

Severe Pit Viper Envenomation with Extended Clinical Signs and Treatment Complications in a Dog

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ABSTRACT

This manuscript describes the extended clinical abnormalities that can occur in severe snake envenomation and the clinical signs associated with antivenom hypersensitivity in a 3 yr old dog. Treatment consisted of IV fluid therapy, analgesics, a vasopressor, cardiac antiarrhythmia drugs, and polyvalent pit viper antivenom. Following initial response to treatment, relapse of clinical signs occurred. Most interesting was the recrudescence of clinical signs on day 7 that may have been caused by the release of deposited venom during surgical debridement of necrotic skin. The resulting extensive clinical signs required multiple vials of antivenom (22 vials over a 7 day period). Both F(ab')₂ antivenom and antivenin (Crotalidae) polyvalent were used in this dog because of availability logistics. It is thought that this large amount of antivenom resulted in type I (anaphylaxis) and type III hypersensitivity (serum sickness) reactions. The dog made a complete clinical recovery. This description of extended, fluctuating clinical abnormalities that were associated with envenomation together with the development of hypersensitivity reactions that were presumably secondary to antivenom administration is information that can be useful for the management of patients afflicted with severe pit viper envenomation. (*J Am Anim Hosp Assoc* 2015; 51:329–337. DOI 10.5326/JAAHA-MS-6234)

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ACP, antivenin (Crotalidae) polyvalent; aPTT, activated partial thromboplastin time; EKG, electrocardiogram; IM, intramuscular(ly); PCV, packed cell volume; PO, *per os*; PT, partial thromboplastin time; RBC, red blood cell

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Introduction

Pit viper envenomation is a well-known condition in areas of the world where poisonous snakes are indigenous. Variables that influence the severity of any poisonous snake bite include type of snake, quantity of venom injected, and the age and size of the victim.¹ Clinical signs can be mild and be of relatively short duration that ranges from 2 to 3 days or they can be extensive and last ≥ 1 wk. It is thought that protracted cases may be due to inadequate treatment and continued absorption from the site of envenomation.² This report describes a dog that had a severe envenomation syndrome following a pit viper snake bite that required the administration of 22 vials of antivenom that subsequently caused anaphylaxis and suspected serum sickness.

Case Report

A 3 yr old spayed female mixed-breed weighing 30 kg was left unattended in the yard for 10 min. The owner's property borders on wooded land in central Florida that is a known habitat of the Eastern diamondback rattlesnake (*Crotalus adamanteus*). There was no wetland on the property, and there had not been any sightings of water moccasin snakes (*Akistrodon piscivorus*). The owners returned to find the dog lying prostrate on the ground and immobile. Two bleeding puncture marks were observed on the ventral neck. Marked facial and cervical swelling developed rapidly over the next 30 min. The dog was immediately taken to an emergency clinic and was subsequently diagnosed with pit viper snake envenomation. At that time, she was described as mentally depressed but awake and able to move. The respirations were exaggerated and tachypneic (50 breaths/min; reference range, 10–34 breaths/min). She was tachycardic (heart rate was 200 beats/min; reference range, 60–120 beats/min) with subjectively weak pulses, slightly prolonged capillary refill time (2 sec; reference range, 1–2 sec), and a normal body temperature (37.9°C; reference range, 37.4–38.8°C). The systolic blood pressure^a was 120 mm Hg (reference range; 90–140 mm Hg). Her neck circumference measured 55 cm 2 hr after admission and subsequently increased to 59 cm 2 hr later. A blood smear examined by the emergency clinician showed spherocytes (with the absence of echinocytes) and severe thrombocytopenia (estimated platelet count was $20 \times 10^9/L$; reference range, $177\text{--}398 \times 10^3/\mu L$). Other laboratory tests showed evidence of prolonged prothrombin time (PT; >100 sec; reference range, 11–17 sec) and activated partial thromboplastin time^b (aPTT; >300 sec; reference range, 72–102 sec), hypokalemia^c (2.4 mmol/L; reference range, 3.8–5 mmol/L), and mild hyponatremia (143 mmol/L; reference range, 146–156 mmol/L). The packed cell volume (PCV) was 60% (reference range, 43–60%) and total solids



