CASE REPORT

Atypical Hemolytic Uremic Syndrome in a Patient With *Bothrops asper* Envenomation

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Bothrops asper envenomation is common in Colombia and is characterized by local tissue injury and venom-induced consumption coagulopathy (VICC). Rarely, thrombotic microangiopathy is associated with envenomation by this species. The case of a 57-y-old man with *B asper* bite and envenomation on the left foot is presented. The patient was admitted 8 h after the event and progressively developed edema, hemorrhage at the site of the bite, and hemorrhagic blisters. His coagulation test results (prothrombin and partial thromboplastin times) were prolonged, and his fibrinogen levels were severely reduced. The diagnosis of VICC was made. Administration of Colombian polyvalent viper antivenom controlled the VICC within a few hours. Subsequently, the patient developed severe microangiopathic anemia, thrombocytopenia, and acute kidney injury. A diagnosis of thrombotic microangiopathy was made, and the patient met the criteria for hemolytic uremic syndrome. Management with hemodialysis in addition to therapeutic plasma exchange and replacement with fresh frozen plasma was indicated. The patient's condition resolved 14 d later. To the best of our knowledge, this is the first case of *B asper* envenomation in which the patient presented with hemolytic uremic syndrome after VICC. A proposal is made regarding the pathogenesis of this chain of events.

Keywords: snakebite, coagulopathy, thrombotic microangiopathy, acute kidney injury

Introduction

Acute kidney injury (AKI) occurs in approximately 5% of cases of envenomation by snakes of the genus *Bothrops* in Colombia.^{1–3} In other areas of the world, such as Asia, AKI can occur in up to 29% of patients after snakebite, and *Echis carinatus*, *Daboia russellii*, *Cryptelytrops* spp, *Trimeresurus* spp, *Protobothrops* spp, *Hypnale hypnale*, and *Hydrophinae* spp are the most frequently involved in this complication.⁴ AKI is mainly related to myotoxic or hemotoxic effects in addition to hypotension.^{5–7} Acute tubular necrosis is the most common cause of AKI (80%), followed by interstitial nephritis (15%) and, more rarely, thrombotic microangiopathy (TMA) (approximately 5% of cases).^{8,9} The species involved in the development of TMA are *Hypnale hypnale*,^{10–13} *Pseudonaja* spp,¹⁴ *Notechis scutatus*,¹⁵ *Daboia russellii*,^{16,17} *Bothrops*

jararaca,^{18,19} *Echis coloratus*,^{20,21} *Bothrops erythromelas*,²² and *Bothrops lanceolatus*.²³ Some cases of TMA may progress to renal cortical necrosis.²⁴

The triad of AKI, thrombocytopenia, and hemolytic anemia with fragmented erythrocytes (schistocytes) is the essential criterion for the diagnosis of hemolytic uremic syndrome (HUS) and has been maintained since HUS was first described.^{25,26} HUS is extremely rare and has only been reported in isolated cases or in a small series of cases of envenomation by *Daboia russellii*,²⁷ *Oxyuranus scutellatus*,²⁸ and *Hypnale hypnale*.²⁹

Neither TMA in general nor HUS in particular has been reported in association with *Bothrops asper* envenomation. The present case study is the first published description of this condition.

Case Report

A 57-y-old male military professional, while on the banks of the Anchicayá River in the Colombian Pacific region (southwestern Colombia), was bitten on his left foot by an adult *B asper*. The species was identified by a ranger.

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Figure 1. *Bothrops asper* (Garman, 1884), “Terciopelo.” Local name in Colombia: “Taya equis.” It is a species of venomous snake of the Viperidae family with a wide distribution in southwestern Colombia. *B. asper* causes the highest number of snake envenomations in Colombia. Its venom is proteolytic, histiolytic, vasculopathic, cardiotoxic, nephrotoxic, and coagulopathic.

The snake was approximately 1.5 m in length; it was collected from the ground and relocated to the surrounding area. *B. asper* is endemic to the area and is widely known as “Taya X” (Figure 1).³ The patient was transferred to our hospital, where he was admitted 8 h after the event. He had history of mild arterial hypertension and was receiving chronic management with hydrochlorothiazide and losartan.

