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Selected Topics: Toxicology

SNAKE EYES: CORAL SNAKE NEUROTOXICITY ASSOCIATED WITH OCULAR ABSORPTION OF VENOM AND SUCCESSFUL TREATMENT WITH EXOTIC ANTIVENOM

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☐ **Abstract—Background: Coral snake bites from *Micrurus fulvius* and *Micrurus tener* account for < 1% of all snake bites in North America. Coral snake envenomation may cause significant neurotoxicity, including respiratory insufficiency, and its onset may be delayed up to 13 h. Case Report: We present a unique patient encounter of *M. tener* venom exposure through the ocular mucous membranes and a small cutaneous bite, resulting in neurotoxicity. To our knowledge, this is the first reported case of systemic neurotoxicity associated with ocular contact with coral snake venom. Our patient developed rapid-onset skeletal muscle weakness, which is very uncommon for *M. tener*, along with cranial nerve deficits. Acquisition of antivenom was challenging, but our patient provides a rare report of resolution of suspected *M. tener* neurotoxicity after receiving Central American coral snake (*Micrurus nigrocinctus*) antivenom. Our patient subsequently developed serum sickness, a known delayed complication of antivenom. Why Should an Emergency Physician Be Aware of This?: The emergency physician should be aware that coral snake venom may be absorbed through different routes. Neurotoxicity and respiratory insufficiency may be fatal and onset may be delayed up to 13 h. North American Coral Snake Antivenom is in very limited supply, so non-Food and Drug Administration-approved alternative coral snake antivenoms may be used for patients demonstrating neurotoxicity. Emergency physicians should be proactive in contacting a toxicologist to procure antivenom, as well as consideration of adjunctive treatments, such as neostigmine. Furthermore, whole immunoglobulin G products, such as antivenom, may result in immediate and delayed reactions.**

☐ **Keywords—coral snake; envenomation; neurotoxicity**

INTRODUCTION

The two most medically important snakes native to North America are the pit vipers (Viperidae family and Crotalinae subfamily) and coral snakes (Elapidae family). Of the coral snakes, three species are native to North America: Eastern coral snake (*Micrurus fulvius*), Texas coral snake (*Micrurus tener*), and Arizona/Sonoran coral snake (*Micruroides euryxanthus)*. In the United States, coral snakes are classically identified by red and black bands, which are separated by yellow bands in between. However, some North American coral snakes have different alternating color patterns, melanism (mostly black), or albinism (mostly white). Coral snakes are elusive and human bites are relatively rare, with only 20–25 bites per year in the United States (1). Only 40% of bites result

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in envenomation due to a relatively inefficient venom delivery system through short, front nonmobile fangs (2).

The venom of *M. fulvius* and *M. tener* contains highly potent α-neurotoxins, causing neurotoxicity by competitive inhibition of the nicotinic acetylcholine receptors at the neuromuscular junction (3). Bites with envenomation may cause ptosis, ophthalmoplegia, dysarthria, and dysphagia, as well as descending motor weakness (although rare in *M. tener* envenomation), which may lead to respiratory insufficiency (1,4). Acute respiratory failure due to respiratory muscle paralysis is the most dangerous sequelae, although only one death in the United States has been reported in the recent past (5). Importantly, neurotoxic effects of bites may be delayed up to 13 h after envenomation (6). Venom from other Elapidae, such as some "spitting" cobras native to Asia and Africa (*Naja* spp.), demonstrate more cytotoxic effects than neurotoxic effects to the exposed eye, causing symptoms of venom ophthalmia: pain, hyperemia, blepharospasm, and corneal erosions (7–10). However, cranial nerve dysfunction without other systemic neurologic effects has been described after ocular absorption from spitting cobras (11).

We report a unique *M. tener* envenomation through the ocular route and a cutaneous bite with an uncommon presentation of cranial nerve dysfunction and skeletal muscle weakness. All symptoms resolved after receiving a Central American coral snake antivenom, which has not been widely studied in *M. tener*, although the patient later experienced a serum sickness reaction.

