CASE REPORT

Airway Compromise After First Rattlesnake Envenomation

Daniel E. Brooks, MD; Kimberlie A. Graeme, MD

From the Department of Medical Toxicology, Good Samaritan Regional Medical Center, Phoenix, AZ. Dr Brooks is now with the Medical Toxicology Service, University of Pittsburgh Medical Center, Pittsburgh, PA. Dr Graeme is now with the Department of Emergency Medicine, Mayo Clinic Hospital, Phoenix, AZ.

The purpose of this report is to describe an unusual presentation of anaphylaxis after first-time rattlesnake envenomation. A patient on a medical toxicology inpatient service is presented who had signs of anaphylaxis, including airway compromise, after first-time rattlesnake envenomation. An epinephrine drip and oral intubation were initiated. This case is unusual in that dermal and gastrointestinal exposure may have been the primary sensitization process that preceded a severe anaphylactic reaction after envenomation. The patient's recovery was prolonged. In conclusion, rattlesnake envenomation may result in rapidly progressive airway compromise, possibly caused by anaphylaxis in patients with previous dermal or gastrointestinal exposure to snake proteins.

Key words: envenomation, snake bite, snake venom, anaphylaxis, toxicology

Introduction

In 1999, 993 rattlesnake bites were reported to the American Association of Poison Control Centers, and others undoubtedly went unreported.¹ That same year, we admitted 52 patients with rattlesnake bites to our tertiary hospital's toxicology service. Generally, patients present with pain, local tissue effects (progressive edema and necrosis), coagulopathy (hypofibrinogenemia and prolongation of prothrombin time), and thrombocytopenia. Rarely, life-threatening complications such as anaphylaxis and airway compromise occur after rattlesnake envenomation.^{2–8} Repeat exposure to snake venom is rarely associated with anaphylaxis or anaphylactoid reactions.^{3,5,9,10} Some fatalities after rattlesnake bites are believed to be caused by anaphylactic reactions, but the contribution of airway compromise is unknown.^{4,6,7}

We report a case of severe anaphylaxis after a first-time rattlesnake bite in a patient with previous, noninvasive exposure to rattlesnakes. The patient experienced life-threatening airway compromise and hypotension, and he was treated with emergent intubation and epi-

nephine. To our knowledge, this is the first reported case of rattlesnake venom-induced anaphylaxis requiring emergent intubation in which there was no simultaneous complicating oral exposure to venom.⁸ This case was also unique in that we suspected that sensitization to rattlesnake proteins may have occurred during previous consumption of rattlesnake meat.

Case Report

A 26-year-old white man was bitten and envenomated in the right hand by what he identified as a sidewinder rattlesnake (*Crotalus cerastes*). He presented to an outlying emergency department within 25 minutes of envenomation. His initial blood pressure was 68/28 mm Hg, and it remained unchanged after a 750-mL bolus of intravenous fluids. Despite aggressive use of intravenous fluids and an epinephrine drip, the patient's systolic blood pressure remained 90 mm Hg or less for 2 hours. He was maintained on the epinephrine drip and was further treated with intravenous steroids and H₁- and H₂-histamine receptor antagonists. Severe upper airway edema developed within 45 minutes of envenomation. Emergent oral endotracheal intubation, which proved difficult because of local edema, was accomplished. The edema was present before the intubation attempts. Adequate oxygenation and ventilation were provided by a

Corresponding author and requests for reprints: Kimberlie A. Graeme, MD, Department of Emergency Medicine, Mayo Clinic Hospital, 5777 East Mayo Blvd, Phoenix, AZ 85054 (e-mail: graeme.kimberlie@mayo.edu).

Figure 1. Patient soon after envenomation. Marked edema of the tongue and submandibular area are noted.

bag-valve mask, with oxygen saturation maintained at more than 90%. Edema had not developed near the envenomation site. No rash or skin changes were noted. The patient had not received any antivenom before the transfer to our facility, and he arrived approximately 4.5 hours after envenomation.

At our facility, the family reported that the patient had not had any previous snake bites but that he often found rattlesnakes at work, which he would capture, decapitate, cook, and consume. The patient had no known medical allergies, asthma, history of atopy, or cardiovascular disease. Our initial evaluation revealed a blood pressure of 107/60 mm Hg and a heart rate of 110 beats/min while the patient was off epinephrine and after he had received 3 L of intravenous fluids. Pulse oximetry revealed an oxygen saturation of 97% on 50% fraction of inspired oxygen. He was afebrile. There was marked edema of the tongue, face, and neck (Figure 1). The lungs were clear to auscultation, with good air exchange and no wheezing. There were 2 puncture wounds on the dorsal aspect of the right hand, consistent with a rattlesnake bite, without ecchymosis, edema, or skin bullae. The remainder of the extremity appeared normal. After the pa-

tient had received vecuronium and benzodiazepine for transport, the neurologic exam was limited. A lateral neck radiograph showed marked soft tissue edema of the neck (Figure 2). Sedation and chemical paralysis were continued for the patient's comfort and to maintain a secure airway.