On admission, the patient was in apparent good condition, with blood pressure of 135/82 mm Hg and heart rate of 78 beats·min⁻¹. His head, neck, and sensory organs were normal, with normal cardiopulmonary, abdominal, and neurologic examination. Extremities were normal, except the dorsum of the left foot, where there was a puncture wound corresponding to a bite with a fang, with active bleeding and the development of an adjacent hemorrhagic blister 1 cm in diameter; moderate edema was also observed (Figure 2).

Admission laboratory examination results showed creatinine at 2.28 mg·dL⁻¹ (normal 0.67–1.17), blood urea nitrogen (BUN) at 40 mg·dL⁻¹ (normal 6–20), hemoglobin at 16.5 g·dL⁻¹ (normal 13.7–17.5), and platelets at 225,000 μ L (normal 163,000–337,000). Leukocytes were 8940/mm³ (normal 4230–9070) with 6600/mm³ neutrophils (normal 1780–5380), 1840/mm³ lymphocytes (normal 1320–3570), 400/mm³ monocytes (normal 300–820), and 100/mm³ eosinophils (normal 40–540). A noncoagulating prothrombin time (PT) and thromboplastin time (TPT), undetectable fibrinogen levels, and D-dimer concentration of 3.5 μ g·dL⁻¹ (normal <0.50) led to the diagnosis of venom-induced consumption coagulopathy (VICC).

A total of 15 vials of polyvalent antivenom was required; the initial dose was 8 vials, according to the recommendations given by national guidelines, depending on the classification of the envenomation,³⁰ and subsequent doses were added every 6 h until the patient’s coagulation tests were normalized. At 6 h, 3 vials were used (PT: noncoagulating, TPT: noncoagulating, fibrinogen: 50 mg·dL⁻¹); 12 h later, 2 vials (PT: 30 s, TPT: 60 s, fibrinogen: 150 mg·dL⁻¹), and 18 h later, 2 vials (PT: 14, TPT: 34, fibrinogen: 175 mg·dL⁻¹). Each vial of polyvalent antivenom (Laboratorios Probiol, Bogotá, Colombia) contains 10 mL of equine polyvalent antivenom, which neutralizes at least 25, 10, and 5 mg of the venom of *B. atrox/asper*, *Crotalus durissus*, and *Lachesis muta*, respectively. The VICC was controlled by 18 h.

Forty-eight hours after admission, the patient presented with oliguria. He was pale and jaundiced. Erythema and increased local heat began to be observed on the back of the left foot. Given suspicion of the onset of an infectious process, piperacillin-tazobactam at a dose adjusted to his kidney function was initiated. Magnetic resonance imaging of the left foot was performed

Figure 2. Punctate wound corresponding to a bite with a fang on the dorsum of the left foot, with evidence of bleeding and the development of an adjacent hemorrhagic blister 1 cm in diameter; moderate edema was also observed.

Figure 3. The possible sequence of events that occurred in our patient. Treatment actions are indicated by horizontal line. Typical venom-induced consumption coagulopathy (VICC) developed due to the effect of various proteins that activate clotting factors. He improved with the application of antivenom. The patient then developed thrombotic microangiopathy (TMA), probably as a consequence of a defect in the regulation of complement that could be activated by the effects of endothelial damage caused by other protein elements of the venom, the presence of an infection, and the use of antivenom. TMA with the presence of clinical and laboratory elements consistent with hemolytic uremic syndrome (TMA/HUS) was successfully controlled with hemodialysis and therapeutic plasma exchange (TPE) with fresh frozen plasma.

and showed considerable soft tissue edema without evidence of fluid collection. There was a decrease in hemoglobin to $10 \text{ g}\cdot\text{dL}^{-1}$. Lactate dehydrogenase (LDH) was $1100 \text{ U}\cdot\text{L}^{-1}$ (normal $135\text{--}225$), haptoglobin was undetectable, and indirect bilirubin was $17 \text{ mg}\cdot\text{dL}^{-1}$ (normal $0.3\text{--}1.9$). These findings are diagnostic of hemolytic anemia. Peripheral blood smears showed schistocytes, a decrease in platelets to $9000 \mu\text{L}$, BUN $78 \text{ mg}\cdot\text{dL}^{-1}$ (normal $7\text{--}20$), creatinine $5.8 \text{ mg}\cdot\text{dL}^{-1}$ (normal $0.59\text{--}1.04$), complement component C3 $98 \text{ mg}\cdot\text{dL}^{-1}$ (normal $90\text{--}180$), and C4 $8 \text{ mg}\cdot\text{dL}^{-1}$ (normal $10\text{--}40$). The findings of hemolytic anemia in conjunction with thrombocytopenia and kidney injury are highly suggestive of TMA. Due to hyperkalemia (potassium $5.49 \text{ meq}\cdot\text{L}^{-1}$), acidosis (pH 7.26 and HCO_3^- 17.1), and edema, we decided to start daily hemodialysis and hemofiltration as needed. Given the suspicion of HUS, we decided to start concomitant therapeutic plasma exchange (TPE) with replacement with fresh frozen plasma. The patient

required 4 TPE sessions. The hemolytic anemia was controlled, and his platelet levels gradually increased.