CASE REPORT

A 22-year-old woman was bitten by a snake on the left thumb while wearing garden gloves. The patient quickly withdrew her hand, removing the snake's grasp of her thumb, but liquid from the snake's mouth made contact with her eyes. She quickly noted a burning sensation in her eyes, followed by numbness and weakness to the entire body below the level of her neck. The patient presented to a community emergency department (ED) soon after the onset of weakness, where a puncture wound was noted on the left thumb, and subsequently she was transferred to the tertiary care hospital for continued care. The snake was identified as a coral snake (*M. tener*) by the patient's cellular phone picture (Figure 1). Upon arrival to our ED 5 h after envenomation, the physical examination demonstrated normal vital signs and no respiratory distress. Cranial nerve examination revealed weakness with periorbital muscle movements bilaterally, with attempted tongue protrusion and shoulder shrug. She endorsed decreased sensation to light touch below the neck and demonstrated 3/5 strength in all extremities. Complete blood count, comprehensive metabolic panel, prothrombin time/international normalized ratio, partial thromboplastin time, creatine phosphokinase, fibrinogen, and urinalysis were normal. A multidisciplinary team contacted Poison Control immediately, who verified that North American Coral Snake Antivenin (NACSAV) was not immediately available. Poison Control helped to locate Central American coral snake (*Micrurus nigrocinctus*) antivenom from a major zoo, approximately 175 miles from our facility. Twelve hours after contacting the Poison Center, the patient received two vials of *M. nigrocinctus* antivenom. The following day, most of her symptoms began to resolve, and she was discharged on hospital day 3.

The patient returned to our ED 6 days after discharge complaining of systemic symptoms that started days after receiving antivenom, as well as a burning maculopapular rash to both upper extremities. The clinical picture was most consistent with serum sickness. The patient's symptoms improved with diphenhydramine, and she was discharged home. She was symptom-free at her follow-up appointment 14 days after the venom exposure.

DISCUSSION

Although the patient sustained a bite to the gloved thumb, her significant level of neurotoxicity may be better explained by the possibility of absorption of venom through the ocular mucous membranes. Coral snake envenomation, whether through cutaneous bites or ocular exposure, may cause significant neurotoxicity. The literature suggests that treatment of coral snake bites may include local wound care (usually minor wounds), minimization of movement, tetanus prophylaxis, and "pressure immobilization bandages" to decrease lymphatic flow (12). Importantly, constricting interventions, such as pressure immobilization bandages and tourniquets, generally should be avoided in the more common cases of cutaneous envenomation from Crotalinae snakes, as their venom is more cytotoxic than Elapidae, and such

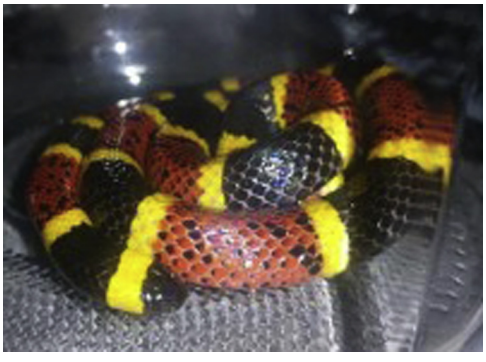

Figure 1. The coral snake captured by the patient. Note the "red on yellow" color pattern.

treatments may further increase local tissue damage (13,14). Ocular exposure warrants copious eye irrigation, while avoiding further membrane contamination. Neurotoxicity and respiratory compromise may not develop until 13 h after the envenomation. Asymptomatic patients should be observed accordingly at an appropriate level of care, with close respiratory monitoring and serial neurologic examinations. Emergency airway equipment should be immediately available. Medications causing sedation or muscular weakness should be avoided. Concerning pulmonary function results include forced vital capacity < 50% of predicted, a maximal negative inspiratory pressure < 30 cm H_2O, or a maximal expiratory pressure < 40 cm H_2O. End-tidal CO_2 may be a useful adjunct. Laboratory tests may be ordered on a symptom-specific basis, although significant coagulopathy and rhabdomyolysis are uncommon.

Patients who demonstrate neurotoxicity with or without respiratory insufficiency warrant consideration of coral snake antivenom. Antivenom options include NACSAV and alternative coral snake antivenoms. NACSAV is a horse-derived, whole immunoglobulin G (IgG) antibody that has been used for *M. fulvius* and *M. tener* envenomation in adults and children. Some case reports suggest that NACSAV decreases need for intubation or duration of muscle paralysis and intubation, whereas other data suggest no differences in intubation rates (15,16). However, NACSAV production ceased in 2006, and it may be located in a distant facility with a significant time delay for delivery (17). It is reasonable to contact a poison center early in the patient presentation, even if asymptomatic, to locate and deliver antivenom. Antivenom administration may be withheld until the development of the first neurotoxic symptoms. Also, all remaining doses of NASCAV have surpassed the original expiration date (2). The U.S. Food and Drug Administration (FDA) extended the expiration date of Lot L67530 through January 31, 2019. If concern exists, risks and benefits of administering previously expired antivenom may be discussed with the FDA Office of Vaccines, Blood, and Biologics (240-402-7800 or, after hours 301-796-8240). If no reaction is present 30 min after the equine test dose (included in the kit), the recommended initial dose of NACSAV is three to five vials by slow intravenous push for both adults and children.

