

Rattlesnake Envenomations

Unusual Case Presentations

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Rattlesnake envenomations are common in some areas of the United States. Although fatal rattlesnake envenomations are rare and usually preventable, morbidity may be significant. Patients may present with localized edema, hypotension, coagulopathy, or thrombocytopenia. Patients with progressive swelling or severe coagulopathy are typically treated with Crotalidae polyvalent antivenin. We present a series of 4 patients with unusual complications of rattlesnake envenomation to illustrate the wide spectrum of disease that may be encountered. These case presentations include anaphylaxis to rattlesnake venom, an acute airway emergency, progressive and marked edema with a large pleural fluid collection, and death. *Arch Intern Med.* 2001;161:474-479

In the United States each year, thousands of persons are bitten by poisonous snakes.^{1,2} Although fatal rattlesnake envenomations are rare and usually preventable, morbidity may be significant.³ Patients envenomated by rattlesnakes experience localized pain and swelling. In addition, hypotension secondary to hypovolemia and coagulopathies manifest as hypofibrinogenemia, prolonged prothrombin time, and thrombocytopenia may develop.¹⁻³ Patients with progressive swelling or coagulopathy are typically treated with Crotalidae polyvalent antivenin (Wyeth Laboratories Inc, Marietta, Pa).

At our tertiary care referral center, we admit approximately 40 to 60 patients per year for rattlesnake envenomation. To illustrate the wide spectrum of disease associated with rattlesnake envenomation, we describe 4 unusual case presentations: anaphylaxis, acute airway emergency, progressive edema complicated by a large pleural fluid collection, and death.

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REPORT OF CASES

CASE 1

A 57-year-old male amateur snake handler presented after *Crotalus atrox* (Western diamondback rattlesnake) envenomation of the right index finger. His history was significant for 5 previous rattlesnake bites. After his second bite, 15 years earlier, he presented with facial, throat, and tongue swelling and a "code arrest" that required aggressive treatment. He received Crotalidae polyvalent antivenin and a fasciotomy with his bite. In the ensuing 10 years, he experienced 3 additional snakebites but did not experience significant symptoms; these were possibly "dry bites," without envenomation. Since his second bite, he often noticed periorbital edema and tearing with prolonged snake handling.

On this admission, he presented with nausea without emesis, diaphoresis, hypotension, and a diffuse urticarial rash over the chest and abdomen. He denied shortness of breath, chest discomfort, or throat swelling. His initial systolic blood pressure was 70 mm Hg, and examination of the chest revealed coarse breath sounds. Treatment with intravenous (IV) fluids, steroids, histamine antagonists, and an IV epinephrine

