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Case Report

Bruised and Bleeding: A Case Report of Acquired Hemophilia A

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INTRODUCTION

Acquired hemophilia A (AHA), also known as acquired factor VIII deficiency, is a rare bleeding disorder with an incidence of up to eight cases per million per year, based on data from European and Canadian populations.[1-3] It results from the development of autoantibodies against factor VIII,[4-6] leading to spontaneous bleeding, most commonly in the skin, muscles, soft tissue, or mucous membranes.[6] Unlike inherited hemophilia, AHA occurs in individuals without a personal or family history of bleeding disorders. Approximately 50% of cases are idiopathic, while the remaining cases are associated with underlying autoimmune conditions, pregnancy, medications, or malignancy.[7]

AHA predominantly affects the elderly, with incidence increasing with age and a median onset in the mid-to-late 70s.[2,3,8] Here, we report the case of an elderly male diagnosed with AHA. He presented with a right thigh hematoma and severe anemia (hemoglobin 3.9 g/dL) following a fall at home three weeks prior. Due to the rarity of AHA, this factor VIII deficiency disorder was not initially considered in the differential diagnosis for adult anemia, leading to a delayed diagnosis and treatment.[1,7]

CASE REPORT

An 82-year-old male was brought to the emergency department from his assisted living facility with a one-week history of fatigue and pallor. On admission, his hemoglobin was critically low at 3.9 g/dL, and he had a healing right lower flank bruise from a fall three weeks prior. His vital signs were stable, and initial labs showed thrombocytosis (platelets 586,000/uL) and an elevated reticulocyte count (13.9%). Lactate dehydrogenase was slightly elevated (333 U/L, reference: 81-234 U/L), but haptoglobin, total bilirubin, and direct/indirect antiglobulin tests were normal. Two units of packed red blood cells (pRBCs) were transfused.

The patient had a history of moderate dementia (type unspecified), depression, Type 2 diabetes, chronic iron-deficiency anemia, degenerative joint disease, chronic obstructive pulmonary disease (from prior tobacco use), and a remote history of surgically resected bladder cancer. No personal or family history of bleeding disorders or prior significant bleeding events were reported. His home medications included donepezil, sertraline, metformin, ferrous sulfate, and ibuprofen. He denied hematochezia, hematuria, hemoptysis, or hematemesis, though staff noted dark stools from iron supplementation.

A computed tomography (CT) scan of the abdomen and pelvis revealed nodular thickening of the urinary bladder, raising suspicion for malignancy. Initial differentials included occult gastrointestinal (GI) bleeding, nutritional deficiency, and hemolytic anemia. Hemolysis was deemed unlikely due to normal bilirubin and antibody levels, and nutritional deficiencies were considered less likely given ongoing iron supplementation and stable weight. Gastroenterology and hematology/oncology were consulted. Esophagogastroduodenoscopy was unremarkable, and colonoscopy was deferred due to poor bowel preparation. The patient received folate, pantoprazole, and a short course of vitamin B12, while iron supplements were temporarily held to monitor for melena. Donepezil and sertraline were continued inpatient.

Despite six pRBC transfusions over four days, the patient was unable to maintain a hemoglobin >7.0 g/dL. By Day 4, frank melena developed, and subcutaneous hematomas appeared in dependent areas (upper and lower back/buttocks). Coagulation studies revealed a significantly prolonged activated partial thromboplastin time (aPTT) of 97 seconds, with normal prothrombin time (PT) and international normalized ratio (INR). Prednisone (1 mg/kg) was initiated.

On Day 6, bleeding diathesis studies confirmed AHA, with severe factor VIII deficiency (<0.5% activity; normal 63-117%) and an FVIII inhibitor titer of 2.4 Bethesda Units (BU). The patient required four additional pRBC transfusions and received recombinant activated factor VII (rFVIIa) from Days 7-9, after which melena resolved and hemoglobin stabilized at 8.5 g/dL. However, over the following days, hemoglobin declined, and subcutaneous hematomas expanded (Figure 1).

By Day 14, another transfusion was required, along with rFVIIa administration on Days 14-15 and intravenous immunoglobulin (IVIG) on Day 15. Hemoglobin initially stabilized at 7.8 g/dL but fell to 6.0 g/dL by Day 18, with melena progressing to significant hematochezia. Despite further transfusions and rFVIIa, the patient succumbed to internal bleeding, severe anemia, and hypovolemic shock on Day 19 (Figure 2).

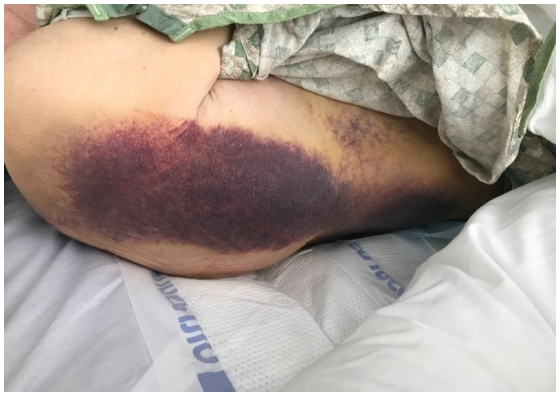

Figure 1. Subcutaneous hematoma on Day 10.

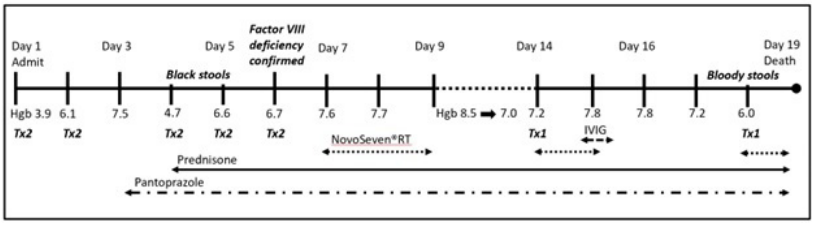

Figure 2. Timeline of key events, including hemoglobin levels, clinical symptoms, and treatments provided to patient during his 19-day hospitalization.
Note: Hgb, hemoglobin (normal range 14.0-18.0 mg/dL); T, Transfusion; NovoSeven® RT, coagulation Factor VIIa, recombinant; IVIG, intravenous immunoglobulin.

