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 homogenous or compound heterozygous FVIII mutations. Skewed X inactivation is the most common cause of HA in females.2

Of the 18,873 individuals with HA receiving care from specialized hemophilia centers in the United States, only 1,127 were females.2

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%.2

In contrast to their male counterparts, females tend to have milder symptoms that present later in life. Common clinical presentations include hemorrhagic and spontaneous bleeding events in mucosal sites, muscles, and gastrointestinal (GI) tract.3,4

Osteochondral complications such as heavy menstrual bleeding, bleeding during pregnancy, post-partum bleeding, and miscarriages may also occur.5,6

Diagnosis can be made by clotting factor tests. The necessity of treatment involves the management of bleeding and replacement of Factor VIII.5

Overall, mortality risk is increased in those with hemophilia, therefore, early detection is essential and prophylactic treatment should be initiated.5,7

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 antiplatelet or anticoagulant 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, fine 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 assay results.

Physical Exam

- Vital signs on admission:
  - Blood Pressure: 165/98 mmHg
  - Pulse: 98 beats per minute
  - Temperature: 37.1°C
  - Respirations: 20 breaths per minute
- O2 99% on nasal cannula
- Patient appears in no acute distress, pleasant, cooperative. Alert and oriented.
- Gross gingival bleeding with blood oozing onto and surrounding teeth.
- Poor dentition.
- Bleeding surrounding right peripheral IV.
- No ecchymoses, petechiae, or purpura was observed on the skin exam. No hematomas.
- Hypertension, scaling, 1+ pitting edema noted bilaterally in lower extremities.
- Diffuse scaling with bilateral 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

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT (sec)</td>
<td>85.5</td>
<td>83.7</td>
<td>84.6</td>
<td>75.7</td>
<td>88.2</td>
</tr>
<tr>
<td>Hgb (g/dL)</td>
<td>11.4</td>
<td>9.6</td>
<td>9.4</td>
<td>8.9</td>
<td>8.3</td>
</tr>
<tr>
<td>Platelet (thousands)</td>
<td>164</td>
<td>197</td>
<td>175</td>
<td>190</td>
<td>197</td>
</tr>
</tbody>
</table>

Table 2. Clinical Differential Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Hemophilia A</td>
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<tr>
<td>Hemophilia C</td>
</tr>
<tr>
<td>Acquired Hemophilia disorder</td>
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<tr>
<td>Von Willebrand’s disease</td>
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<tr>
<td>Antithrombin III deficiency</td>
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<tr>
<td>Decreased intravascular viscosity</td>
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<tr>
<td>Vitamin C deficiency (anaemia)</td>
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<tr>
<td>Factor disorders</td>
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</tbody>
</table>

Table 3. Clinical Differential Diagnosis

| 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. |
| 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 ecchymoses, 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 desmopressin 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.
- Difficultly obtaining hemostatic b party at initial hospital and tertiary center led to consideration of a superﬁned acquired hemophilia.
- The patient was started on rituximab but maintained an allergic response and monoclonal antibody therapy was discontinued.

Discussion

- Acquired hemophilia occurs when autoantibodies develop against coagulation factors.8-10
- Acquired hemophilia is idiopathic in 50% of cases, but can be caused by autoimmune diseases, malignancy, pregnancy, dermatologic issues, and drug administration.8-10
- 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.11,12
- Mixing tests are essential for differentiation between deficiency vs autoimmune derived hemophilia. aPTT will not correct in those with autoantibodies against these factors.11,12
- First line treatment of those actively bleeding is use of by-passing agents such as Factor VIII and activated prothrombin complex concentrate. Replenishment of coagulation factors can also help in events of acute bleeding. Maintenance therapy includes immunomodulatory therapies.11,12

Conclusion

- Though uncommon, hemophilia A can still manifest in females.
- IA should be considered in the differential diagnoses of a female presenting with prolonged or spontaneous bleeding. A major risk factor for IA 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 immunosuppressive therapy and by-passing agents.

References