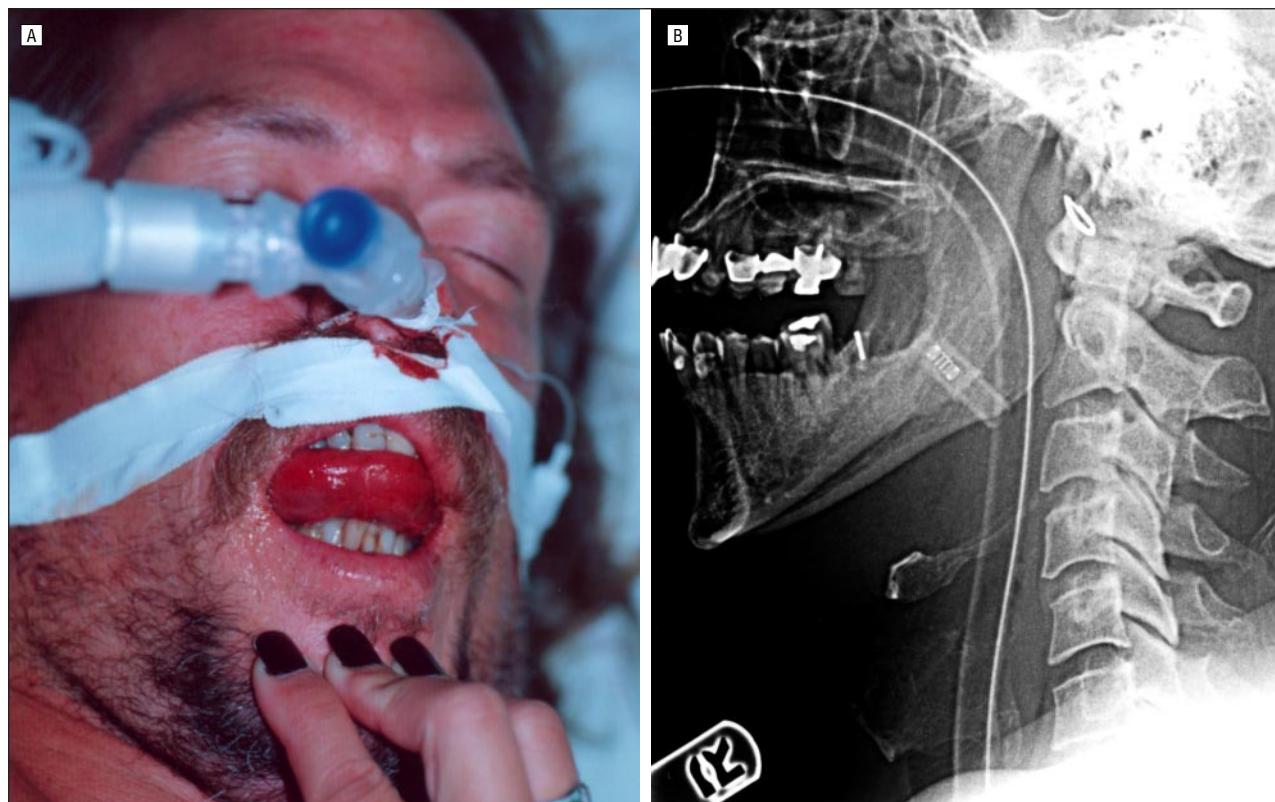


Figure 1. A, Glossal swelling after envenomation to the tongue. B, Radiograph of the lateral aspect of the neck revealing submandibular and paratracheal edema.

drip at 4 $\mu\text{g}/\text{min}$ resulted in an increase in systolic blood pressure to 110 mm Hg and resolution of the rash.

Capillary leak secondary to a severe envenomation may have contributed to his hypotension. Because of the severity of his envenomation, with associated hypotension that required epinephrine, 20 vials of Crotalidae polyvalent antivenin were infused, with coadministration of epinephrine at 4 $\mu\text{g}/\text{min}$, without further complication. He never demonstrated coagulopathy or thrombocytopenia and demonstrated only mild swelling of the hand. He was discharged the following day with a prescription for a steroid taper and hydroxyzine to be initiated at the beginning of serum sickness symptoms. Eight days after treatment, he was readmitted to the hospital for severe serum sickness, with rash, pruritus, throat tightness, and shortness of breath, which resolved with histamine₁ and histamine₂ antagonists, subcutaneous epinephrine, and steroids (methylprednisolone sodium succinate). He did not experience any long-term sequelae on follow-up.

CASE 2

An intoxicated 45-year-old man was bitten on the tongue after placing his pet rattlesnake's head in his mouth, attempting to calm the snake. He complained of immediate pain and swelling to his tongue and arrived in the emergency department within 30 minutes. His history was significant for a previous rattlesnake bite but he had not received antivenin.

Initial vital signs revealed a heart rate of 105/min, blood pressure of 143/92 mm Hg, and respiratory rate of 18/min. Oxygen saturation was 100% on room air. The results of physical examination were remarkable for an enlarged tongue with a "hot potato voice," without evidence of drooling or stridor. Neck was nonedematous. Chest was clear without wheezing. Skin was without rash. Laboratory studies revealed the following values: prothrombin time, 11.6 seconds (reference range, 11.0-13.2 seconds); international normalized ratio, 0.93; plasma fibrinogen concentration, 7.23 $\mu\text{mol}/\text{L}$ (reference range, 5.29-13.2 $\mu\text{mol}/\text{L}$); and plate-

let count of $171 \times 10^9/\text{L}$ (reference range, $130\text{-}450 \times 10^9/\text{L}$). He underwent emergent prophylactic fiberoptic nasotracheal intubation to secure his airway.

