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A Case Demonstrating High Early Mortality in Patients with Acquired Hemophilia A

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Abstract

A 78-year-old female presented with a hemoglobin of 5.3g/dL. CT scan showed a soft tissue hematoma within the left gluteus medius muscle. She reported skin bruising and hematuria. Activated partial prothrombin time (aPTT) was elevated at 78s and mixing study showed incomplete correction to 51.3s. Factor VIII activity was low at 3% with an inhibitor of 17.5 Bethesda Units (BU). A diagnosis of acquired hemophilia was made and factor VIII inhibitor bypassing agent (FEIBA) was initiated. Cyclophosphamide and prednisone were started for immunosuppression. Initially, the hematuria resolved, and aPTT and hematoma size remained stable. Suddenly on day fourteen, Hb dropped by 2g/dL and a repeat CT showed an intramuscular hematoma of the left iliopsoas with hemorrhagic tracking into the pelvis. Cyclophosphamide was switched to rituximab and recombinant Factor VIIa (rFVIIa) was added to FEIBA. Unfortunately, the patient went into hemorrhagic shock, multi-organ failure, and passed away.

Keywords: Hemophilia A; Autoantibodies; Bleeding disorders; Coagulation cascade

Introduction

Acquired hemophilia A (AHA) is a rare, life-threatening bleeding disorder caused by autoantibodies to factor VIII with an incidence of 0.2-1/1,000,000 people/year in the United States [1] and has a mortality rate of 5-10% [2,3]. This case highlights the relatively high mortality associated with AHA, the importance of prompt recognition to initiate treatment, and the need for more data on the possible role of using more robust immunosuppression with Rituximab in the up-front setting to potentially mitigate the mortality rate from this rare disorder.

Case Presentation

A 78-year-old female with a past medical history of paroxysmal atrial fibrillation, not on anticoagulation due to recent hematuria post right ureteral stent, initially presented to an outside hospital with a chief complaint of left hip pain and was prescribed steroids for a clinical diagnosis of trochanteric bursitis and discharged home. Two days later, the patient returned to the emergency department with complaints of abdominal discomfort, generalized weakness, dizziness, and persistent left hip pain. Review of systems was positive for a 9-month history of easy bruising. The patient at that time denied hematochezia, melena, hematemesis, or any other active bleeding. Physical examination was not significant for any bruising or hematoma. The initial laboratory workup showed a hemoglobin of 5.3g/dl [Normal: 12.3-15.3g/dL] as displayed in Table 1. PTT on arrival was 49s. PT/INR were within normal limits. Patient was initially transfused 2 units of packed red blood cells (pRBCs). Patient thereafter developed several signs of bleeding including hematuria and melanotic stools. Urine analysis was positive for 3+ blood and given her previous history of ureteral stent placement, she was treated with ceftriaxone and managed conservatively by urology.

For the patient's melanotic stools, an upper endoscopy was completed which was significant for a Dieulafoy's lesion within the fundus of the stomach for which adequate hemostasis was achieved with the placement of two clips. Workup also included carotid dopplers which showed complete occlusion of the internal carotid artery bilaterally. As her physical examination was significant for swelling and pain at the left hip and thigh, the patient received further imaging with a computed tomography (CT) scan. CT scan of the abdomen and pelvis revealed no bleed or hematomas, mild right hydronephrosis with a chronic stent in place was noted. CT scan of the left femur without contrast showed a soft tissue hematoma within the left gluteus medius muscle measuring 9.2x4.1cm. The patient had received a total of 5 units of packed red blood cells and 2 units of fresh frozen plasma (FFP) through her hospital stay. Her hemoglobin stabilized; however, her PTT continued to uptrend. PT/INR remained within normal range. Patient was then transferred to Allegheny General Hospital for suspected coagulopathy.

Investigations

On arrival to Allegheny General Hospital, a repeat workup for the patients anemia was completed. Initial lab values were as listed in Table 1.

Table 1: Initial laboratory workup on presentation at outside hospital and on admission to Allegheny General Hospital.

	Lab Values at Outside Hospital	**Lab Value at Allegheny General Hospital**	**Normal Range**
WBC	15.7 k/mcl ↑	14.72 k/mcl ↑	4.4-11.30 k/mcl
Hemoglobin	5.3 g/dL ↓	8.5 g/dL ↓	12.3-15.3 g/dL
Hematocrit	16.0 % ↓	25.3 % ↓	36.0-45.0%
MCV	103.5 fL ↑	91.3 fL	80.0-96.0 fL
Platelet Count	220 k/mcl	340 k/mcl	145-445 k/mcl
Reticulocyte Count	----	0.097 m/mcl	0.020-0.140 m/mcl
Haptoglobin	----	<10 mg/dL	16-200 mg/dL
Lactate Dehydrogenase	Within normal limits per documentation	382 U/L	110-215 U/L
Prothrombin time (PT)	10.3 s	13.5 s	11.8-14.3 s

