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CASE REPORT

Acquired Factor XIII Deficiency Inducing Recurrent and Fatal Bleeding, Description of a Case

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Abstract: Factor XIII deficiency may be inherited or acquired. Inherited deficiency is associated with signs and symptoms of minor bleeding from a young age, and possible major bleeding complications, in particular during pregnancy. On the other hand, acquired factor XIII deficiency is usually associated with severe symptoms of major bleeding, in particular during surgery. In this paper, we report an interesting case of recurrent major bleeding with subsequent fatal bleeding in an adult man diagnosed with acquired factor XIII deficiency.

Keywords: factor XIII deficiency, acquired haemophilia, blood disorders, bleeding, fatal bleeding

Background

Factor XIII is a zymogen which, after activation in factor XIIIa, is able to stabilise the fibrin and therefore the clot.[1] Its inherited deficiency is relatively rare but clinical manifestations may be severe with major recurrent bleeding and slow wound healing.[1] Main clinical manifestations are recorded in the obstetric setting with recurrent menometrorrhagia and/or recurrent miscarriages,[2] but intracranial haemorrhage and gastrointestinal bleeding have also been frequently described.

On the other hand, acquired factor XIII deficiency is very rare and due to the presence of alloantibodies or autoantibodies toward subunit alpha of factor XIII;[3] clinical haemorrhagic manifestations are very severe in the acquired form and its treatment is very difficult in the case of elective or urgent surgery.[3]

In this paper, we report a very rare case of recurrent bleeding with final fatal bleeding in the presence of acquired factor XIII deficiency.

Case History

A 67-year-old man was affected with atrial fibrillation in prophylaxis with apixaban 5 mg twice daily, diabetes and obesity (height 168 cm, weight 114 kg, BMI 40); he was admitted to the Emergency Room for fever, anaemia and diarrhoea not responsive to classic drugs (loperamide per os and neomycin per os). Laboratory findings revealed worsening kidney failure with creatinine 2.3 mg/dL, moderate anaemia (haemoglobin 6 g/dL) and reduced prothrombin time (PT 50%, INR 1.9) associated with prolonged aPTT (ratio 3.2). Due to the abnormal PT and aPTT values and kidney failure, apixaban was stopped and blood transfusion of 3 units was performed with restoration of haemoglobin levels (7.9 g/dl); in the meantime, restoration of PT and aPTT (PT 54% - INR 1.89 - aPTT ratio 2.9) was not recorded.

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Antibiotic therapy for diarrhoea was started (piperacillin 2.250 mg 4 times daily) with reduction in fever.

However, after 2 days, a sudden gastrointestinal bleeding appeared with new decrease of haemoglobin (5.8 g/dL), and a new blood transfusion of 3 units was planned. According to a new laboratory check, abnormal PT and aPTT (PT 51% INR 1.9, aPTT ratio 2.21) persisted; as this was the fourth day after apixaban suspension, a mix pool aPTT test with normal plasma 1/1 was required and revealed an interference on aPTT due to the presence of clotting inhibitors.

Plasma levels of clotting factors were looked for and the results revealed low levels of factor XIII only (i.e. 14%) without abnormalities of other clotting factors (Table 1).

As the presence of clotting inhibitors is frequently associated with that of other autoantibodies, some autoimmune tests and a check for anticardiolipin antibodies were planned, without revealing any pathological findings as reported in Table 2.

On the other hand, from a therapeutic point of view, there was a clinical dilemma to counteract clotting inhibitors: prednisone was not indicated for recent gastrointestinal bleeding, while cyclophosphamide for severe anaemia, rituximab was considered but it has few references in the presence of inhibitors for factor XIII. It was decided to use fresh frozen plasma (three units) and rFVIIa in order to manage recurrent bleeding with apparent clinical improvement. However, after 36 hrs, a further haemorrhagic complication occurred (intracranial haemorrhage of right side) with associated coma (Glasgow Coma Scale 8). New blood samples were planned and revealed moderate anaemia (7 g/dl) and persistent abnormal PT and aPTT (PT 71%, 1.3 INR and aPTT 1.98 ratio). Being an intracranial haemorrhage in deep areas, surgery was not indicated and death occurred 2 days after.

Table 1 Clotting Tests of the Reported Patient

Test	Clotting Factors Values (ag)	Clotting Factors Values (%)	Normal values
PT (INR)	1.9	/	0.8–1.2
aPTT (ratio)	2.21	/	0.8–1.2
Mix pool test with plasma 1\1	1.8	/	<1.3
Factor V	101	105	80–120
Factor VIII	110	99	6–40
Factor IX	102	104	80–120
Factor X	95	81	80–120
Factor XI	110	98	80–120
Factor XII	110	98	80–120
Factor XIII	14	65	80–120
Fibrinogen (mg/dl)	285	/	200–400

Table 2 Results of Other Tests for the Reported Case

Test	Patient's Values (ag)	Normal Values
C-Reactive Protein (mg/dL)	1.2	< 1.0
Rheumatoid factor (any isotype) (U/mL)	21	< 50
Antinuclear antibodies (ANA)	Absent	Absent
Anticardiolipin antibodies IGG (U/GPL)	10	<20
Anticardiolipin antibodies IGM (U/MPL)	11	< 20
Lupus anticoagulant	Absent	Absent

Discussion

The deficiency of factor XIII may be inherited or acquired, and it is associated with bleeding disorders.[4] It is relatively rare and for inherited deficiency, the largest series enrolled no more than 92 patients[3] with minor spontaneous bleeding or post-traumatic and major bleeding (i.e. gastrointestinal bleeding or intracranial haemorrhages).[5] Acquired factor XIII deficiency is even more rare than inherited deficiency but its clinical presentation may be very severe with mainly major bleeding also at the onset of the disease, and fatal bleeding is frequently described in these patients.[4] For this reason, pharmacological treatment of acquired factor XIII deficiency is very challenging.[6] The presence of comorbidities such as anaemia, infections or kidney failure could lead to some extra issues relating to clinical management, in particular for cyclophosphamide and prednisone, while immunological drugs such as rituximab have not been tested on large series.[6,7] The administration of plasma may be effective for a few hours in order to improve clinical features, but the progression of the disease may go on per se.

This clinical case confirmed the progressive nature of the disease, without correction of clotting abnormalities with fresh frozen plasma or the use of rVIIa.

The administration of recombinant factor XIII has been described in other similar cases, but the availability of the drug is very rare for inpatients around the world, also due

to the rapid evolution of clinical features. In our case, the initial presentation of anaemia has been followed by two major bleedings, one of them fatal. Therefore, the presence of anaemia with prolonged aPTT without restoration after check with mix pool test should be of help for clinicians in early diagnosis of acquired factor XIII deficiency, in order to start an appropriate and timely treatment, in particular for inpatients.

Ethics and Consent

Written informed consent has been obtained from the first degree relatives of the patient to have the case details published.

No institutional approval was needed to publish the case by all involved authors.

Disclosure

The authors report no conflicts of interest in this work.

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