In our intensive care unit, 4 hours after envenomation, the patient was sedated, without obvious distress. Vital signs demonstrated a heart rate of 97/min, blood pressure of 158/90 mm Hg, and respiratory rate of 16/min. Oxygen saturation was 100% on 30% fraction of inspired oxygen. The results of physical examination were unremarkable except for a large protruding tongue and submandibular swelling (**Figure 1A**). Laboratory studies revealed the following values: serum ethanol, 26.0 $\mu\text{mol}/\text{L}$; plasma fibrinogen, 6.94 $\mu\text{mol}/\text{L}$; prothrombin time, 13.5 seconds; and international normalized ratio, 1.3. A radiograph of the lateral aspect of the neck was remarkable for paucity of air except within the endotracheal tube (Figure 1B).

Forty vials of IV Crotalidae polyvalent antivenin were infused over 8 hours, without complication. The patient did not develop a

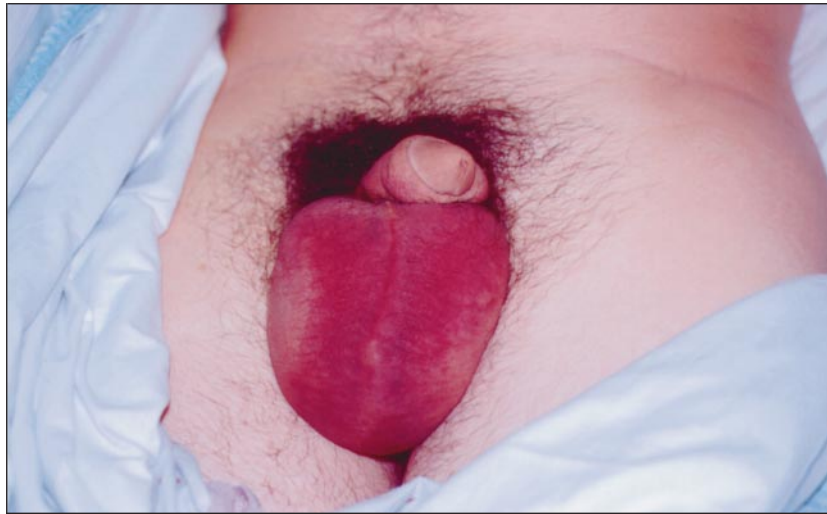


Figure 2. Progressive edema and ecchymosis of the scrotum after envenomation of an upper extremity.

coagulopathy or thrombocytopenia. He remained intubated for 5 days and was extubated when fiberoptic nasopharyngolaryngoscopy demonstrated a marked decrease in laryngeal swelling. He did well after extubation and never developed evidence of glossal sloughing.

CASE 3

A healthy 22-year-old man presented to the emergency department stating that he had been bitten on the wrist by a sidewinder rattlesnake, *Crotalus cerastes*, 1 hour before arrival. The patient was intoxicated and had been “playing” with a recently captured snake. He reported previous treatment with antivenin for a similar envenomation 3 years earlier.

In our intensive care unit, 4 hours after envenomation, he was hypotensive with a blood pressure of 82/35 mm Hg, heart rate of 80/min, and respiratory rate of 16/min. Oxygen saturation was 99% on room air. Physical examination results were remarkable for 2 puncture marks on the volar aspect of the right wrist, with severe swelling and tenderness extending from the wrist to the axilla. The chest was clear, and the results of the remainder of the physical examination were unremarkable. Laboratory studies revealed a prolonged prothrombin time (14.8 seconds) and international normalized ratio (1.5) with a normal plasma fibrinogen level (5.03

$\mu\text{mol/L}$) and platelet count ($218 \times 10^9/\text{L}$).

The patient’s hypotension responded to IV infusion of 1 L of isotonic sodium chloride solution. He was observed in the hospital but was judged not to be a candidate for antivenin therapy because of his previous antivenin treatment, which placed him at increased risk of anaphylaxis on repeated exposure to horse serum. Supportive care included elevation of his right upper extremity and IV fluids at a rate of 150 mL/h.

On his second hospital day, he experienced repeated emesis and again developed hypotension, with a systolic blood pressure of 65 mm Hg and a heart rate of 140/min. Laboratory studies revealed the following values: hemoglobin, 177 g/L (reference range, 130–180 g/L); hematocrit, 0.54 (reference range, 0.40–0.53); and serum creatinine, 150 $\mu\text{mol/L}$ (1.7 mg/dL) (reference range, 53–133 $\mu\text{mol/L}$ [0.6–1.5 mg/dL]). Urine output was 200 mL during 12 hours. Five liters of isotonic sodium chloride solution was infused during the next 16 hours and urine output doubled. Electrolytes remained unremarkable except for mild hyponatremia with a sodium level of 132 mmol/L (reference range, 135–145 mmol/L). A second examination of the right upper extremity revealed decreased swelling of the wrist but increased swelling of the upper arm and shoulder.

