Acquired Factor VIII Inhibitor Presenting As Diffuse Spontaneous Ecchymosis

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Citation

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Abstract

Acquired factor VIII hemophilia (also called acquired hemophilia A) is a rare bleeding diathesis with a high mortality rate. Factor VIII inhibitors present a challenging management dilemma for community practitioners. Treatment needs to be directed at both active bleeding issues as well as immune suppression to decrease the level of antibodies that adversely decrease clotting factor activity. We present a case of a 79-year-old male who was diagnosed with acquired factor VIII inhibitor during admission for a rash. Written informed consent was obtained from the patient for publication of this case report.

INTRODUCTION

Acquired factor VIII hemophilia (also called acquired hemophilia A) is a rare bleeding diathesis with a high mortality rate. Factor VIII inhibitors present a challenging management dilemma for community practitioners. Treatment needs to be directed at both active bleeding issues as well as immune suppression to decrease the level of antibodies that adversely decrease clotting factor activity. We present a case of a 79-year-old male who was diagnosed with acquired factor VIII inhibitor during admission for a rash. Written informed consent was obtained from the patient for publication of this case report.

CASE

A 79 year old black male presented to the Emergency Department (ED) complaining of a painful rash. The rash appeared on his right arm, two weeks earlier, with a pustule that ruptured becoming hypopigmented with surrounding hyperpigmentation. After noticing this initial lesion, he developed similar rashes on his left arm and right buttock.

The patient had not suffered any recent illnesses or changes in health prior to the rash appearing. He denied any other new or unusual bleeding. His family history was negative for bleeding disorders, coronary artery disease or malignancy. Other than this rash, the patient had no other pain related complaints.

In the ED, the patient was found to have new onset atrial fibrillation. He was also anemic with hemoglobin of 8.9. One year earlier he had a hemoglobin level of 14.3. He was admitted to the hospital for observation and further evaluation.

A baseline coagulation panel was obtained following admission given the need to start anticoagulation for atrial fibrillation. His coagulation panel was normal except for a partial thromboplastin time (PTT) of 94 (normal range 23.9-37.8); repeated PTTs showed values that peaked at 141.

His rash in conjunction with the elevated PTT sparked a multidisciplinary investigation. Other than a new normocytic anemia, his complete blood count was within normal limits. His estimated sedimentation rate and fibrinogen were also elevated. His lactate dehydrogenase was mildly elevated at 286 (normal range 108-212), but this laboratory results were drawn following a blood transfusion; a peripheral blood smear did not show evidence of hemolysis (see Table 1).

Further evaluation of the elevated PTT was pursued; a mixing study and an evaluation of intrinsic pathway clotting factor activities were conducted (Figure 1). Antiphospholipid antibody evaluation was also performed, including anticardiolipin antibody panel, lupus anticoagulant, and beta-2 glycoprotein antibodies. The mixing study showed incomplete correction of the PTT after mixing and a further prolongation of the mixed PTT at one hour. A repeat mixing study was performed and confirmed the presence of an inhibitor (Table 2).

While waiting for laboratory results, the patient underwent biopsies of the affected areas; these showed extravasated blood with no evidence of vasculitis or vasculopathy. His antiphospholipid antibody testing was within normal limits. The initial evaluation of his clotting factor activity levels showed an undetectable Factor VIII activity supporting the diagnosis of a factor VIII inhibitor.

During his hospital stay he was started on 1mg/kg of prednisone for treatment of a suspected factor inhibitor and his rash began to slowly fade and became non-tender. Unable to obtain timely laboratory results, the patient was transferred to an academic tertiary care hospital with an on-site coagulation laboratory capability. Here his diagnosis was confirmed and he was started on rituximab. Lacking a durable remission of his inhibitor antibody production, he was later transitioned to a combination cyclophosphamide and steroids. While his inhibitor levels remain elevated, he has had no further recurrence of his rash or other bleeding complications.