FIGURE 1 Photograph of the dog soon after admission showing marked facial hemorrhagic lymphedema and obtundation.

were 64 g/L (reference range, 54–69 g/L). The serum was markedly hemolyzed. The platelet count^d was $36 \times 10^9/L$ (reference range, $175\text{--}500 \times 10^3/\mu L$). The electrocardiogram (EKG)^e initially showed no dysrhythmias. The dog received IV fluids^f (3.3 mL/kg/hr) supplemented with potassium chloride (40 mmol/L)^g, diphenhydramine^h, [2.2 mg/kg intramuscularly (IM)], enrofloxacinⁱ (10 mg/kg IV), fresh-frozen plasma (8.3 mL/kg) followed by stored plasma (2 mL/kg) over 5 hr, and two vials of antivenin (Crotalidae) polyvalent [ACP^j; one vial at the time of admission and a second vial 5 hr later (total: two vials)]. She also received buprenorphine^k (0.01 mg/kg IV), dexamethasone Na phosphate^l (0.13 mg/kg IV), and famotidine^m (1 mg/kg IV). Although the dog's vital signs remained normal, the progressive head swelling, muscular



FIGURE 2 Photograph of the dog showing severe mental depression, prostration, and continued hemorrhagic lymphedema formation on day 2.

weakness, and continued mental depression prompted her referral to the university hospital 11 hr after initial presentation.

The dog was obtunded at the time of arrival to the referral emergency hospital (**Figures 1, 2**). The body weight remained 30 kg. Her temperature was 37.4°C, femoral pulses were weak and rapid at 244 beats/min (reference range, 60–120 beats/min), and the respiratory effort was labored with normal lung sounds on auscultation. Active hemorrhage was present on the ventral neck and diffuse hemorrhagic lymphedema involved the entire face. The indirect systolic blood pressure was low (65 mm Hg; reference range, 90–140 mm Hg systolic). The activated clotting time (ACTⁿ) was >999 sec (reference range, 90–120 sec), PCV was 34%, serum lactate^o was 5.3 mmol/L (reference range, <2.5 mmol/L), and total solids were 46 g/L. An EKG^p showed persistent ventricular tachycardia with a heart rate of 244 beats/min. Initial emergency treatment consisted of two vials of crotalid polyvalent F(ab')₂^q antivenom administered IV over 30 min (total: two vials of ACP and two vials of F(ab')₂), an IV bolus of 0.9% Na chloride^r (10 mL/kg) was administered over the first 15 min and subsequently repeated *q* 15 min over the first hour, and methadone^s (0.1 mg/kg IV).

During the first 24 hr of hospitalization, the dog remained moderately hypotensive with the indirect systolic blood pressure fluctuating between 60 and 100 mm Hg (reference range, 90–140 mm Hg). She also had persistent ventricular tachycardia (heart rate ranged between 180 and 250 mm Hg), decreased mentation, and generalized weakness. In addition to the two vials of ACP that she had received at the first emergency clinic and the two vials of F(ab')₂ that she received at the time of admission at the referral hospital, she was given an additional seven vials of F(ab')₂ antivenom (total: nine vials of F(ab')₂ and two vials of ACP given at the referring hospital), fresh-frozen plasma (16.6 mL/kg IV), IV fluids^t (1.3–2 mL/kg/hr IV), several additional boluses of 0.9% Na chloride (10 mL/kg IV), phenylephrine^u by constant rate infusion ranging between 0.5 and 2 µg/kg/min IV, and lidocaine^v (50 µg/kg/min IV) as a constant rate infusion. The previously administered enrofloxacin was discontinued. Additionally, in response to the decline in PCV from 34 to 17% over 19 hr due to a combination of hemolysis and external and third space hemorrhage, she was administered 8.3 mL/kg of packed red blood cells (RBCs). Her vital signs and systolic blood pressure normalized and remained stable in the early morning of day 2. The ventricular tachycardia became infrequent and intermittent, and the heart rate ranged from 160 to 184 beats/min. The lidocaine infusion was discontinued. The temperature ranged from 37.3 to 38.4°C, and her mentation improved. The ACT was 118 sec. by the end of the second day.