Twenty days after admission, the patient had significant improvement of the left foot injury. He presented with normal urine output and improved laboratory parameters: hemoglobin $9.8 \text{ g}\cdot\text{dL}^{-1}$; leukocytes $4752/\text{mm}^3$, with $2450/\text{mm}^3$ neutrophils, $1250/\text{mm}^3$ lymphocytes, $50/\text{mm}^3$ monocytes, $2/\text{mm}^3$ eosinophils, and $234,000/\text{mm}^3$ platelets; BUN $24 \text{ mg}\cdot\text{dL}^{-1}$; creatinine $1.6 \text{ mg}\cdot\text{dL}^{-1}$; LDH $110 \text{ mg}\cdot\text{dL}^{-1}$; indirect bilirubin $0.9 \text{ mg}\cdot\text{dL}^{-1}$; sodium $139 \text{ meq}\cdot\text{L}^{-1}$; and potassium $4.7 \text{ meq}\cdot\text{L}^{-1}$. Complement components were C3 $102 \text{ mg}\cdot\text{dL}^{-1}$, C4 $14 \text{ mg}\cdot\text{dL}^{-1}$, creatine phosphokinase (CPK) $98 \text{ U}\cdot\text{L}^{-1}$, aspartate aminotransferase (AST) $24 \text{ UI}\cdot\text{L}^{-1}$, and alanine aminotransferase (ALT) $18 \text{ UI}\cdot\text{L}^{-1}$.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This report was approved for publication by the ethics committee of Fundación Valle del Lili.

Discussion

VICC is a coagulopathy that occurs in envenomation by snakes whose venom contains proteases that act by stimulating coagulation factors or simulating their structure and function. Clotting factors are rapidly consumed, clotting times are prolonged, hypofibrinogenemia develops, and D-dimer increases.³¹ In the specific case of snakes of the genus *Bothrops*, prothrombin activators,^{32,33} factor X activators,³⁴ and thrombin-like enzymes³⁵ have been identified. Similar to thrombin, thrombin-like enzymes share the property of the transitioning fibrinogen to fibrin, but they do not activate factor XIII, which is responsible for stabilization of fibrin clotting, and thus lead to VICC. VICC is resolved by the synthesis of new coagulation factors and neutralization of toxins. The main complication is bleeding. VICC differs from disseminated intravascular coagulation in several ways: It does not present with any evidence of systemic microthrombi and end-organ failure³⁶ and has other etiologic, pathophysiological, and prognostic factors.³⁷

Our patient presented with classic VICC with fibrinogen consumption, prolonged coagulation tests with clinical evidence of a bleeding tendency based on bleeding from the bite orifice, and the presence of hemorrhagic blisters. The patient responded adequately when treated with Colombian polyvalent viper antivenom, and his coagulation tests were normalized within a few hours of treatment. After recovery from VICC, the patient presented low urine output with uremia, his platelet levels began to decrease, and severe hemolysis developed, with evidence of schistocytes in the peripheral blood smear. This indicated the presence of TMA in the absence of criteria for thrombotic thrombocytopenic purpura that met the criteria for HUS. Similar cases have been reported that initially presented as VICC and were followed by the development of thrombocytopenia, TMA, and AKI.¹⁴ The predilection toward kidney involvement seems to be characteristic of TMA associated with HUS caused by snake envenomation, a finding that should be differentiated from occasional initial prothrombotic phenomena in the presence of envenomation by vipers, which tends to affect the cerebral arteries, specifically those at the base of the skull.³⁸