Partial Thromboplastin Time (PTT)	49 s ↑	78 s ↑	23-34 s
International Normalized Ratio (INR)	1.0	1.1	0.9-1.1
B12	235 pg/mL	1359 pg/mL ↑	232-1245 pg/mL
Folate	8.5 ng/mL	10.5 ng/mL	>4.7 mg/mL
Total Bilirubin	0.9 mg/dL	0.9 mg/dL	0-1.2 mg/dL
Direct Bilirubin	----	0.2 mg/dL	0-0.3 mg/dL
AST	16 U/L	11 U/L	0-32 U/L
ALT	13 U/L	11 U/L	0-33 U/L

The cause of this patient's normocytic anemia likely was secondary to patient's acute blood loss anemia given ongoing hematuria and recent gastrointestinal bleed. She required one unit of packed red blood cells on admission to our hospital. Additionally, any nutritional deficiencies were excluded as seen in Table 1. Direct Coombs test was negative given hemolysis and transthoracic echo showed a calcified aortic valve with mild aortic stenosis. Repeat coagulation panel revealed an elevated PTT of 78s as seen in Table 1 and a mixing study showed incomplete correction to 51.3s.

The findings of an elevated aPTT with a normal PT prompted a few initial differential diagnoses, including factor deficiency and factor inhibition. The patient's complete hospital and medication records were reviewed and it was found that she had not recently received heparin, eliminating heparin related PTT prolongation as an etiology. The following factor levels listed in Table 2 were all within normal limits.

Table 2: Coagulation Cascade Factor Levels.

Factor	Factor Level	Normal Range
II	0.81 U/mL	0.78-1.23 U/mL
VIII	0.03 U/mL ↓	0.50-1.51 U/mL
IX	1.43 U/mL	0.62-1.47 U/mL
XI	1.03 U/mL	0.78-1.53 U/mL
XII	0.71 U/mL	0.51-1.81 U/mL

The above findings along with partial correction of PTT on mixing study ruled out intrinsic pathway factor deficiencies. The potential causes for incomplete correction of PTT on mixing study include presence of either lupus anticoagulant or factor VIII inhibitor. Therefore, a dilute Russell viper venom test (DRVVT) and hexagonal antibodies were checked to rule out a lupus anticoagulant and both returned negative.

It should be noted that lupus anticoagulant and factor VIII inhibitor can coexist in the same patient [9]. However, lupus anticoagulant often present clinical findings of hypercoagulability rather than bleeding. Finally, along with the patient's factor VIII activity being found to be low at 3%, a factor VIII inhibitor level of 17.5 BU (Normal: <0.5 BU) was detected. In the setting of active bleeding at multiple sites and above lab findings, a diagnosis of acquired hemophilia A was made [4].

Treatment

Acquired hemophilia A is managed with a two-pronged approach that includes use of by passing agents such as factor VIII inhibitor bypassing agent (FEIBA) or recombinant factor 7 or porcine factor 8 to control bleeding and achieve hemostasis along with use of immunosuppression to decrease the factor VIII inhibitor levels. Therefore, the patient was started on IV FEIBA with a loading dose of 75u/kg and then maintenance dose of 50u/kg q6 hours. The patient was also treated with 100mg of PO cyclophosphamide and 1mg/kg of PO prednisone daily for immunosuppression. After a few days of treatment, the patient's hematuria and GI bleeding started to resolve, and the left gluteus medius hematoma remained stable. This was reflected in the lab work with a stable hemoglobin ranging from 9.0-10.0g/dL and a stable aPTT ranging in the 60s. She did require one unit of pRBCs in this interim.

Unfortunately, on day 14 of her hospital course (while patient remained on FEIBA) the patient's hemoglobin suddenly dropped from 10.5g/dL to 7.9g/dL. This time the CT abdomen and pelvis showed an expanding intramuscular hematoma of the left psoas and iliacus muscles with a small amount of hemorrhagic material tracking into the left pelvis. She was promptly started on alternating doses of 7mg of IV recombinant Factor VII and 50u/kg of IV FEIBA every 6hours such that she received one of them every 3hours. She was additionally started on an intravenous infusion of 375mg/m2 of IV Rituximab in place of cyclophosphamide as her Factor VIII activity failed to improve remaining low from 0.03-0.06U/mL and her factor VIII inhibitor remaining persistently elevated at 19.0 BU.

Outcome and follow-up

Despite our efforts, the bleeding continued, and the patient went into hemorrhagic shock with multi-organ failure as seen by her worsening kidney function, liver function and elevated lactic acid.

Table 3: Laboratory values at the end of patient's hospital course.

	Lab Value	**Normal Range**
BUN	68 mg/dL	8-23 mg/dL
Creatinine	2.94 mg/dL	0.50-0.90 mg/dL
AST	368 U/L	0-32 U/L
ALT	335 U/L	0-33 U/L
Lactic acid	7.1 mmol/L	0.5-2.0 mmol/L

After goals of care discussions with the family, and further discussion of the patient's clinical status, the patient was converted to comfort measures only. Shortly thereafter, the patient passed away with the family at bedside.