FIGURE 3 Photograph of the dog showing clinical improvement with less facial swelling and the ability to ambulate on day 3.

Days 3–5 of hospitalization were characterized by intermittent obtundation, worsening hemorrhagic lymphedema involving her head and neck, anemia (PCV was 13%), hypoproteinemia (total solids were 40 g/L), and pigmenturia. She was administered



FIGURE 4 Photograph of the dog preoperatively on day 5 showing less facial swelling.



FIGURE 5 Photograph of the wound site before necrosectomy.

another 6 vials of $F(ab')_2$ antivenom (total: 17 vials) IV with 8.3 mL/kg mL of canine packed RBCs and IV crystalloid solution administered at varying rates of 1.3–2.6 mL/kg/hr during the treatment period. Her clinical signs improved, she was becoming more alert and willing to ambulate (**Figures 3, 4**). At that time, the hospital supply of $F(ab')_2$ antivenom was depleted and further antivenom treatment consisted of only ACP. The dog was also administered an additional 8.3 mL/kg of packed RBCs IV. Serum biochemical analysis and ACT were repeated and all values were normal except total solids were 46 g/L. Despite the blood products that were administered over the first 3 days, the dog's ionized Ca remained normal, ranging from 1.27 to 1.31 mmol/L (reference range, 1.18–1.35 mmol/L). Na bicarbonate^w was administered at a rate of 0.25 mEq/kg/hr for 21 hr to attenuate any renal tubular damage that might occur from pigmenturia. Following normalization of the ACT, repeated coagulation tests were not performed after the third day.

By the morning of day 5, the ventral cervical swelling that had been characterized by hemorrhagic edema had progressed to a large 14 cm × 14 cm necrotic malodorous area (**Figure 5**). Fine-needle aspiration of the tissue to collect samples for aerobic and anaerobic bacterial culture and sensitivity was performed. Cytology results yielded numerous toxic neutrophils and intracellular cocci. No gram stain was done. Ampicillin Na/sulbactam Na^x was initiated (15 mg/kg IV q 8 hr) until the pending culture and sensitivity results became available. Later that same day, the dog became obtunded again and another vial of ACP was administered (total: 18 vials). She again responded favorably. The EKG was improved, showing mainly a normal sinus rhythm with occasional unifocal premature ventricular complexes.

By day 6, the cervical skin necrosis had worsened. Enrofloxacin (10 mg/kg IV q 24 hr) and metronidazole^y (10 mg/kg IV q 12 hr) were added to the treatment regime, and surgical debridement



FIGURE 6 Photograph of the wound during necrosectomy.

of the necrotic tissue in the neck was deemed essential. All of the necrotic tissue on the ventral neck was sharply debrided (**Figure 6**) and copiously lavaged with 0.9% sterile saline prior to placement of a wet-to-dry dressing using 0.9% sterile saline and gauze. The surgical debridement was done with the intent of placing a vacuum-assisted closure system^z in the wound on the following day. Methadone (0.19 mg/kg q 4–6 hr IV) was reinstituted for postoperative pain management.

The surgical procedure was performed without complication; however, repeat facial hemorrhagic lymphedema occurred within the first hour of recovery, which worsened over the next 24 hr (**Figure 7**). Further, paroxysmal ventricular tachycardia and runs of premature ventricular contractions returned. One additional vial of ACP (total: 19 vials) was administered approximately 12 hr after surgery (day 7 of hospitalization) to counteract additional signs of



FIGURE 7 Photograph showing recurrent facial hemorrhagic lymphedema shortly after surgery on day 6.

