Acute Acquired Hemophilia A Following Snake Bite: A Case Report and Clinical Insights

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Patient: Male, 51-year-old
Final Diagnosis: Acute acquired hemophilia A
Symptoms: Bruising • pain
Clinical Procedure: — Specialty: Hematology

Objective: Rare disease
Background: Coagulopathies can manifest on a spectrum, from minor mucosal bleeding to life-threatening hemorrhage. Minor cases can be discovered in the setting of known risk factors, such as malignancy, old age, immunosuppression. However, acquired hemophilia A diagnosed after a snake bite is of lesser-known incidence and can present in a more acute, potentially life- or limb-threatening fashion. To properly diagnose this coagulopathy, one must be familiar with the related signs, symptoms, and laboratory findings so that swift diagnosis can follow. Diagnosis is key for early proper management, as displayed in the following case.

Case Report: Our case report details a male patient presenting with diffuse bruising after a snake bite. Initially, on presentation to outside facilities, the diagnosis of acquired hemophilia A was not found. However, upon worsening of bruising in the setting of previous treatments initiated for the patient, he presented to our facility, where he subsequently received a diagnosis with acquired hemophilia A. He developed compartment syndrome due to excessive bleeding, requiring surgical intervention. With proper diagnosis, his bleeding diathesis was corrected with multiple rounds of repletion of factors and immunosuppression. His follow-up laboratory test results and examinations have shown continued resolution of his symptoms.

Conclusions: As acquired hemophilia A is less often linked with snake bites, this case highlights the importance of considering this disease process as a differential in patients with bleeding diathesis after a snake bite. The coagulation dysfunction can be severe, and, as such, early identification of this diagnosis leads to more targeted and effective therapy.

Keywords: Blood • Hemophilia A • Snake Bites

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Introduction

Acquired hemophilia A is a coagulation disorder often seen in patients with autoimmune conditions, old age, or pregnancy [1]. Factor VIII (FVIII) is one of the clotting factors found in the intrinsic pathway of the coagulation cascade. When levels are deficient and/or the function of FVIII is diminished, usually due to inhibition by autoantibodies in the case of hemophilia A, risk of bleeding increases [1]. In acquired hemophilia A, inhibitor levels are usually elevated, with FVIII activity being low [1]. Diagnosis is often delayed and occurs after developing mucocutaneous bleeding, without a known history of bleeding disorders. There is also a well-documented association with defects in coagulation induced by snake bites; however, acquired hemophilia after a snake bite has been reported in very few case reports.

Case Report

A 50-year-old man with a past medical history of type 2 diabetes mellitus and hypertension presented with bruising in bilateral arms and left thigh, with progressive worsening for the preceding 3 weeks. The patient was working in his yard, 3 weeks prior to the presentation, when he was presumably bitten by a snake (of unknown species and descriptive characteristics), resulting in 2 punctate lesions on his left forearm. Subsequently, he developed left forearm bruising and skin sloughing. The bruising progressed to include the left lower extremity and groin and right forearm. He presented to an urgent care facility because of the progressive bruising and received steroids for a suspected allergic reaction. His case was evaluated by Poison Control (a statewide service available via telephone and staffed by healthcare professionals who provide advice on possible or known toxin exposures), who recommended no antivenom. His right forearm pain progressively worsened, prompting his presentation to our hospital.

Physical examination was significant for ecchymosis of the left arm, right arm, and medial and posterior left thigh and leg (Figures 1-4). Laboratory workup was significant for hemoglobin/hematocrit of 7.3/24.1 (g/mL), platelet count of 607 K/μL, reticulocyte level of 6.3%, immature reticulocyte fraction of 40%, prothrombin time/international normalized ratio (INR) of 13.3 s/1.14, prolonged activated partial thromboplastin time (aPTT) of 75.7, fibrinogen level of 543 mg/dL, D-dimer level of 3753 mg/mL, sodium level of 132 mmol/L, blood urea nitrogen/creatinine of 23/1.30 mg/dL creatinine kinase level of 688 U/L, and a mixing study which did not correct, indicative of an inhibitor. Factor activity assays showed 0% FVIII level and FVIII inhibitor level of 34 Bethesda units (BU). Laboratory test results indicated acquired hemophilia A. Rheumatoid factor and antinuclear antibody tests were negative, making an autoimmune etiology less likely.

In the setting of progressive ecchymosis and pain, there was concern for compartment syndrome. Computed tomography (CT) of the right forearm showed hematoma, concerning for necrotizing fasciitis. CT of the abdomen and pelvis showed left retroperitoneal and intramuscular hematomas. It did not show any masses or lymph node enlargement concerning for malignancy.

The patient underwent an emergent fasciotomy of the right upper extremity for compartment syndrome (Figure 5). Throughout the course of his hospital stay, he required 30 units of 7000
mcg of Novoseven (r-FVIIa), 22 units of packed red blood cells, 9 units of fresh frozen plasma, 3 units of cryoprecipitate, as well as an anti-inhibitor coagulant complex, FVIII inhibitor bypassing agent. Novoseven was administered as a bypassing agent to the inhibited FVIII. He was initiated on prednisone 80 mg and immunosuppression with cyclophosphamide 150 mg for inhibitor eradication.

