Clinical Manifestations of Hemophilia A in a Female Patient

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Introduction

- Hemophilia A (HA) is a rare bleeding disorder in females caused by a deficiency in coagulation factor VIII, a protein necessary for blood clotting. This leads to events of prolonged bleeding that occur spontaneously or by trauma.[1,2]
- Females with clinical and diagnostic manifestations of HA express homozygous or compound heterozygous *F8* mutations. Skewed X inactivation is the most common cause of HA in females.[1,3]
- Of the 18,873 individuals with HA receiving care from specialized hemophilia centers in the United States, only 1,157 were females.[4]
- HA is classified based on Factor VIII activity levels. Those with mild HA have Factor VIII activity levels between 5-40%. Those with moderate HA activity levels are between 1-5%, and severe HA Factor VIII levels are <1%.[5]
- In contrast to their male counterparts, females tend to have milder symptoms that present later in life. Common clinical presentations include hemarthrosis and spontaneous bleeding events in mucosal sites, muscles, and gastrointestinal (GI) tract.[2,4]
- Gynecological complications such as heavy menstrual bleeding, bleeding during pregnancy, post-partum bleeding, and miscarriages may also occur.[2]
- Diagnosis can be made by clotting factor tests. The mainstay of treatment involves the management of bleeding and replenishment of Factor VIII.[5,6]
- Overall, mortality risk is increased in those with hemophilia; therefore, early detection is essential and prophylactic treatment should be initiated.[5,7]

Figure 1. Possible hereditary causes of Hemophilia A[8]

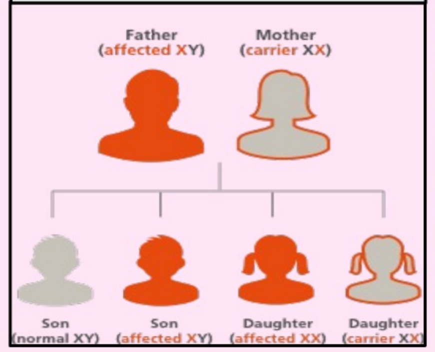
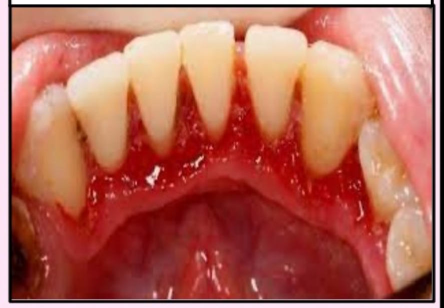


Figure 2. Gingival bleeding[9]



Case Description

History

- Sixty-five-year-old Caucasian female.
- One week history of productive cough, shortness of breath, fatigue, easy bruising, dizziness, weakness, and abdominal pain.
- Spontaneous onset of progressive gingival bleeding the morning of admission.
- Denied use of anticoagulation or antiplatelet medications, recent weight loss, fever, diarrhea, epistaxis, or chest pain .
- Easy bruising since childhood. No history of spontaneous bleeding, recent travel history or sick contacts.
- History significant for tooth extraction in two months prior complicated by eight days of persistent gingival bleeding requiring hospitalization, five transfusions, and administration of desmopressin (DDAVP) and Factor VIII.
- Clinically diagnosed with Hemophilia A with Factor VIII deficiency during previous hospital course but received no assays back.
- Past medical history: COPD, obstructive sleep apnea, hypertension, seizures, stroke, polysubstance use, atrial fibrillation, mitral valve prolapse, pernicious anemia, fibromyalgia, GERD, and depression.
- Past surgical history: hysterectomy and oophorectomy.
- Medications: albuterol 2.5 mg, pantoprazole 40 mg, methadone 105 mg, baclofen 20 mg, phenytoin 300 mg, levetiracetam 1000 mg daily, metoprolol 25 mg, escitalopram 10 mg, and aripiprazole 7 mg.
- Allergies: prochlorperazine, meperidine, and sulfa drugs.
- Family history: 3 maternal male cousins with hemophilia A.
- Social history: 25-year cigarette smoking pack life. Current cigar smoker.
- Review of systems positive for decreased appetite, night sweats, chills, blurry vision, nasal congestion, and muscle pain.