In HUS, there is endothelial damage, which in the kidney manifests as thickening of the vascular walls with detachment of the endothelial cells of the glomerular basement membrane and the formation of microthrombi with variable degrees of vessel occlusion, a condition that causes erythrocytes to rupture when passing through this partially occluded microvasculature.³⁹ Two forms of HUS have been described: typical and atypical. The most

frequent (90% of cases) is typical (or classic) HUS, which is associated with a diarrheal syndrome caused by *Escherichia coli* O157:H7, a producer of Shiga toxin, which binds to Gb3 receptors (globotriaosylceramide) on the surface of endothelial cells and causes their lysis directly or through activation of proinflammatory and/or procoagulant mechanisms.⁴⁰ The majority of patients with typical HUS progress satisfactorily; however, approximately 10% progress to chronic kidney disease.⁴¹

In atypical HUS (less than 10% of HUS cases), the disease develops with no relation to infection with *Escherichia coli* O157:H7 and has been associated with mutations of various complement proteins that favor its activation against different stimuli. Some of these mutations associated with atypical HUS are activators, such as those described in factor B⁴² or C3,⁴³ as well as mutations of regulatory proteins such as factor H,^{44,45} factor I,⁴⁶ and MCP (membrane cofactor protein-CD46).^{47,48} This knowledge has led to the development of therapeutic strategies aimed at inhibiting the complement cascade, as in the case of eculizumab, a monoclonal antibody directed against the C5 protein.⁴⁹ Patients with atypical HUS have a less favorable prognosis and more frequently develop chronic kidney failure,⁵⁰ which justifies the use of inhibitory treatment strategies in patients with associated mutations.⁵¹ The etiologic factors that can trigger atypical HUS in a genetically susceptible individual include various viral or bacterial infections, autoimmune disease, the use of oral contraceptives, chemotherapeutic agents, pregnancy, and postpartum status, among others.^{52,53}

In the particular case of snake envenomation leading to the development of atypical HUS, we are not aware of a study of any mutations in the related complement cascade proteins. The outcomes of these patients and the results of different proposed treatments, such as the use of fresh frozen plasma¹⁰ and TPE,⁵⁴ have been reported mainly in observational studies,⁵⁵ such as that of Wijewickrama et al. in a series of 103 patients with *Hypnale* spp envenomation.⁵⁶ A randomized controlled study did not demonstrate the utility of fresh frozen plasma.⁵⁷ There is no experience with the use of eculizumab.

Thus, we present a patient with *B asper* envenomation who developed typical VICC that responded adequately to polyvalent antivenom for Colombian vipers and who, 56 h after the bite and after initiation of established treatment, presented with TMA associated with HUS. By definition, it was atypical HUS, which has a variable etiology, including a genetic predisposition toward unregulated complement activation in response to different events that cause vascular endothelial damage. In this case, there could be a genetic predisposition and an external condition related to the venom components,

including phospholipase A2,⁵⁸ metalloproteinases/disintegrins,^{59,60} and L-amino-acid oxidases,⁶¹ among others. Microorganisms that were inoculated during the bite could also be involved in the development of atypical HUS; less likely is an adverse reaction to the antivenom, which can cause serum sickness, an immune complex-mediated immune reaction that clinically manifests as arthritis, rash, nephritis, and consumption of complement.⁶² Our patient presented a slight decrease in the C3 component of complement, which could be related to its activation in the presence of HUS and/or a slight immune complex-mediated reaction to the use of antivenom. Figure 3 schematically shows the pathogenic events that may be related to the patient's clinical presentation.

VICC in our patient was managed with antivenom, and he had an adequate clinical response. The TMA and HUS were managed with TPE with fresh frozen plasma despite the fact that there is no evidence of a consistent response in this type of case. The disease resolved 3 weeks later. Piperacillin-tazobactam was added to his treatment after suspicion of the onset of a local infection. To the best of our knowledge, this is the first case of *B asper* envenomation in which the patient presented with TMA with manifestations related to HUS after VICC typical of this type of envenomation. Although our patient had an adequate response with fresh frozen plasma and TPE, further studies need to be performed to assess the significance of these treatments in these types of patients.

In 2009, cases of VICC were retrospectively analyzed⁶³ and showed that the use of coagulation factors (fresh frozen plasma and/or cryoprecipitate) after the use of antivenom is associated with earlier improvement of coagulation function. However, it is important to note that there is evidence that the use of fresh frozen plasma did not reduce coagulopathy in Russell's viper envenomation,⁵⁷ and some low-quality studies (especially in animal models)⁶⁴ show that the use of fresh frozen plasma can be deleterious, increasing the presence of thrombotic complications; for this reason, antivenom is the mainstay of the treatment of VICC and should always be administered.

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