During the next 5 days, edema progressed to include the entire right

thorax, abdomen, scrotum, and leg to the knee (**Figure 2**). Laboratory studies revealed thrombocytopenia (nadir of $34 \times 10^9/\text{L}$ platelets on day 3) and coagulopathy (plasma fibrinogen level of 3.00 $\mu\text{mol/L}$ on day 3, a peak prothrombin time of 22.9 seconds, and an international normalized ratio of 3.6 on day 2). The wound site never developed bullae or necrosis.

On day 3, the patient reported severe pain in his right flank. Blood pressure was 140/80 mm Hg with a heart rate of 80/min. The right flank and abdomen were markedly edematous and tender to palpation. Laboratory studies revealed the following values: hemoglobin, 127 g/L; hematocrit, 0.37; and platelet count, $34 \times 10^9/\text{L}$. Computed tomography of the chest and abdomen, obtained to rule out retroperitoneal bleeding, revealed extensive edema of the extra-abdominal soft tissues of the right side of the chest and abdomen and a large right-sided pleural fluid collection (**Figure 3**). Despite a mild cough, the patient never demonstrated significant respiratory compromise.

By hospital day 6, the patient’s edema, coagulopathy, and thrombocytopenia began to resolve (prothrombin time, 13.1 seconds; international normalized ratio, 1.2; fibrinogen, 6.50 $\mu\text{mol/L}$; and platelet count, $89 \times 10^9/\text{L}$). He was discharged home on day 7, and on follow-up 10 days later, he had full recovery except for minimal swelling of his right upper extremity.

CASE 4

A 21 year-old-man was found deceased on the floor of his apartment. History obtained from friends and family revealed that he had found a rattlesnake at a construction site where he worked 2 months earlier and had kept it as a pet. He was often seen playing with and kissing the snake, which was kept in a terrarium in his apartment. The night of his death, he was last seen at midnight, apparently intoxicated, letting the snake slither around his arms, neck, and head. Eighteen hours later, his father found him deceased. The snake was recovered by the Arizona Herpetological Society, identified as a Western dia-

mondback rattlesnake, and released into the wild.

Investigation of the apartment revealed many opened beer cans. Small drops of blood on the floor were found near the terrarium and led to the bathroom, where blood and emesis were noted. Trace blood also trailed back into the living room, where the decedent was found.

Forensic investigation of the decedent's body revealed no evidence of trauma except for 2 puncture holes surrounded by ecchymoses on the dorsal lateral aspect of the right forearm, consistent with a rattlesnake bite. Sections obtained directly beneath the wounds revealed marked hemorrhage into the underlying soft tissue and muscle but no evidence of intravascular envenomation. Marked swelling extended from the right upper shoulder to the mandible and included the tongue, lips, and face (**Figure 4**). There was also significant bilateral swelling of the laryngeal mucosa and epiglottis. Tissue dissection revealed marked hemorrhage in the right lateral aspect of the neck surrounding the trachea, epiglottis, and thyroid. The results of dissection of the internal organs were unremarkable except for the lungs, which were moderately congested and edematous, with hemorrhage.

The results of toxicologic evaluation were unremarkable except for a vitreous ethanol level of 75.9 mmol/L, which correlates to a whole blood level of 65.1 mmol/L. The medical examiner concluded that the decedent died from complications of rattlesnake envenomation.

COMMENT

Rattlesnakes belong to the family of pit vipers known as Crotalidae. Approximately 75% of rattlesnake bites result in envenomation; the remaining 25% are "dry" bites.^{1,4,5} Rattlesnake venom is a complex mixture of enzymes, metalloproteinases, and other compounds designed to immobilize, kill, and begin digestion of prey.¹ Although human beings are not rattlesnake prey, envenomations may occur through unintentional interaction or, more commonly, following intentional encounters with snakes.



Figure 3. Computed tomographic scan of the chest showing significant soft tissue edema and right pleural fluid collection.



Figure 4. Facial and neck swelling in a man who died of complications of a rattlesnake bite.

Actual presentations differ among patients because the composition of the venom is known to vary greatly among snakes and envenomations from the same snake.