envenomation. That was followed 1 hr later by an acute onset of clinical deterioration characterized by fever (39.8°C), abdominal tensing, skin twitching, dull mentation, and a drop in systolic blood pressure to 65 mm Hg. The proximity of those signs to the antivenom administration led to a suspicion of either an anaphylactoid or anaphylactic reaction. Treatment consisted of saline 0.9% in three IV boluses (15 mL/kg *q* 15 min) with epinephrine^{aa} (0.01 mg/kg IM), diphenhydramine (1 mg/kg IM), and dexamethasone^{bb} (0.2 mg/kg IV). The epinephrine dose was repeated 30 min later. Improvement was apparent 2 hr later when the systolic blood pressure was recorded at 100 and 115 mm Hg and the dog becoming more alert. The abdominal discomfort was attributed to the anaphylaxis and it disappeared without any additional drugs for analgesia. An additional 2 vials of ACP (total: 21 vials) were administered in light of the severity of her exacerbated signs of envenomation, and treatment for anaphylaxis continued to stabilize her systolic blood pressure at 100 mm Hg.

The dog's body weight increased from 28 kg on day 7 to 31.2 kg on day 8, and generalized cool pitting edema developed primarily in her distal extremities. The PCV and total solids had decreased from 32% and 65 g/L, respectively, before surgery to 17% and 42 g/L, respectively, postoperatively. Wound management was continued and the commercial vacuum-assisted closure system was applied to facilitate wound drainage. Because of the persistent swelling and concern for incompletely resolved envenomation, 1 vial of ACP (total: 22 vials, including 7 vials of ACP) was administered via slow IV infusion. That was soon followed by an increase in temperature and respiratory rate over the next 30 min. The suspected type I hypersensitivity reaction was treated with diphenhydramine (1 mg/kg IM), epinephrine (0.01 mg/kg IM), and dexamethasone (0.17 mg/kg IV). The dog responded well, and the antivenom treatment was permanently discontinued.

Extended treatment consisting of dexamethasone (0.17 mg/kg IV) and diphenhydramine (1 mg/kg IV) was provided on days 9 and 10 because the generalized pitting edema and persistent vague abdominal discomfort were presumably associated with acquired serum sickness caused mainly by the ACP and perhaps by other antigens that the dog had received. The wound bacterial culture and sensitivity test results returned as 90% *Escherichia coli*, which was sensitive only to amikacin and imipenem/cilastatin Na, prompting the antibiotic treatment to be changed to imipenem/cilastatin Na^{cc} (8.6 mg/kg subcutaneously *q* 8 hr). By day 10, the dog appeared stable (**Figure 8**). She was bright and alert, although she still had some residual limb edema. She had lost 1.6 kg body weight, which was attributed to body water loss that paralleled the decreased edema. A complete blood cell count showed various RBC morphological changes, including spherocytes and occasional



FIGURE 8 Photograph showing resorbing facial hemorrhagic edema on day 10.

schistocytes with a PCV of 22% and platelet count of 103×10^9 . Additional surgical debridement was performed without any recurring facial edema and the vacuum-assisted closure system was reapplied over a nanocrystalline silver dressing^{dd}.

From day 11 to 13 of hospitalization, the dog had decreased facial and limb edema, the blood pressure and appetite returned to normal, and progressive wound healing was noted. The vacuum-assisted closure system was removed on day 12, and a nanocrystalline silver wound dressing was applied to the wound bed and covered with a superficial adhesive iodine-impregnated drape^{ee}. A urinalysis performed on day 13 showed a specific gravity of 1.018, 3+ proteinuria (by the sulfosalicylic acid method and an inactive microscopic sediment examination). The urine protein/creatinine ratio was 8.3 (reference range, <0.5). On day 13, the wound was closed primarily. The procedure and postoperative recovery went well without complication. The dog was discharged the following day with imipenem/cilastatin Na (9 mg/kg subcutaneously *q* 8 hr), benazepril^{ff} (0.18 mg/kg *per os* (PO) *q* 24 hr), prednisone^{gg} (0.5 mg/kg PO *q* 12 hr), diphenhydramine (0.8 mg/kg PO *q* 12 hr), and tramadol^{hh} (1.8 mg/kg PO *q* 12 hr as needed).

The dog did well at home over the next 4 days, but she was re-presented because the owner noticed red swellings on the dog's axillae and cranioventral thorax. The abnormal physical examination findings included edema in the thoracic inlet area and swollen prescapular and axillary lymph nodes. The lymphatic vessels draining those lymph nodes were palpable as prominent cord-like structures medial to the jugular veins. Fine-needle aspirates of the lymph nodes and the distal lymphatic vessels were performed and the samples submitted for cytology and culture. They showed marked neutrophilic, with lesser macrophagic, inflammation with

cellular degeneration and proteinaceous debris consistent with necrosis. The culture yielded no bacterial growth after 48 hr. The clinical diagnosis was lymphadenitis and lymphangitis associated with serum sickness. Outpatient treatment consisted of prednisone (0.7 mg/kg PO *q* 12 hr), diphenhydramine (0.9 mg/kg PO *q* 12 hr), tramadol (1.9 mg/kg PO *q* 12 hr as needed), and benazepril (0.18 mg/kg PO *q* 24 hr).

The dog responded well at home over the next 48 hr as shown by a return of normal appetite, attitude, and ambulation. One week later, she was clinically normal, and the lymphangitis had resolved. The surgical site was healed and the sutures were removed. The outpatient treatment consisted of a tapering doses of prednisone as well as diphenhydramine, and benazepril over the next 5 days and subsequently discontinued. The final recheck examination on day 45 found the dog clinically normal with a urine protein/creatinine ratio of 0.2. The prednisone dose was changed to 0.16 mg/kg PO *q* 2 days for the next 2 wk and then discontinued. The benazepril treatment was also discontinued.

Discussion

The clinical course of the dog described in this report was unique because of the extended clinical signs of envenomation, the episodes of anaphylaxis, and suspected serum sickness that occurred over a 2 wk period following the snake bite encounter. The accumulated large dose of antivenom (22 vials) was given because of the extended clinical signs. Perhaps this large total dose might have been avoidable if larger amounts of antivenom had been administered initially. Although the actual snake bite incident in this dog was not observed, the clinical signs were typical of severe pit viper envenomation, including rapid onset of obtundation, hypotension, coagulopathy, bite wounds with prolonged bleeding from the bite site, hemorrhagic lymphedema, and delayed tissue necrosis.^{3,4} Eastern diamondback rattlesnake was the most likely culprit because of the dog's geographical location and the clinical signs that are typical for that particular pit viper.⁵ The owners stated that Eastern diamondback rattlesnakes were routinely seen in the woods adjacent to their property and that other types of pit vipers, such as the water moccasin and timber rattlesnake, were not reported in the same area.

The initial therapeutic objectives for this dog included neutralizing as much of the venom as possible, normalizing the blood pressure and heart rhythm, pain control, and to prevent any complications that might arise from bleeding, hemolysis, and rhabdomyolysis. In the authors' experience, most cases of Eastern diamondback rattlesnake envenomations become clinically stable within the first 48 hr then show gradual improvement over the next

2–5 days after the patient receives ample amounts of antivenom and IV crystalloid fluids.

Antibiotics were not initially administered to the dog described in this report at the referral hospital because infection was not an issue until the end of the first week. O₂ therapy was not given to this dog, although its beneficial effect on the myocardium during periods of arrhythmia might have complimented the therapeutic efforts. The potential nephrotoxic effects of pigmenturia were a concern during the early hospital period. Treatments for pigmenturia entailed eliminating the cause and preventing the development of acute kidney injury. Medications that have been reported useful include furosemide, mannitol, fluid diuresis, and Na bicarbonate.⁶ Na bicarbonate was used to prevent the circulating muscle and hemoglobin pigments from precipitating in the acid urine.⁶ Isotonic fluid diuresis was also used to complement that effort.