DISCUSSION

Over the past few decades, there has been a slight uptick in the incidence rate of AHA secondary to greater awareness of AHA and/or underdiagnosis in previous studies.[1] Nevertheless, the true incidence is likely underestimated since AHA often is not considered on the differential for bleeding in an elderly patient,[6] possibly due to a higher propensity of GI bleeds in this population coupled with the higher likelihood of using non-steroidal anti-inflammatory drugs and anticoagulants. AHA was not included in the initial differential diagnosis in this case. Instead, our initial working diagnosis was lower GI bleed, possibly from a colorectal cancer or diverticular bleed, given patient's age, history of dark stools, no recent colonoscopy per assisted living staff, and history of iron deficiency anemia. As such, gastroenterology was consulted first rather than hematology. This resulted in diagnostic and treatment delays, and ultimately a fatal bleed 19 days after initial presentation despite aggressive treatments.

The hallmark of AHA is an isolated prolongation of aPTT, with normal PT and platelet count in patients with no personal or family history of bleeding disorders.[6] Though our patient met criteria for AHA, the prolonged aPTT was initially overlooked as a lab error. Due to low suspicion for AHA, the aPTT was not initially repeated, subsequently delaying diagnosis and treatment by six days. Delayed diagnosis of AHA is common since clinicians often do not have a high index of suspicion for an acquired bleeding disorder, coupled with misinterpretation of lab results.[9] One retrospective study reported the median time to diagnosis from onset of bleeding was 14 days.[10] Patients on anticoagulation therapy further confound diagnosis and delay treatment.[10] Delayed diagnosis have been associated with poorer treatment outcomes and higher mortality rates.[10,11]

The mainstay of AHA treatment involves immunosuppressive therapy and blood products. Prednisone was started on Day four due to initial concerns for non-immune hemolytic anemia. Recombinant Factor VIIa was started on Day seven following AHA diagnosis. This two-pronged treatment approach served to eradicate autoantibodies and circumvent the neutralized FVIII, thus controlling bleeding. Hemoglobin stabilized within one day of starting recombinant FVIIa; however, by Day 14, rebleeding occurred with a drop in hemoglobin. Bleeding recurrence after initial response to therapy is common: the European Acquired Haemophilia Registry reported bleeding recurrence in 25% of cases, with a median time to bleeding recurrence of 14 days.[11] Our patient was restarted on recombinant FVIIa, as well as treated with IVIG and solumedrol, in addition to ongoing prednisone. His hemoglobin once again stabilized for four days; however, by Day 18, our patient developed melena, transitioning to frank blood and expired hours later.

Despite optimal treatment, fatal bleeding occurs in up to 10% of AHA cases.[2,8,11] Collins and colleagues reported bleeding was the cause of death in 9.1% of cases at a median of 19 days,[2] similar to the timeline of our patient. Eradication of autoantibodies is challenging, and patients may repeatedly bleed during the weeks to months of treatment required to eliminate the autoantibodies.[12] The addition of cyclophosphamide may have improved our patient's outcome since the combination of prednisone and cyclophosphamide has been shown to achieve complete remission with undetectable inhibitor levels more often than with prednisone alone.[13] However, in our case, we suspect an underlying malignancy was driving autoantibody production. Without treating the neoplasm, autoantibody eradication would have been difficult. Our patient had a history of bladder cancer with CT imaging during his admission concerning for bladder cancer recurrence. Unfortunately, he was too critically ill to initiate cancer treatment. Sallah and colleagues found that over 50% of cancer patients with AHA were unable to achieve undetectable factor VIII inhibitor levels despite immunosuppressive treatment and died from bleeding within two months of AHA diagnosis.[9]

Most hemorrhagic deaths associated with AHA occur within the first few weeks after initial presentation as observed with our patient.[4,6,7] Resuming the patient's home sertraline and donepezil may have contributed to our patient's predisposition for ongoing GI bleeding. Selective serotonin reuptake inhibitors (SSRI) use has been associated with increased risk of bleeding, particularly in the GI tract.[14,15] SSRI-related bleeding likely is underreported due to limited awareness among patients and physicians of this increased risk of bleeding.[14] Serotonin is needed for primary platelet activation and aggregation.[15,16] SSRIs reduce storage of serotonin in platelet granules.[15] Diminished serotonin storage in platelets may interfere with platelet aggregation, and subsequent hemostasis.[16] Taken together, continuing home sertraline may have exacerbated bleeding in our patient who already was predisposed to elevated bleeding risk from advanced age and an underlying bleeding disorder. Acetylcholinesterase (AChE) inhibitors, including donepezil, have been implicated in increased risk for bruising and bleeding.[17-20] A recent ex vivo study examining human platelet activation found donepezil inhibited platelet activation, and posited that drugs inhibiting AChE may promote bleeding.[21] It remains unclear if continuing our patient's home donepezil may have contributed to his fatal bleed.

CONCLUSIONS

Important teaching points from this case include the following: AHA should be on the differential when considering an elderly patient with bleeding due to the potential for a life-threatening bleed. Physicians need a high index of suspicion for this acquired bleeding disorder along with careful interpretation of laboratory results. More awareness is needed regarding the increased risk of bleeding with commonly used medications, particularly in patients with an underlying bleeding disorder.

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