Laboratory studies at the transferring hospital revealed a WBC count of $6.8 \times 10^9/L$, hemoglobin 15.4 g/dL, hematocrit 0.46, platelet count $289 \times 10^9/L$, prothrombin time of 12.8 seconds (normal, 11.5–13.4 seconds), and fibrinogen 5.06 $\mu\text{mol/L}$ (normal, 4.41–10.29 $\mu\text{mol/L}$). Acidosis (pH 7.1, PCO_2 48 mm Hg, bicarbonate 15.2 mmol/L, and base deficit 14.5 mmol/L) and normal electrolytes and renal function were noted. The initial creatine kinase concentration was 184 U/L (normal, 25–225 U/L), and an ethanol level was noted at 56.2 mmol/L (259 mg/dL). An electrocardiogram revealed no evidence of ischemia or infarction. The troponin I level was $<.3 \mu\text{g/L}$.

Six hours after envenomation, repeat blood work revealed a developing coagulopathy (prothrombin time 15.5 seconds and fibrinogen nadir 1.38 $\mu\text{mol/L}$) without thrombocytopenia. Antivenom was administered be-

Figure 2. Radiograph of soft tissues of the neck. Minimal air pockets are noted anterior to the endotracheal tube above and below the inferiorly displaced epiglottis.

cause of worsening hematologic parameters despite the lack of local tissue effects such as swelling and ecchymosis. Horse serum skin testing was nonreactive, and 20 vials of Crotalidae Polyvalent Antivenin (Wyeth-Ayerst Pharmaceuticals, St Davids, PA) were administered according to our practice, beginning 10 hours after the bite.^{2,11} After antivenom administration, the coagulopathy and defibrination resolved, with normalization of the prothrombin time to 13.3 seconds and of the fibrinogen to 5.32 $\mu\text{mol/L}$ within 24 hours.

At 10 hours after envenomation, the patient had grossly red urine. Urinalysis revealed a large amount of blood by dipstick but only 2 to 5 RBCs per high-power field. While awaiting laboratory differentiation among hemolysis, disseminated intravascular coagulation, and rhabdomyolysis, we administered 8 units of cryoprecipitate and 2 units of fresh-frozen plasma for central-catheter placement. Laboratory results showed no evidence of hemolysis, and hemoglobin, hematocrit, and plasma-free hemoglobin remained stable.

Rhabdomyolysis was suspected, and the urine was alkalized with sodium bicarbonate-containing intravenous fluids at 175 mL/h to reduce the formation of myohemoglobin-Tamm-Horsfall protein complexes as protection against renal failure.¹² Serum creatine kinase peaked at 120 087 U/L. The patient experienced acute renal failure, and hemodialysis was required by hospital day 5.

Of note, 14 hours after envenomation, serum creatine kinase was 23 861 U/L, with a relative MB index of 36.0, suggestive of cardiac injury. The patient's electrocardiogram was unchanged, and an echocardiogram revealed a low-normal ejection fraction of 30% without further abnormalities, which was consistent with stunned myocardium. Repeat echocardiography performed 5 days later was normal. Liver transaminase levels increased early after envenomation, likely because of initial hypotension, with a peak aspartate transaminase level of 3698 U/L (normal, 10–41 U/L) and an alanine aminotransferase level of 742 U/L (normal, 2–55 U/L).

Figure 3. Patient 3 months after envenomation.

on hospital day 2. Transaminases were nearly normal at the time of transfer to a skilled nursing facility on hospital day 13.

Although the patient initially had no local effects of the envenomation, at 72 hours, there was significant edema of the entire right upper extremity. No clinical evidence of compartment syndrome was noted, with compartment pressures ranging from 15 to 20 mm Hg. Marked facial and airway edema persisted, and a tracheostomy was performed.

Nine days after antivenom administration, a rash consistent with serum sickness developed and was treated with intravenous steroids and hydroxyzine. The patient also received intravenous antibiotics for aspiration pneumonia, sinusitis, and sepsis.