Due to persistently low FVIII levels and elevated FVIII inhibitor titers, the patient received 2 cycles of rituximab 700 mg weekly. Hemostasis was achieved on day 11 of hospitalization (on day of initiation of rituximab), as well as up-trending of FVIII activity, down-trending inhibitor levels, and stabilization of aPTT and hemoglobin (Table 1).

The patient has been following up in the hematology clinic. He did continue to receive prednisone as well as cycles of rituximab.

<table>
<thead>
<tr>
<th>Date</th>
<th>Factor VIII activity (%)</th>
<th>Factor VIII inhibitor (BU)</th>
<th>aPTT (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital day 7</td>
<td>10</td>
<td>32</td>
<td>49.9</td>
</tr>
<tr>
<td>Hospital day 20</td>
<td>2</td>
<td>19</td>
<td>47.7</td>
</tr>
<tr>
<td>Day 10 after hospitalization</td>
<td>4</td>
<td>12</td>
<td>68.6</td>
</tr>
<tr>
<td>1 Month after hospitalization</td>
<td>2</td>
<td>33</td>
<td>40.8</td>
</tr>
<tr>
<td>2 Months after hospitalization</td>
<td>38</td>
<td>0</td>
<td>40.1</td>
</tr>
<tr>
<td>3 Months after hospitalization</td>
<td>38</td>
<td>1</td>
<td>42.8</td>
</tr>
<tr>
<td>15 Months after hospitalization</td>
<td>62</td>
<td>5</td>
<td>45.8</td>
</tr>
<tr>
<td>16 Months after hospitalization</td>
<td>68</td>
<td>0</td>
<td>40.1</td>
</tr>
<tr>
<td>18 Months after hospitalization</td>
<td>132</td>
<td>0</td>
<td>31.9</td>
</tr>
</tbody>
</table>

The table follows the improvement/resolution of patient’s coagulopathy via trending his factor VIII activity (measured in%), factor VIII inhibitor level (measured in Bethesda units [BU]) and aPTT, during his hospital stay and post-discharge follow-up.
Cytoxan and rituximab after discharge. He has completed 7 weeks of cyclophosphamide 150 mg, 2 additional cycles of rituximab 700 mg weekly, and a prednisone taper, with no recurrence of symptoms. Inhibitor levels remained at 0% approximately 5 months after discharge and have remained as such at the time of writing this article. The patient’s FVIII and inhibitor levels are being monitored every 3 months, and the inhibitor has been undetectable for over 12 months, without any additional treatment.

Discussion

The pathogenesis of acquired hemophilia A is autoimmune in nature, with the culprit being an autoantibody, usually IgG, against FVIII [2]. This condition is defined by the presence of an inhibitor against the cofactor FVIII, which links the intrinsic pathway to thrombin formation [1]. Accordingly, a percentage of these cases are associated with autoimmune disorders, such as rheumatoid arthritis and systemic lupus [2]. However, there are cases associated with times of decreased immunity, such as pregnancy, malignancy, and older age. Even still, 50% of cases are idiopathic in nature [2]. Many of these cases are diagnosed later in the course of illness. Our association of interest is acquired hemophilia A after snake bites, of which the proposed mechanisms are further elucidated below.

Procoagulant toxins are responsible for the defects in coagulation observed in snake bites. Venom-induced consumption coagulopathy can precipitate hemorrhage, even in response to minor trauma [3]. Prothrombin activators, serine proteases, can be implicated in the consumptive coagulopathy, which can develop in the setting of a snake bite [3]. Envenomation via snake bite has varied effects on coagulation, depending on the type of snake. Copperhead snake bites, the most common type in the United States, have not been associated with significant defects in coagulopathy, they are however native to the southeastern United States, with our patient’s case occurring in this region [4]. Tiger snake bites, conversely, have not been previously published in whole or in part. Tiger snakebites. Ann Emerg Med. 2015;65(4):404-9

Achievement of hemostasis and eradication of the inhibitor via immunosuppression are the main tenets of treatment. Hemostasis is ideally achieved through bypassing agents, such as activated partial cryoprecipitate complex or recombinant factor VII, recombinant porcine FVIII, and human FVIII, the latter being the least favorable [1]. Therapy for suppression of the inhibitor is based on FVIII activity (FVIII: C) and inhibitor titers. If FVIII: C is less than 1% or inhibitor titers are greater than 20 BU, a combination with glucocorticoids and cyclophosphamide or rituximab, with addition of the other agent in 4 weeks if levels remain low, are the suggested treatment options [1]. Alternatively, if FVIII: C is greater than or equal to 1% and inhibitor titers are less than 20 BU, monotherapy with glucocorticoids can be initiated, with addition of one of the above agents after a 4-week trial if the patient is not responding [1]. Acquired hemophilia A can carry a high morbidity due to bleeding complications or adverse effects of treatment. However, more than 70% of patients treated with immunosuppression achieve complete remission during their first round of treatment [2].

Conclusions

Our case report elucidates a rare presentation of acquired hemophilia A after a snake bite. Acquired hemophilia A was diagnosed after 4 weeks of progressively worsening bleeding that caused necrotizing fasciitis. High clinical suspicion of acquired hemophilia A after a snake bite is essential for prompt diagnosis, management, and prevention of life-threatening complications.

Declaration of Figures’ Authenticity

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References: