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ANAPHYLATIC REACTION AFTER *Crotalus* ENVENOMATION TREATMENT IN A DOG: CASE REPORT

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ABSTRACT: *Crotalus* envenomation is the second most frequent condition caused by venomous snakes attacking dogs and cats in Brazil. Affected animals show severe neurological and muscular involvement, lower motor neuron signs and myalgia due to extensive rabdomiolysis. The present case report is about *Crotalus* envenomation in a dog which showed severe clinical and laboratory abnormalities. After treatment with antivenom (specific antidote) and clinical support, the dog totally recovered from that condition.

KEY WORDS: *Crotalus*, dogs, snake bites, therapeutics, anaphylaxis.

CONFLICTS OF INTEREST: There is no conflict.

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INTRODUCTION

Accidents caused by snakes constitute a public health problem worldwide (2-5). The South-American rattlesnake (*Crotalus durissus terrificus*) is the only Brazilian species of the genus *Crotalus*. It lives in semi-arid areas covered with bushes in 25% of the Brazilian territory. In Brazil, such species cause the second most frequent snake envenomation in men and animals (3, 6, 13, 15).

There are very few epidemiological data in veterinary medicine, but some reports show that dogs are more frequently affected than cats. In dogs, the incidence of snakebites is similar to or higher than that in man (3, 13, 15).

Rattlesnake venom is highly absorbed via lymphatic vessels. It has high content of proteolytic enzymes, such as crotoxin, Phospholipase A_2 (PLA_2), crotamine and myotoxin. These proteolitic enzymes cause neurotoxicity as well as cardiohemodynamic, metabolic and myotoxic effects (6, 11, 13, 15).

Neurotoxicity results from the action of crotoxin, which inhibits the release of acetylcholine, preventing pre-synaptic stimuli (1, 6, 8). Cardiohemodynamic and metabolic effects result from increased vascular permeability, vasodilation, hypotension, hemoconcentration, metabolic acidosis, blood clot abnormalities and fibrinolysis (1, 8, 11, 12). PLA_2 is the major enzyme that causes all these changes, increasing blood prostaglandin ($PGF_{2\alpha}$, PGE_2 and PGI_2) and inhibiting blood clot factors (8). Myotoxicity caused by *Crotalus* venom induces general rabdomyolysis, which results from the effects of *Crotalus* myotoxin, PLA_2 and crotamine on Type I muscle fibers (rich in myoglobin), injuring the cell membrane and tearing its organelles (3, 6, 8, 11, 12, 15).

Clinically, affected animals show mild local signs, such as short-lasting pain and edema. Systemic signs appear within the first minutes or hours after the snakebite. Such signs include palpebral ptosis, mydriasis, myasthenic facies, paraplegia, decreased muscle reflexes and myalgia. In severe cases, the venom causes Acute Renal Failure (ARF) and high myoglobulinemia. Major laboratory changes are increased Mean Corpuscular Volume (MCV), hypoproteinemia, leukocytosis, neutrophilia with left shift, initial eosinopenia followed by eosinophilia, increased clotting time, and increased blood levels of Creatine Kinase (CK), Aspartate Aminotransferase (AST), creatinine, and Blood Urea Nitrogen (BUN) (1, 6, 8, 11, 13).

Treatment must be initiated as soon as possible with Intravenous (IV) fluids and antivenom by slow infusion (it can be diluted in crystalloid fluid). The dose is

calculated to neutralize 150 to 300mg of venom. Anaphylatic or anaphylactoid reaction may occur, regardless previous sensitization. Therefore, administration of antihistamines and corticosteroids is recommended before treatment (2, 8, 11). This article reports an adverse systemic reaction following *Crotalus* antivenom treatment in a dog.

CASE REPORT

A four-year-old German shepherd, weighed 35kg, was presented at the Veterinary Hospital of Federal University of Viçosa 24 hours after snakebite. The snake, killed by the dog's owners, was identified as a rattlesnake. The dog was promptly treated by its owners with 10 vials of specific antivenom, subcutaneously. The physical examination at the Veterinary Hospital showed bradycardia, hypothermia, apathy, prostration, tetraparesis, muscle hypotonicity, general myalgia, mild palpebral ptosis, mydriasis and mild edema at the site of the snakebite

Blood count showed erythrocytosis, increased MCV, leukocytosis with regenerative left shift, lymphopenia and eosinopenia. Blood chemistry showed normal BUN and creatinine, and highly increased levels of AST (Table 1). Urinalysis showed dark red and turbid urine, hypersthenuria, acidic pH, proteinuria, hematuria, pyuria and large amounts of amorphous urate crystals.