On hospital day 13, the patient was transferred to a skilled nursing facility for continued tracheostomy management and hemodialysis. Three months later, he confirmed that he had handled and consumed numerous rattlesnakes but had never been bitten before. The patient's recovery was prolonged. It was associated with recurrent

large bowel enterocutaneous fistulas, sepsis, malnutrition, and significant weight loss (Figure 3).

Discussion

Anaphylaxis after rattlesnake envenomation has been reported several times.²⁻⁷ In one case, apparent anaphylaxis-induced airway compromise required intubation. That case was complicated by oral exposure to venom when the victim made an x-shaped incision through a single fang mark and applied oral suction to the wound.⁸

In a recent review of 289 rattlesnake bite patients treated by a medical toxicology service, 29 patients (10%) reported having been bitten previously.¹³ Venom-induced anaphylaxis was rare, occurring in only 3 patients (1%). For all rattlesnake bite admissions, airway compromise requiring intubation, with or without anaphylaxis, was also rare, occurring in 2 cases (0.7%)—the one presented here and another because of airway swelling from tongue envenomation.

Generally, in previously reported cases of venom-in-

duced anaphylaxis, bronchospasm or a subjective sensation of tightening of the throat without airway compromise was noted. These cases generally resolved with pharmacotherapy and did not require intubation.^{2-7,14} Previously reported fatalities might actually have been due to anaphylaxis and possibly airway compromise, although this is difficult to assess post mortem and is not clearly delineated in the literature.^{4,7}

Although both anaphylaxis and anaphylactoid reactions have been reported after rattlesnake envenomation, we speculate that our patient had anaphylaxis. There is a subtle, mainly pathophysiologic, difference between an anaphylactic and an anaphylactoid reaction, although the clinical presentation and management are identical. Anaphylaxis occurs in patients who have been previously sensitized to an allergen and is independent of dose, whereas anaphylactoid reactions are dose-dependent and do not require previous exposure or sensitization to an allergen.¹⁵ Although it is possible that our patient suffered an anaphylactoid reaction because of a large venom load,⁹ this does not seem likely because the patient did not have the initial local signs of significant envenomation. He initially had no swelling or ecchymosis of the bite site, as is generally seen within hours of significant envenomation.

Recent work has shown evidence that snakebite anaphylaxis may be immunoglobulin (Ig)E mediated, particularly with repeated exposure to venom.¹⁶ We suspect that our patient was sensitized to snake antigens during his handling and consumption of rattlesnakes. He may have become sensitized to airborne venom spray when handling rattlesnakes. This may have resulted in the production of IgE antibodies, which were activated during re-exposure with the rattlesnake bite. Another patient was reported to have allergic symptoms (tearing and periorbital edema) whenever he handled snakes after his second rattlesnake bite; later, when re-envenomed, he experienced true anaphylaxis.⁷ This finding suggests common proteins or cross-reactivity between the venom and antigenic factors present in the meat or on the skin. Alternatively, there may be residual venom proteins on the snakeskin or airborne venom spray to which handlers become exposed. Although speculative, this could explain an anaphylactic reaction seen in our patient after a first-time envenomation. Previous work indicates that dermal exposure to several species of snake proteins results in the formation of IgE and IgG antibodies against the venom of those species.¹⁷ The sensitization to antigens found in various pit viper venoms shows some cross-reactivity; patients bitten by a pit viper of one species may later show hypersensitivity when bitten by a pit viper of another species.⁵

This case is unusual in that handling and eating rat-

tlesnakes may have initiated the primary sensitization process that preceded a severe anaphylactic reaction after first-time rattlesnake envenomation. Interestingly, allergy to honey from honeybees has been associated with sensitization to honeybee venom.¹⁸ Similar, though less severe, cross-reactivity involving egg proteins, feather allergies, and the consumption of chicken meat has been reported.^{19,20}

Our patient also had increased creatine kinase levels. The increased levels may have been due, in part, to tongue swelling and trauma from repeated intubation attempts; however, the markedly increased relative MB index suggested some myocardial involvement, as did the echocardiogram.²¹⁻²³

A limitation of this report is that we failed to challenge the patient with gastrointestinal exposure to rattlesnake meat to see whether an allergic reaction developed. The patient was instructed to avoid all contact with rattlesnakes and to carry an epinephrine kit in case of accidental re-exposure.

Rattlesnake envenomation may result in rapidly progressive airway compromise. We speculate that anaphylaxis in patients with previous dermal or gastrointestinal exposure to snake proteins may occur after first-time rattlesnake envenomation.

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