If NACSAV is unavailable, Poison Centers may recommend coral snake "exotic" species antivenoms, which may be procured from zoos. Examples include Instituto Clodomiro Picado's Central American coral snake (*M. nigrocinctus*) antivenom, Instituto Bioclon's Coralmyn (Mexico) and Instituto Butantan's antielapidico serum (Brazil). The equine-based Central American coral snake (*M. nigrocinctus*) antivenom is effective in neutralizing *M. fulvius* venom, but effectiveness against *M. tener* is not widely cited (18). Our case is a rare report of the efficacy of *M. nigrocinctus* antivenom in *M. tener* envenomation. The antivenom instructions recommend an initial dose of 10 vials. Upon the dosing advice of the dispensing zoo toxicologist, our patient improved overnight after receiving two vials. Coralmyn is effective in neutralizing both *M. fulvius* and *M. tener* (19). Because these antivenoms are not currently FDA approved, seeking approval for "compassionate use" should be considered, if time allows, by contacting the FDA Office of Vaccines, Blood, and Biologics or your hospital's Institutional Review Board. FDA requires completion of "expanded access" paperwork within 15 working days. Hospitals should contact the FDA Center for Biologics Evaluation and Research at 1-800-835-4709 for more details. An additional possible future antivenom option includes an equine-based $F(ab')_2$, currently used in Brazil but still in clinical trials in the United States (20).

Immediate and delayed hypersensitivity reactions may occur after receiving whole IgG products (9). The incidence of equine-based crotalid antivenom side effects and reactions are increased with increased doses of whole IgG, so minimal dosing is desired, with guidance from a Poison Center (21). The incidence of immediate reactions to *M. nigrocinctus* antivenom is 15–25%, but incidence of delayed reactions is not well defined (22). After a nonreactive test dose, our patient developed a delayed serum sickness 4 days after receiving two vials of *M. nigrocinctus* antivenom that was successfully tempered with diphenhydramine. Hypersensitivity reactions are treated in the standard manner.

If the patient develops neurotoxicity and antivenom is not available or will be delayed, another pharmacologic treatment option is a trial dose of an anticholinesterase, such as neostigmine. Neostigmine acts by restoring neuromuscular transmission by increasing concentrations of acetylcholine in the neuromuscular junction to compete with venom at the nicotinic receptor. Neostigmine has demonstrated some effectiveness in reversing toxic effects from the venom of *M. frontalis* and *M. fulvius* (23,24). Pretreatment with atropine or glycopyrrolate should be considered to prevent potential excessive cholinergic effects of neostigmine.

The limitations of our patient encounter include the inability to diagnostically verify that the liquid in her eyes was coral snake venom. Further, the symptoms may be due to cutaneous bite envenomation alone. Moreover, it is possible that her symptoms of neurotoxicity were unconsciously produced as a psychosomatic disorder or consciously simulated. However, we believe a somatoform disorder or conscious simulation is less likely given the lack of history of behavioral disorder and no behavioral health complaints on examination.

In summary, our patient encounter allows consideration that both coral snake bites and ocular exposure to its venom may result in neurotoxicity. Neurotoxic symptoms may be significant, including respiratory insufficiency, which may be delayed. Observation of the asymptomatic patient in an appropriate facility with pulmonary and neurologic monitoring is important. Antivenom should be considered at the first signs of neurotoxicity. The limited supply of antivenoms should prompt consideration of its early procurement, even in the asymptomatic patient. Further, our case suggests Central American coral snake (*M. nigrocinctus*) antivenom may be effective against *M. tener* venom. Immediate and delayed reactions should be anticipated in response to whole-body antivenoms. Consultation with a toxicologist is recommended for a shared treatment strategy.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Coral snake envenomation is uncommon, but may be life threatening. The emergency physician should be aware that onset of neurotoxicity and respiratory insufficiency may be delayed. North American Coral Snake Antivenom is in very limited supply, so non-FDA-approved alternative coral snake antivenoms may be used for patients demonstrating neurotoxicity. Emergency physicians should be proactive in contacting a toxicologist to discuss the utility and procurement of antivenom, as well as consideration of adjunctive treatments, such as neostigmine.

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