It has been well established that the most important aspects of medically managing a poisonous snake bite victim rests on counteracting hypotension and neutralizing the venom by administering adequate doses of antivenom as soon as possible.^{1,2,5,7,8} Other medications, such as cardiac antiarrhythmia drugs and blood products, are used on an as-needed basis and after considering the potential for adverse effects (as in the case of blood products that is mentioned below). The use of other drugs such as glucocorticoids, antihistamines, antibiotics, nonsteroidal anti-inflammatory medications, and plasma substitutes have little evidence to support their efficacy despite the fact that they are commonly used in many veterinary practices. A more extensive and evidenced-based medicine description about those other drugs has been recently reviewed.⁸

Blood products were used for the dog described herein at both hospitals. They were deemed essential when the dog failed to stabilize after the initial treatment of IV crystalloid solutions, antivenom, and vasopressor drugs. Fresh-frozen plasma was given with the intent of replenishing lost coagulation factors and to combat venom-induced coagulopathy. That pattern of thinking is common amongst many clinicians but it might not be correct in the context of treating coagulopathy caused by pit vipers. Administration of blood products to human victims has been reported as ineffective because the addition of the extra substrate in fresh-frozen plasma or cryoprecipitate may cause a procoagulant effect unless all of the venom has been neutralized.^{7–9} Such an effect can actually enhance fibrinolysis. It is important to remember that the coagulopathy is generally a direct effect of the hemorrhagins found in the venom. Therefore, the first treatment objective should entail removal of the toxin through administration of ample amounts of antivenom prior to blood component therapy.⁷

Administration of plasma, packed RBCs, or whole blood is best omitted unless aggressive antivenom therapy and other therapeutic efforts have failed to stop the coagulopathy or the patient is experiencing continued hemorrhage or detrimental effects of anemia.⁷ IV colloid treatment to increase plasma oncotic pressure was not considered because the large volumes of plasma required were not available to replace the colloidal requirements. Plasma colloid substitutes were not given for several reasons, including the potential for adverse effects on platelet function (especially in a thrombocytopenic patient), the potential adverse effects on renal function, and lack of documented efficacy.⁷⁻⁹ Although heparin might offset any procoagulant effect of the venom or the plasma, heparin is not recommended because of its ineffectiveness for treating venom-induced coagulopathy and because of its potentiating effect on antithrombin. Those therapeutic concerns are more thoroughly reviewed elsewhere.⁸

The dog described herein showed the usual clinical signs caused by regional pit vipers, including hemorrhagic lymphedema, cardiac arrhythmias, and marked mental depression. All symptoms initially responded to antivenom treatment only to worsen as the effects of the antivenom diminished. That was explained in a study by Dart et al. (1997) that proposed the amount of venom injected may have overwhelmed the capacity of the antivenom to neutralize all venom components.¹ It is also possible that the antivenom neutralized circulating venom initially but as continued absorption occurred no unbound antivenom remained, allowing for continued venom-associated injury. Those same authors stated that continued absorption of the venom from the bite site, after the antivenom is excreted from the body, allows the venom to continue its damaging effects unopposed by antivenom. This study's findings in addition to Dart's report support the administration of additional antivenom if previously alleviated symptoms reoccur.

The dog described herein initially had marked thrombocytopenia and prolonged PT and aPTT, which are typical signs of envenomation-induced coagulopathy caused by the Eastern diamondback rattlesnake. Defibrination and venom-induced thrombocytopenia without coexisting disseminated intravascular coagulation is associated with most North American rattlesnake envenomations. It is defined by a low fibrinogen and platelet count, increased fibrin split products, normal D-dimer concentration, and prolonged PT and aPTT.⁹ The primary fibrinogenolysis has no thrombin activation of factor XIII and thus no fibrin cross-linking with subsequent normal D-dimer concentrations.¹⁰ After the coagulation tests approached normal by the second referral hospital day (ACT decreased from >999 to 118 sec), they were not repeated, preventing any detection of recurrent coagulation abnormalities. That clinical decision was made because the results of the ACT at

that point had little or no influence on the decision to administer more antivenom to the patient, which was decided based on cardiovascular parameters and subjective assessment of facial swelling, both of which recurred despite normalization of the ACT.

The reappearance of clinical abnormalities following necrosectomy was first interpreted as the phenomena known as recurrence.¹ A relatively recent phenomenon of recurrent envenomation has been reported in humans treated with the Fab polyvalent antivenom, which is defined as the return of any venom effect after documentation that the abnormality had resolved with treatment.¹ The return of progressive swelling after initial control is described as local recurrence, whereas coagulopathy recurrence is described as the return of abnormal bleeding parameters (i.e., thrombocytopenia, prolonged PT and/or aPTT, elevated fibrin split products, low fibrinogen). Recurrence occurs as a result of the diminished presence of the Fab antivenom while venom re-enters the circulation from the tissue deposit site(s). Recurrent envenomation has not been reported in veterinary patients, and the decision to curtail additional coagulation testing in the dog described in this report after day 3 prevented detection of recurrent coagulation test abnormalities.