The dog was intravenously medicated with lactated Ringer's solution followed by intramuscular injection of promethazine (Phenergan injection®; 0.4mg/kg). Fifteen minutes later, a new antivenom dose was given to the dog (anti-*Bothrops* and anti-*Crotalus* serum, Vincofarma®, five 10ml-vials, intravenously, diluted in 0.9% NaCl, 15-20 minutes infusion). After receiving the antivenom, the dog showed restlessness, tachypnea and tachycardia. It was promptly treated with oxygen and IV dexamethasone (5mg/kg) and 7.5% hypertonic sodium chloride (7%, 4ml/kg); in the next hours, the animal showed signs of clinical improvement.

Subsequently, urethral catheterization was carried out in order to empty and flush the bladder with isotonic fluids and measure urine output.

Twenty-four hours following therapy with IV fluids, the dog was much better and maintained normal diuresis. The urinary catheter was removed, and enrofloxacin (10 mg/kg, subcutaneously) was prescribed for 10 days.

Laboratory tests were repeated. The results showed a decrease in MCV, White Blood Cell (WBC) and AST levels, normal creatinine value, and a decrease in

myoglobulinuria (Table 2). The dog was followed-up for more four days, with maintenance of fluid therapy, and totally recovered from the condition.

Table 1. Abnormalities in blood cell count and blood chemistry 24 hours after *Crotalus* envenomation.

Blood Cell Count	
Red blood cells (mm^3)	6,700,000
Mean corpuscular volume (%)	44.3
White blood cells (mm^3)	40,600
Segmented neutrophils (%)	87
Bands (%)	08
Lymphocytes (%)	04
Blood Chemistry	
Blood urea nitrogen (mg/dl)	46.55
Creatinine (mg/dl)	0.8
Aspartate aminotransferase (UI/l)	165

Table 2. Abnormalities in blood cell count and blood chemistry after anti-*Crotalus* treatment.

Blood Cell Count	
Red blood cells (mm^3)	5,080,000
Mean corpuscular volume (%)	33.3
White blood cells (mm^3)	34.400
Segmented neutrophils (%)	92
Bands (%)	03
Lymphocytes (%)	05
Blood Chemistry	
Creatinine (mg/dl)	1.08
Aspartate aminotransferase (UI/l)	159.06

DISCUSSION

The dog presented in this article showed neurological signs similar to those mentioned in previous reports (1, 2, 6, 11, 14). Therefore, a definitive diagnosis could be established through clinical signs, snake identification and absence of significant edema or necrosis at the site of the snakebite.

Blood analysis showed results similar to the findings presented in literature, which resulted from vasodilation, increased vascular permeability, interstitial fluid loss caused by *Crotalus* venom, and possibly increased levels of blood adrenocorticotropic hormone (ACTH) due to stress caused by the snakebite (3, 6, 8, 11, 14). Findings about WBC in the present report were already described in cattle attacked by *Crotalus* snakes, with transitory changes between maximum and minimal ranges within a few hours (3, 8). The physiopathology of such mechanism is unknown; however, it may also occur in dogs.

In human medicine, 40% of the patients also show eosinophilia and increased clotting time resulting from the venom's clotting effect a few days following the snakebite (1, 7, 8). Although recommended in every case, clotting time was not assessed because there were no signs of hemorrhage and an antivenom injection had already been administered. Besides, hemorrhage caused by *Crotalus* snakebite is uncommon in animals (7, 8). Peripheral eosinophilia was not observed, corroborating reports that such alteration is infrequent and transitory (6, 8).

Changes in blood chemistry and urinalysis are due to intense rabdomyolisis, releasing myoglobin in the blood and urine (3, 11, 14). Such condition is more frequently associated with ARF in men, when compared to dogs (1, 3, 11), possibly because the latter are more resistant to the venom (7, 8, 11). The dog of the present report showed no signs of ARF.

The therapeutic approach followed those recommended in literature (1, 2, 6, 11, 14) (i.e. early injection of antivenom), but with some alterations (previous under dosing and non-indicated administration route). Possibly, this approach was fundamental to improve the dog's condition. A second administration of the antivenom was done because the clinical signs were still present.

In veterinary medicine, there are reports indicating a second antivenom dose 24 hours after the first treatment in the case of clinical signs persistence (3, 17). However, such procedure could not be found in human medicine literature.

Although recommended by some experts (15), an intradermal test before a second antivenom injection was not performed due to its low specificity and because the treatment is indicated even for sensitive patients (3). To reduce the risks of a hypersensitive reaction, subcutaneous antihistamine was administered before the new antivenom application. But despite of this approach, the dog exhibited cardio-respiratory abnormalities.

Adverse reaction to antivenom therapy has been well documented in human beings. Such reactions may be of two types: Premature (PR) and Late Reactions (LR). Premature reactions tend to occur during antivenom infusion and the following two hours after application. These adverse reactions are usually considered of mild severity. Wheal, shivering, cough, nausea, abdominal pain, pruritus and facial flushing are the most common signs observed. Rarely were such reactions severe, leading to signs of anaphylactic or anaphylactoid reaction manifested by hypotension, cardiac arrhythmia and airway obstruction. The PR physiopathology is not completely understood, but the production of anaphylotoxins mediated by complement is the more accepted theory. The LR or “serum sickness” occurs from five to 24 days after treatment and is characterized by fever, joint pain, lymphadenomegaly, wheal, proteinuria, and probably involves immune complex interactions and complement cascade activation (1).

