8%). Urealysis tests showed bright positive results. Standard dose rituximab at 375 mg/m^2 weekly for four weeks was used, azathioprine and methylprednisolone as immunosuppressive therapy, hematuresis is disappears. No relapse in terms of bleeding was observed so far.

Discussion

Acquired FXIII deficiency, including autoimmune and non-autoimmune type, occurs in elderly patients with multiple diseases [3]. Autoimmune FXIII deficiency is caused by the generation of FXIII inhibitors [4]. These inhibitors are associated with autoimmune diseases, malignant diseases, and medications [5,6]. Non-autoimmune FXIII deficiency result from decreased synthesis and increased consumption of FXIII [4]. Bleeding symptoms of autoimmune FXIII deficiency are more severe than those of non-autoimmune FXIII deficiency. Autoimmune FXIII deficiency requires hemostatic therapy and immunosuppressive agents, such as steroids [7], in order to reduce inhibitor concentration. Autoimmune FXIII deficiency is a very few but severe disorder [2]. FXIII deficiency should be considered in patients with bleeding symptoms when APTT, PT and PLT count are normal [8].

Here, we reported a case of autoimmune acquired FXIII deficiency. It is necessary to perform immunological tests to measure levels of FXIII inhibitors to diagnose autoimmune acquired FXIII deficiency, however, there is difficult to measure FXIII inhibitors using immunological tests under current practice condition at our hospitals. Thus we only performed the preliminary screening test of urea lysis tests for FXIII deficiency, meanwhile a correcting test of urea lysis was also performed [5]. The results implied that the presence of FXIII inhibitor in the patient plasma.

Due to the rarity of FXIII deficiency, there are no comparative clinical studies to guide treatment recommendation in China. The primary management aims in acquired FXIII deficiency are to control significant bleeding and finding a potential underlying cause. For autoimmune acquired FXIII deficiency, initial bleeding requires replacement followed by eradication of the inhibitor with Immunosuppressive Therapy (IST) [7]. Inhibitor eradication in this patient is achieved with IST using cyclophosphamide therapy in combination with methylprednisolone, however, there remain a risk of recurrent severe bleeding since the inhibitor can not be completely eradicated. In fact, in more than one year, this patient occurred bleeding symptoms twice after discontinuation of immunosuppressants. When the patient thirdly admitted to our hospital with bleeding symptom, we chose Rituximab regimen as second-line treatment in combination with azathioprine and methylprednisolone to the patient. After the final administration of Rituximab, hematuresis was disappears and no relapse in terms of bleeding was observed so far. The use of upfront Rituximab with corticosteroids is increasing and is associated with shorter times to complete remission. Appears to be equally effective and well tolerated compared to other regimes, treatment with reduced toxicity and improved outcomes. Patients diagnosed with acquired FXIII deficiency are managed with IST, adverse events were mostly associated with prolonged steroid. These included infection, insomnia, delirium, osteoporosis, fluid retention. Cyclophosphamide was associated haematologic toxicity. While Rituximab was very well tolerated [9]. Rituximab represents a therapeutic advance and attractive alternative in FXIII deficiency management. Rituximab regime for first-line treatment is not clear.

When patient received complex multi-agent IST regimens including steroids, cyclophosphamide and rituximab, infection risk associated with immunosuppressive therapy in elderly patients may outweigh the bleeding risk. In this case series, the patient occurred an infection of the urinary system. It implied that intensity of IST should be stratified.

Conclusion

Elderly patients are most commonly affected and present unique management challenges. Due to comorbidities and general fragility, IST for inhibitor eradication is essential to ameliorate the risk of bleeding and should be attempted in the majority of patients. Combination therapy with steroid and Rituximab appears to be effective and well tolerated. However prospective studies are needed to further assess the potential role of this regimen.

Declarations

Ethics statement: Ethics Committee approval was obtained from the Institutional Ethics Committee of Tianjin First Center Hospital.

Conflict of interest statement: The authors declare that they have no competing interests.

Author contribution statement: Li Geng wrote original draft, Juan Mu, Yili Jiang and Tao Sui reviewed and revised the manuscript.

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