Figure 1

Coagulation Cascade

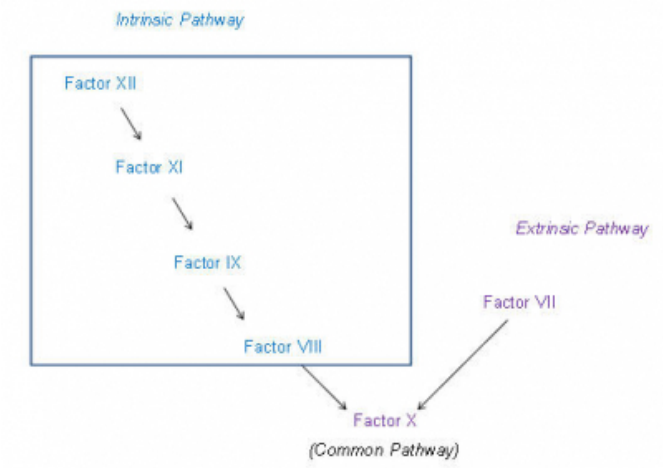

Table 1

Initial Laboratory Results

Test	Values Obtained
WBC	8.6
Platelet	427
Hemoglobin	***8.9***
Hematocrit	26.4
RDW	19.4
LDH	286 (108-212)
Fibrinogen	506 (222-483)
ESR	55
PT	12.8
Partial Thromboplastin Time (PTT)	***94.2*** *(23.9-37.8)*
INR	1.1
Peripheral smear	No hemolysis

Table 2

Factor Inhibitor Work-up

Factor Work-up	Values
1st Mixing Study	***74.4 (23.9-37.8) Delayed***
2nd Mixing Study	***41.7 (23.9-37.8) Delayed***
Activity Assays	
Factor VII Activity	97 (50-150) Corrected
Factor IX Activity	132 (60-160) Corrected
Factor X Activity	135 (70-150) Corrected
Factor II Activity	114 (70-150) Corrected
Factor VIII Activity	***<1 (50-180) Delayed 44.3 (0.4 or less)***
Factor VIII Inhibitor	***Present***
Anticardiolipin Ab	Negative IgA,IgG, IgM-
Beta-2-glycoprotein	Negative
Antiphospholipid Ab	Negative
Lupus Anticoagulant	Negative

DISCUSSION

Acquired Factor VIII Inhibitor is a rare medical condition.

An estimated 1.3-1.5 cases per million occur per year. It is typically found in individuals over 50 years of age and is associated with malignancy, postpartum, drug reaction or autoimmune disease like rheumatoid arthritis or systemic lupus erythematosis (SLE).1

While antiphospholipid antibodies act as inhibitors during a mixing study, they are more often clinically associated with thrombosis and not with bleeding complications. These antibodies can either be an isolated finding, or they can be found in association with other rheumatologic conditions such as SLE.

Mixing studies are necessary tests to evaluate significantly elevated PTT. The mixing study differentiates a factor deficiency from the presence of an antibody inhibitor to a clotting protein in the coagulation pathway. While awaiting more in-depth laboratory results, a family physician can order a mixing study and have a result within 1-2 hours.

In a mixing study, the patient's plasma is mixed with a control plasma specimen, and the PTT is evaluated at baseline, following mixing with the control plasma. The mixed specimen, control and patient specimens are then incubated at 37°C for 1 and 2 hours and re-measured. If there is a prolongation >10 seconds over the control value, the test is positive for the presence of an inhibitor and factor activity level evaluation is warranted. The Bethesda assay is a mixing study for Factor VIII and one Bethesda unit is the amount of inhibitor needed to neutralize 50% of 1 unit of FVIII in normal plasma.2

Treatment involves both the acute management of bleeding and subsequently, long term elimination and suppression of the inhibitor.3 For massive bleeding, concentrates of recombinant human factor VIIa, factor VIII, or activated prothrombin complex can all be used depending on availability and the severity of the situation. To suppress the inhibitor, immunosuppression is usually pursued with agents such as corticosteroids, cyclophosphamide, or rituximab. Factor inhibitors may ultimately decline or spontaneously disappear on their own.4

When a coagulation panel shows an abnormally elevated PTT with normal PT in the setting of suspected bleeding, there needs to be a concern for acquired factor inhibitor and further evaluation is indicated. This patient was fortunate with his mild presentation and the workup initiated based on a laboratory abnormality alone. This patient was evaluated for underlying malignancy and rheumatologic disease and no underlying cause for his Factor VIII inhibitor has been found with his case appearing to be idiopathic.

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