There are scarce scientific reports on antivenom adverse reaction in dogs. If the clinical signs showed by the dog after the second antivenom therapy were due to anaphylactic or anaphylactoid reaction, it was unusual. The dog differs from the other domestic animals because its major organ involved in acute anaphylaxis is the liver instead of the lung (19). The reported clinical signs of systemic anaphylaxis in dogs included initial excitement, vomiting, defecation, and urination. Progressively, respiratory depression, distress and cardiovascular collapse may develop. Besides excitement, the dog described here did not have gastrointestinal signs neither urinary voiding. However, drug hypersensitivity may manifest in different ways and may be characterized by one or all of the following clinical signs: hypotension, bronchospasm, angioedema, urticaria, erythema, pruritus, pharyngeal or laryngeal edema, vomiting and colic (10).

An alphabetic approach to adverse drug reactions has been proposed: type A (augmented), type B (bizarre), type C (chronic), type D (delayed), type E (end of treatment), type F (failure), and type G (gaffes). Type B (bizarre) reactions are

unexpected or aberrant responses that are unrelated to the drug's pharmacological effect, are not dose-dependent, and are unpredictable (idiosyncratic). Type B reactions include allergic and pseudoallergic (nonimmunologic reactions) and aberrant responses (10).

Anaphylaxis is an immune-mediated event. Non-immune interactions leading to anaphylaxis are known as anaphylactoid reactions. Systemic anaphylaxis is an acute, life-threatening reaction resulting from the generation of endogenous chemical mediators. On the first exposure to an antigen in susceptible individuals, Immunoglobulin E (IgE) is produced and binds to the surface receptors of mast cells and basophils. On the second exposure to the antigen, the subsequent antigen-antibody complex triggers calcium influx into the effector cell, which results in an intracellular event that culminates in degranulation. Histamine causes smooth-muscle contraction in the bronchi, gastrointestinal tract, uterus and bladder. It also acts on blood vessel walls to increase vascular permeability and edema. Heparin leads to incoagulability, urticaria and fever. Eosinophil and neutrophil chemotactic factors, proteolytic enzymes, serotonin and adenosine are additional chemical mediators. The actions of these mediators include chemotaxis to leukocytes, intravascular coagulation and activation of complement (9). The clinical signs of Type I hypersensitivity result from the response of the animal to the inflammatory mediators, the location and number of the cells stimulated, the amount of antigen involved, and the route of antigen access. The clinical signs of anaphylaxis differ among domestic animal species (19).

The dog presented in this report probably developed an adverse drug reaction because the clinical signs were seen shortly after the second antivenom application. However, vomiting, voiding and defecation, typically related to anaphylaxis, did not occur. The clinical signs were not so severe possibly because of the pre-treatment with antihistamines. Corticosteroids, although indicated for acute allergic reactions, act too slowly to be helpful in the initial management, but they can prevent late-phase reactions and complications caused by secondary mediators (9).

Despite the lack of indication for hypertonic saline use in the treatment of anaphylactic reactions (18), it was used because of the possibility of a hypotensive shock. The use of IV bolus of hypertonic saline in dogs and cats with hypovolemic shock increases the arterial pressure and the cardiac output and help to restore the acid-base equilibrium (16).

The antivenom volume and infusion velocity also influence the manifestation of such side effects, but they were used according to the manufacturer recommendations. The guidelines to crotalic antivenom use in humans include using a dilution of 1:2 to 1:5 in 0.9% saline or 5% glucose in 20 to 60 minutes. Although secondary bacterial infection is not traditionally described following *Crotalus* snakebite, an antibiotic therapy was done as a preventive measure because of the rich bacterial flora present in the snakes' oral cavity (e.g. *Clostridium* sp, and Gram-positive bacteria) (1).

The full recovery of the dog in the present report could be the result of the early antivenom therapy, the dog's natural resistance to the crotalic venom, the low amount of venom inoculated or some combination thereof (1, 7, 11).

As the dog showed clinical improvement after the second antivenom dose, it could be thought that this therapy could be indicated despite the previous treatment and risk of anaphylactic reaction. On the other hand, if this procedure is indicated based on clinical evaluation, all precautions should be in hand to treat any possible complication. These include laryngoscopy, surgical blades, syringes, endotracheal tubes, adrenaline (1:1000), antihistamines and glicocorticoides (1, 2, 6, 11, 14). Early injection of antivenom, even if not ideally used such as in the case described here, was probably fundamental for the patient recovery.

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