Discussion

Here, we present a case of acquired hemophilia A (AHA), a rare bleeding disorder caused by production of autoantibodies to factor VIII in an individual with no personal or family history of bleeding disorders or autoimmune disease. The age distribution of acquired hemophilia is biphasic, with a small peak in women in the immediate postpartum period, followed by the majority of cases occurring in elderly patients. In two major prospective studies in Europe, 80% of diagnoses occurred in patients 65 years or older, with the median age being 74 and 78 in each study, respectively [4,5]. In our patient the age at diagnosis was 78.

Clinically, patients with AHA tend to present with mucosal, GI, or soft tissue hemorrhages, unlike congenital hemophilia A, which often presents with hemarthrosis6. In one study, 70% of patients presented with severe bleeding episodes requiring hemostatic therapy [3]. AHA is commonly a life-threatening bleeding disorder, with a mortality rate of 5-10% of patients. However, the overall mortality rate has been reported to be as high as 43%, with contributing factors to mortality including delayed diagnosis, impact of underlying diseases, and complications of immunosuppressive therapy, including sepsis [3,7]. Our patient presented with left hip pain and was found to have a left gluteus muscle hematoma, gastrointestinal bleeding, and hematuria.

Table 4: Treatment options and indications for patients with acquired hemophilia A and severe bleeding.

Agent	**Medication Category**	**Indication**	**Mechanism of Action**
Factor Eight Inhibitor Bypassing Activity (FEIBA)	Bypass Agent	Patients with severe bleeding despite inhibitor levels	-Development of thrombin -Direct activation of Factor X via activated Factor VII
Recombinant Factor VII	Bypass Agent	Patients with severe bleeding, despite inhibitor levels	-Direct activation of Factor X via activated Factor VII
Recombinant porcine Factor VIII	Factor VIII analog	Patients with severe bleeding that cannot tolerate bypass agents	-Replaces Factor VIII -AHA autoantibodies have low cross reactivity with recombinant porcine factor VIII
Glucocorticoids (prednisone, dexamethasone)	Immunosuppressive	1st line immunosuppressive agent	-Immunosuppression to decrease production of inhibitor -Can be used in combination with cyclophosphamide or Rituximab
Cyclophosphamide	Immunosuppressive	1st line immunosuppressive agent in conjunction with steroids	-Alkylating agent, immunosuppression to decrease production of inhibitor
Rituximab	Immunosuppressive	2nd line immunosuppressive agent	-Anti CD20 monoclonal antibody, immunosuppression to decrease production of inhibitor

Acquired hemophilia A typically involves two different treatment options, each with a specific purpose as shown in Table 4. First, bypassing agents such as FEIBA, recombinant factor VIIa (NOVO7) can be used for hemostasis. Recombinant porcine factor VIII can additionally be used as a Factor VII mimic. FEIBA contains both prothrombin and factor X to help develop thrombin. NOVO7 and FEIBA both include activated factor VIIa which directly activates factor X. Both agents work together, by working on different portions of the coagulation cascade to eliminate the need for factor VIII or bypassing Factor VIII. Secondly, Factor VIII inhibitor production can also be decreased with immunosuppression using steroids and cyclophosphamide. For patients with life threatening bleeding who do not respond to initial factor replacement, plasmapheresis can be considered [8-10].

Rituximab can be used as a second-line therapy in addition to steroids. Recent prospective studies however show that Rituximab monotherapy is as effective as a combination of Rituximab and other immunosuppressive agents in order to reach inhibitor levels <0.5 BU [11]. Other treatment options that have previously been used include Desmopressin (DDAVP) and human Factor VIII concentrates. These agents are only recommended if no bypassing agents are available [8].

Our patient received appropriate therapy with FEIBA 50u/kg q6 hrs, cyclophosphamide 100mg daily, and prednisone 1mg/kg daily, which resolved hematuria and GI bleeding. However, progressive soft tissue bleeding and lack of improvement in factor VIII activity required the addition of rituximab and rFVIIa. Unfortunately, the patient quickly progressed to hemorrhagic shock and multi-organ failure. The patient was converted to comfort measures only based on the family's understanding of the patient's wishes prior to her acute decompensation and ultimately, the patient did not survive.

Conclusion

This case presentation seeks to increase awareness of acquired hemophilia A as a cause of severe bleeding in elderly patients and to demonstrate high mortality rate associated with disease. Acquired hemophilia must be a part of the differential in patients who present with bleeding in the setting of an elevated aPTT and normal PT with no other cause of derangements. Prompt treatment with a variation of hemostatic therapy and immunosuppression should be considered once hemophilia is diagnosed.

Authors Contributions

Shivani Shah: Conceptualization, writing original manuscript and Editing/reviewing manuscript.

Ryan Sweeney: Conceptualization and Writing original manuscript.

Maitreyee Rai: Conceptualization, Editing/reviewing manuscript.

Deep Shah: Conceptualization, Editing/reviewing manuscript.

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