Physical Exam

- Vital signs on admission:
  - Blood Pressure: 165/98 mmHg
  - Pulse: 84 beats per minute
  - Temperature: 37.1°F
  - Respirations: 20 breaths per minute
  - **O2**: 96% (on nasal cannula)
- Patient appears in no acute distress, pleasant, cooperative. Alert and oriented.
- Gross gingival bleeding with dried bloody crusting on and surrounding lips.
- Poor dentition.
- Bleeding surrounding right peripheral IV.
- No ecchymosis, petechiae, or purpura was observed on the skin exam. No hemarthrosis.
- Hyperpigmentation, scaling, 1+ pitting edema noted bilaterally in lower extremities.
- Diffuse wheezing bilaterally with diminished air movement on the pulmonary exam. No use of accessory muscles.
- Remainder of the physical exam was within normal limits.

Table 1. aPTT, Hgb, and platelet levels during hospital course

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
aPTT (secs)	85.5	83.7	84.6	75.7	88.2	94.8
Hgb (g/dL)	11.4	9.6	9.4	8.9	8.3	7.4
Platelet (thous/mm)	164	197	175	190	197	224

Table 2. Clinical Differential Diagnosis

Hemophilia B
Hemophilia C
Acquired Hemophilia disorder
Von Willebrand's disease
Antithrombin III deficiency
Disseminated intravascular coagulation
Vitamin C deficiency (scurvy)
Platelet disorders

Diagnostic Results

- Table 1 outlines patient's hemoglobin (Hgb), platelet count, and activated partial thromboplastin time (aPTT) throughout hospital course.
- PT and INR stayed within normal limits.
- Fibrinogen levels was within normal limit.
- Factor VIII assays were drawn with subsequent Factor VIII administration; however, as a send out lab, results were not finalized during the first hospital admission course.

Hospital Course

- During ED admission, the patient received DDAVP and was brought to the medical floor.
- Patient continued to experience gingival bleeding at no other bleeding sites but the oral cavity. No ecchymosis, petechiae, or purpura were noted.
- Persistent symptoms of fatigue, weakness, nausea, and vomiting throughout stay.
- Patient was treated with DDAVP, Factor VIII, tranexamic acid, and thrombin solution.

Patient Outcome

- After a hospital admission of one week, the patient was transported to a tertiary hospital for management of care. Length of stay at subsequent hospital is unknown.
- Patient's treatment plan continued with DDAVP, Factor VIII, tranexamic acid, and thrombin solution.
- Factor VIII activity assays were drawn and reported to be <30% at tertiary hospital center. The patient was subsequently diagnosed with Hemophilia A disorder with Factor VIII deficiency.
- Difficulty obtaining hemostasis both at initial hospital and tertiary center led to consideration of a superimposed acquired hemophilia.
- The patient was started on rituximab but mounted an allergic response and monoclonal antibody therapy was discontinued.

Discussion

- Acquired hemophilia occurs when autoantibodies develop against coagulation factors.[10,11]
- Acquired hemophilia is idiopathic in 50% of cases, but can be caused by autoimmune diseases, malignancy, pregnancy, dermatologic issues, and drug administration.[11]
- It is important to keep in mind that a congenital hemophilia disorder can be superimposed with an acquired hemophilia, which may complicate treatment and require advanced management.[12,13]
- Mixing tests are essential for confirmation between deficiency vs autoimmune derived hemophilias. aPTT will not correct in those with autoantibodies against these factors.[10,11]
- First line treatment of those acutely bleeding is use of by-passing agents such as Factor VIIa and activated prothrombin complex concentrate. Replenishment of coagulation factors can also help in events of acute bleeding. Maintenance therapy includes immunomodulator therapy.[10,11,13]

Conclusion

- Though uncommon, hemophilia A can still manifest in females.
- HA should be considered in the differential diagnosis of a female presenting with prolonged or spontaneous bleeding. A major risk factor for HA includes those with a significant family history.
- Important diagnostic tools include CBC, coagulation tests, and activity levels assays with antibodies to determine level of deficiency and subsequent treatment protocol.
- In those with a complicated course, consideration of acquired hemophilia may be necessary and treatment should be augmented with immunosuppressant therapy and by-passing agents.

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