Human envenomations may result in marked tissue edema, necrosis, hypotension secondary to hypovolemia, severe coagulopathy (hypofibrinogenemia and prolongation of the prothrombin time), and thrombocytopenia. Rarely, anaphy-

laxis from the bite, disseminated intravascular coagulation, or death occur.¹⁻⁴

Treatment consists of supportive care, IV fluids, and antivenin administration when progressive swelling or significant coagulopathy occur. When antivenin is deemed necessary, we typically administer 15 to 20 vials as an initial dose and then give an additional 10 vial doses as needed based on the patient's clini-

cal response. Measurement of intracompartmental pressures and selective tissue decompression may occasionally be necessary. The determination of whether to use antivenin rests on the clinical judgment of the treating physician. Relative contraindications to infusing antivenin include allergy to horse serum, which could occur if the patient had previously received Crotalidae polyvalent antivenin or other horse products such as *Latrodectus* (black widow spider) antivenin, and current use of β -adrenergic blocking agents, which predispose to allergic reactions and make treatment of these reactions with epinephrine difficult.¹ We generally refrain from using antivenin to treat non-life-threatening envenomations in patients with a history of either coronary artery disease, in whom treatment of allergic reaction with epinephrine may be dangerous, or reactive airway disease, which, in our experience, also tends to predispose to more severe allergic reaction.

ANAPHYLAXIS

Allergic sensitization to rattlesnake venom was first reported in 1930, whereas anaphylaxis was not reported until 1965.⁶ These reactions are likely due to heterologous proteins, including enzymes and biogenic amines, in the rattlesnake venom. These proteins act as antigens and induce allergic reactions, including anaphylaxis in previously sensitized patients. There are few reports of serious allergic reactions to snakebites even in people who have been bitten numerous times.⁷

Our patient was likely sensitized to venom proteins during his previous snake handling and snakebites. Allergic sensitization was evident from the local mucous membrane reactions, including coryza, rhinorrhea, ocular pruritus, lacrimation, and periorbital edema, that he experienced when working with crotalids. He developed signs and symptoms of anaphylaxis immediately after *C. atrox* envenomation, despite the absence of a previous history of atopy or anaphylactic reactions to other antigens. Similar allergic sensitization has been reported in snake handlers exposed

to dry venoms, presumably through inhalation or mucous membrane contact.^{6,8,9}

Review of the literature revealed 3 similar cases and 1 limited case series of anaphylaxis after rattlesnake envenomation.^{6,8,10,11} In 1 case, a 22-year-old man developed urticaria, hypotension, and bronchospasm immediately after his second envenomation by an unknown type of rattlesnake. He responded to IV fluids, subcutaneous epinephrine, diphenhydramine, and methylprednisolone.⁸ Another reported case of anaphylaxis occurred in a professional snake handler who had demonstrated sensitivity to snake proteins by previous skin testing. Within 90 minutes of envenomation, he collapsed and was noted to be cyanotic, wheezing, and unresponsive.⁶ Ryan and Caravati¹⁰ reported a herpetologist envenomated by *Crotalus catalinensis* who presented with vomiting, abdominal cramping, diaphoresis, pruritic rash, confusion, and dyspnea that responded to IV fluids and steroids. The same patient presented 3 years later after envenomation by *Crotalus viridis viridis*, with similar symptoms that resolved with IV fluids, steroids, and epinephrine. Schmutz and Stahel¹¹ report a series of allergic reactions, including anaphylaxis, in patients bitten more than once by various members of the Crotalidae family. At our tertiary care referral center, we have seen 2 other cases of anaphylaxis after Crotalidae envenomation in the last 10 years (among more than 400 people with rattlesnake bites).

Anaphylactic reactions after exposure to venom proteins of Crotalidae occur rapidly and can be treated with IV fluids, IV steroids, histamine antagonists, and epinephrine. Patients with anaphylactic reactions to snake venom should be warned of possible life-threatening reactions with further exposure to snake venom and should consider carrying epinephrine for subcutaneous self-injection should symptomatic reexposure occur.