Antibiotic use is rarely indicated in snake bite victims, and most experienced clinicians do not use them initially. Although there are a multitude of bacterial organisms in the snake's mouth, the transmission of infection is rare.^{5,8,9} This is attributed to the dilutional effects associated with the hemorrhagic lymphedema and perhaps to the proteolytic effects of several components of snake venom. The described dog did not show evidence of wound necrosis until day 5 of hospitalization. The *Escherichia coli* that was cultured from the wound was the only organism isolated, and its multiple antibiotic resistance could reflect that it was a nosocomial infection. The decision to treat the dog with antibiotics in addition to providing surgical drainage was a clinical judgment because the clinicians wished to avoid further complications caused by a secondary infection. Ampicillin Na/sulbactam Na, enrofloxacin, and metronidazole were initially given to provide broad-spectrum cover. When the culture and sensitivity results returned 5 days later showing sensitivity to imipenem/cilastatin and amikacin, the treatment was switched to imipenem/cilastatin Na based on those results.

Anaphylaxis was diagnosed on day 7 based on the acute onset of new clinical signs of hypotension, abdominal discomfort, and fever, all occurring 1 hr after the ACP injection. The dilemma at that moment was distinguishing the new clinical signs from those that were caused by the venom. The decision to identify the episode as anaphylaxis in the patient was based on the peracute abnormalities occurring soon after the ACP injection and the

additional signs that followed, such as the generalized edema.¹¹ The dog's clinical response to treatment for type I hypersensitivity also contributed to the criteria used for clinical diagnosis.

Serum sickness is a type III hypersensitivity reaction and is presumed to have complicated this dog's recovery after day 7 based on the clinical signs and the time of occurrence after the introduction to a new antigen.¹² In one retrospective study involving humans treated with ACP, 50% experienced serum sickness, with larger doses (more than eight vials) correlating with high rates of sickness (83%).¹³ In another large retrospective study spanning 10 yr of rattlesnake bites in children receiving ACP, 38% developed serum sickness.¹⁴ The diagnosis of antivenom-associated serum sickness in humans is commonly made on clinical grounds and based on the timing of the onset of signs following treatment.¹³ It is a clinical syndrome that involves a combination of signs as a result of antigen-antibody complexes. In humans, those signs include fever, diffuse rash, intense urticaria, arthralgia, hematuria, and constitutional symptoms that can persist for several days. Those signs usually begin 3–5 days following antigen exposure. Many of the adverse events noted in the dog described herein were attributed to the multiple vials of antivenom administered, which included seven vials of ACP. That particular antivenom (ACP) is a partially purified product that retains large amounts of proteins in the Fc component of the molecule, and it is that component that stimulates the antigen-antibody complex formation. Neither venom levels nor complement levels were measured in the dog described in this report because of limited availability and the anticipated delayed return of test results. Because serum sickness in humans has been commonly associated with ACP administration, efforts have been made to produce the more purified antivenoms, such as Fab and F(ab')₂, but hypersensitivities can still occur with the more purified products, albeit at a much lower frequency.^{2,15}

The proteinuria that was documented with a urine protein/creatinine ratio of 8.4 on day 13 of hospitalization could have been due to several factors, including antigen-antibody complexes associated with type III hypersensitivity, direct renal damage caused by the venom, injury caused by pigmenturia associated with hemolysis and rhabdomyolysis, microthrombi at the glomerulus associated with hemostatic dysfunction, or directly caused by the antivenom protein.¹⁶ One study involving the examination of serial urinalyses in human patients with North American crotalid envenomation showed that the Fab fragments of antivenom were one of the reasons for albuminuria in their patients, and that same effect has been shown in dogs.^{16,17}