AIRWAY OBSTRUCTION AND PROGRESSIVE SWELLING

Rattlesnake envenomation typically leads to progressive local

edema, may lead to skin necrosis, and rarely results in elevated compartment pressures. The edema is rarely life threatening. Complete recovery from soft tissue injury may require several weeks and is not always complete.^{1,4}

Tissue edema, which occurs rapidly after envenomation, results from various venom components acting to digest tissue and further the spread of the venom. Local tissue necrosis may occur secondary to the metalloproteinases, which activate tumor necrosis factor α , a mediator of the inflammatory response. Tumor necrosis factor α stimulates the production of host metalloproteinases, which can directly injure tissue by degrading proteins in the extracellular matrix.¹ Progressive damage ensues secondary to increased permeability of capillary endothelial cells and damage to the basement membrane of vessel walls, leading to extravasation of blood and fluid into the surrounding tissues.^{1,12}

Most snakebites involve the extremities. Facial and tongue envenomations are rarely reported.¹³⁻¹⁵ In the past 10 years, we have seen 2 other cases of airway compromise, one from a tongue envenomation and the other from an envenomation to the lip. Our patient, who was bitten on the tongue, experienced rapidly progressive hypoglossal swelling that required emergent fiberoptic bronchoscopy for nasotracheal intubation within 60 minutes of envenomation. Had his airway not been immediately secured, death may have ensued as the tissue edema progressed to include his face, neck, pharynx, hypopharynx, and larynx. Crotalidae polyvalent antivenin has been shown in animals to limit the degree of swelling.¹⁶ However, in our patient, airway swelling progressed rapidly despite antivenin treatment.

Our third patient, who presented with progressive swelling after an envenomation of his wrist, was not treated with antivenin because he had previously received horse serum, placing him at increased risk for development of an anaphylactic reaction. Since he demonstrated a response to IV fluids and initially lacked a severe thrombocytopenia or

coagulopathy, we thought the risk of anaphylaxis outweighed the benefit of antivenin treatment. Had we considered his envenomation to be life threatening, we would have administered antivenin with extreme caution. We did not perform a skin test to check for sensitization because our clinical decision making would not have been altered based on the result. Many patients who develop allergic reactions following antivenin administration have had a negative skin test result, and, conversely, patients who have a positive skin test result may not demonstrate a reaction to antivenin infusion.¹

This case illustrates that the extent of swelling resulting from an extremity envenomation may be extensive and progress for several days. The course of the progression of tissue edema, in this patient, was 120 hours and at its fullest extended from the envenomated wrist to the chest wall, abdominal wall, flank, scrotum, and knee. In addition, he developed significant back pain secondary to massive tissue edema and a large pleural fluid collection.

In our experience, even patients who do not receive antivenin rarely demonstrate swelling this extensive, and we have not previously noted pleural involvement. We suspect that the pleural fluid represented an effusion, although it is possible that it was sanguinous. The drop in hemoglobin was consistent with hemodilution from the large volume of saline administered. Although our patient ultimately had a good outcome, his morbidity following the envenomation was unusual compared with other people with snakebites.

DEATH

Fatalities from rattlesnake envenomation are rare and typically involve

unusual circumstances, such as an inability to access medical care or direct penetration of a fang into the circulatory system with intravascular envenomation ensuing. In the latter, death may occur within minutes. Causes of deaths include hypotension secondary to hypovolemia, severe coagulopathy, anaphylaxis, airway obstruction secondary to progressive swelling, and disseminated intravascular coagulation.^{3,17,18}

The exact cause of death in our fourth patient is unclear. His death may be explained by several scenarios. First, although he had no known history of an allergy to rattlesnakes, we know that he had been exposed to his pet for 2 months and may have been sensitized to venom. He may have developed anaphylaxis, possibly with disseminated intravascular coagulation. Second, he may have developed airway compromise secondary to progressive swelling. The autopsy report revealed facial swelling along with encroachment of the soft tissue structures on the larynx. This swelling, in addition to his inebriation, may have led to hypoxia. Lastly, it is possible that significant hematologic abnormalities and hypovolemia resulted in death, with evidence of bleeding and emesis found in his apartment and hemorrhages in the neck and lungs revealed on autopsy.

CONCLUSIONS

The clinical presentation and course of disease resulting from rattlesnake envenomation can vary greatly. Caution must be exercised when caring for these patients, since extensive swelling may threaten life or limb. Anaphylaxis must be considered in the differential diagnosis of hypotension with rattlesnake envenomation. We recommend that patients with suspected anaphylaxis to rattle-

snake venoms be instructed to avoid future contact with Crotalidae and be discharged with a subcutaneous epinephrine kit in case unintentional exposure occurs.

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