Treatment for serum sickness is supportive and includes discontinuing the sensitizing drug along with the administration of any combination of nonsteroidal anti-inflammatory drugs, anti-

histamines, or glucocorticoids.^{13,18} Benazepril was prescribed for this dog to offset any glomerular hypertension.¹⁹

In retrospect, it is possible that the hypersensitivity reactions could have been avoided if lower amounts of antivenom, especially ACP, had been administered. However, the patient's complete clinical recovery may not have occurred had she not received additional vials of antivenom to counteract her severe envenomation syndrome and recurrent clinical signs. Perhaps earlier resolution could have been achieved, and side effects avoided, had more aggressive antivenom therapy been initiated within the first 4–8 hr after envenomation. That possibility bears further investigation.

Conclusion

In conclusion, this patient showed the adverse effects of severe snake envenomation and the need for extensive therapeutic intervention which included relatively high doses of antivenom that were administered over a several day period. This dog also showed the clinical signs of type I and type III hypersensitivity complications caused by the large doses of antivenom. ■

FOOTNOTES

- ^a Doppler Flow Detector; Parks Medical Electronics, Aloha, OR
- ^b Coag Dx Analyzer; IDEXX Laboratories, Westbrook, ME
- ^c Vetscan ISTAT 8; Abbott Point of Care Laboratories, Abbott Park, IL
- ^d Laser Cyte Hematology Analyzer; IDEXX Laboratories, Westbrook, ME
- ^e SurgiVet Vital Signs Monitor; Smiths Medical ASD Inc., St. Paul, MN
- ^f Acetated Ringer's; Hospira, Lake Forest, IL
- ^g Potassium chloride 40 mEq; Hospira, Lake Forest, IL
- ^h Diphenhydramine HCl Injection; West-Ward Pharmaceuticals, Eatontown, NJ
- ⁱ Baytril Injectable Solution 2.27%; Bayer Health Care, Shawnee Mission, KS
- ^j Antivenin (Crotalidae) Polyvalent; Fort Dodge Laboratories, Fort Dodge, IA
- ^k Buprenex; Reckitt Benckiser Health Care (UK) Limited, UK
- ^l Dexium-SP; Bimeda Inc., LeSeur, MN
- ^m Famotidine injection 10 mg/mL; Baxter Healthcare Corporation, Deerfield, IL
- ⁿ ACT II; Medtronic, Minneapolis, MN
- ^o Stat Profile Critical Care Express; Nova Biomedical, Waltham, MA
- ^p IntelliVue TRx; Philips Healthcare, Andover, MA
- ^q Antivipmyn; Bioclon, Mexico City, Mexico
- ^r 0.9% NaCl Injection; Baxter Healthcare, Deerfield, IL
- ^s Methadone HCl Injection; Bioniche Pharma, Lake Forest, IL
- ^t Lactated Ringer's Injection; Baxter Healthcare, Deerfield, IL
- ^u Phenylephrine HCl Injection; West-Ward Pharmaceuticals, Eatontown, NJ
- ^v Lidocaine 2%; Vet One, Boise, ID
- ^w Na Bicarbonate 8.4% for Injection; Hospira, Lake Forest, IL
- ^x Unasyn; Sagent Pharmaceuticals, Schaumburg, IL
- ^y Metronidazole; Baxter Health Care, Deerfield, IL
- ^z V.A.C. GranuFoam Dressing; KCI, San Antonio, TX
- ^{aa} Epinephrine; Amphastar, So. El Monte, CA
- ^{bb} Dexamethasone; MWI, Boise, ID

cc Imipenem and cilastatin; Hospira, Lake Forest, IL
 dd Anticoat 7; Smith & Nephew Ltd., England
 ee Ioban 2 Antimicrobial Incise Drape; 3M, St. Paul, MN
 ff Benazepril HCl 5 mg; Amneal Pharmaceuticals of New York, Hauppauge, NY
 gg Prednisone 5 mg; West-Ward Pharmaceutical, Eatontown, NJ
 hh Tramadol HCl 50 mg; Amneal Pharmaceuticals of New York, Hauppauge, NY

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