

BRIEF COMMUNICATION

Non-front-fanged colubroid (“colubrid”) snakebites: Three cases of local envenoming by the mangrove or ringed cat-eyed snake (*Boiga dendrophila*; Colubridae, Colubrinae), the Western beaked snake (*Rhamphiophis oxyrhynchus*; Lamprophiidae, Psammophinae) and the rain forest cat-eyed snake (*Leptodeira frenata*; Dipsadidae)

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Context. Non-front-fanged colubroid snakes (NFFC; formerly and artificially taxonomically assembled as “colubrids”) comprise the majority of extant ophidian species. Although the medical risks of bites by a handful of species have been documented, the majority of these snakes have oral products (Duvernoy’s secretions, or venoms) with unknown biomedical properties/unverified functions and their potential for causing harm in humans is unknown. **Case details.** Described are three cases of local envenoming from NFFC bites inflicted respectively by the mangrove or ringed cat-eyed snake (*Boiga dendrophila*, Colubridae), the Western beaked snake (*Rhamphiophis oxyrhynchus*, Lamprophiidae) and the rain forest cat-eyed snake (*Leptodeira frenata*, Dipsadidae). The effects ranged from mild pain, edema and erythema to severe pain, progressive edema, and blistering with slowly resolving arthralgia; there were no systemic effects. **Discussion.** Although these three taxa occasionally inflict bites with mild to moderate local effects, there is no current evidence of systemic involvement. Two of these cases were reported to one of the authors for medical evaluation, and although verified, thus constitute reliably reported cases, but low-quality evidence. Type-1 local hypersensitivity may contribute to some cases, but most local effects observed or reported in these three cases were consistent with the effects of venom/oral product components.

Keywords “Colubrid” bites; Snakebites; *Boiga*; *Rhamphiophis*; *Leptodeira*; Medical hazard; Oral secretion; “Rear-fanged”; Venom; Local envenoming

Introduction

Non-front-fanged colubroid snakes (NFFC) comprise a diverse group of at least 2,350 species. Some of these snakes were previously and inaccurately placed together in the family Colubridae, and this led to the incorrect classification of a significant number of species. These snakes were previously termed, “rear-fanged”, “opisthoglyphous”, or “aglyphous” “colubrids” in reference to their posterior or mid-maxillary dentition that may or may not have external grooves, but lack completely enclosed internal lumens or canals. Some of the posterior or mid-maxillary dentition of

an undetermined number of these snakes is associated with a low-pressure gland that secretes its contents into the oral cavity via ducts that open at the level of the buccal mucosa of the associated teeth, or generally into the oral cavity. This gland has often been considered distinct and termed “Duvernoy’s gland” because of its considered functional morphological differences from those of elapid, viperid, and atractaspine lamprophiid venom glands, but has been grouped by some investigators with other squamate venom glands on the basis of established phylogenetic relationships and/or the presence in their glands/oral secretions or tissues of toxins, or their transcripts/genes that are shared among front-fanged snakes (FFC), for example, viperids, elapids, and atractaspine lamprophiids. Although a relative handful of toxins present in the oral secretions/venoms and glands of NFFC have been well characterized, the majority of NFFC produce oral products that have unknown properties and/or functions.^{1,2}

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The functional morphology of venom/secretion delivery of these snakes is relevant to medical concerns due to their low-pressure system and its association with non-canalculated maxillary teeth, NFFC venoms or Duvernoy's secretions are *inoculated*, rather than injected into a prey or a human victim. Therefore, putative quantities of venom/secretion delivered to a human victim may often be relatively limited volumes, and could be influenced by the duration of the bite (e.g., how long the snake is attached), as well as the distance/extent that the snake advances its jaws ("pterygoid walk") while biting. However, some NFFC are certainly capable of inflicting medically significant "quick release" bites.^{1,3}

Five species of NFFC, the African boomslang (*Dispholidus typus*, Colubridae, Colubrinae), African twig, vine or bird snakes (*Thelotornis kirtlandii* and *T. capensis*, Colubridae, Colubrinae), and the Asian red-necked keel back (*Rhabdophis subminiatus*, Natricidae) and tiger keel back (*R. tigrinus*, Natricidae), have caused life-threatening and/or fatal human envenomings.^{1,2} While some observations suggest that many common smaller species of NFFC present a low medical risk, such assessment must be cautiously tempered because of the limited available comprehensive data; some can produce significant local morbidity, and the vast majority of NFFC have not been studied at all.¹ For these reasons, careful documentation of the clinical effects of NFFC bites is important even when featuring relatively mild local effects because this facilitates the construction of a medically accurate risk profile for a given species.

We present here three cases of bites by three taxa of NFFC that caused mild-to-moderate local pathology.

Case reports

Case #1. Mangrove or ringed cat-eyed snake, *Boiga dendrophila*

In early November 2011, a 17-y/o female semiprofessional "snake handler" presented to the Emergency Department of a district hospital in rural Malaysia following a bite on the metacarpal of the fourth digit, right hand by her "pet" *Boiga dendrophila*, a recently wild-caught specimen approximately 1.5 m in total length (Fig. 1A–C). She was bitten while handling the snake when accidentally touching a wound on the snake's head. It took approximately 30 s for her to free her fingers from the snake's mouth. She did not specifically describe any advancement of the snake's jaws during the bite. There was brief bleeding from the puncture wounds/bite marks that she washed with tap water. There was mild swelling initially, which progressed from the finger and involved the hand (Fig. 1A and B).

It was noted that although the patient reported no significant medical history or co-morbidities, she had participated for several years in the family business of providing shows featuring snake handling, and reported nine previous bites from their "pet" snakes. The last had occurred one month prior to the current bite at which time she reported being bitten on the fifth digit on the right hand by another *B. dendrophila*, but stated that her bite in this case was "much worse". The appearance of the wound after this bite prompted her



Fig. 1. Local effects of a bite by a 1.5-m mangrove, or ringed cat-eyed snake, *Boiga dendrophila* (Case #1). This taxon is heavy bodied, arboreal, common in parts of its range (Indonesia, Western Malaysia, Singapore, Cambodia, Vietnam through Thailand, and the Philippines), and is popular in private collections. Panel (A) Dorsal view of fourth digit, right hand, 21 h after bite. Note the erythema, mild ecchymoses, and digital edema with progression limited to the immediate carpal region (photo copyright to Mohd Shukruddeen Salleh, used with permission). Panel (B) Ventral view of the fourth digit, right hand 21 h after bite. Note the multiple puncture marks on the metacarpal. There is more intense erythema, ecchymoses, and edema in the skin on the metacarpal (photo copyright to Mohd Shukruddeen Salleh, used with permission). Panel (C) A representative specimen of *B. dendrophila* (Thailand; photo copyright to Taksa Vasaruchapong, used with permission).

to seek medical help, and presented approximately 21 h after being bitten. One of the authors (AKI) was consulted about the patient shortly after arrival in hospital, and another (SAW) was consulted shortly thereafter.

Examination of the hand revealed multiple puncture wounds on the fourth digit with several probably inflicted by the enlarged posterior maxillary teeth (Fig. 1B). She had mild pain (described as 2/10) over the bruised finger and hand, and reported mild pruritis involving the bitten area, but no wheals, angioedema, dysphagia, periorbital edema, or wheezing were noted. There was also no fever, numbness, axillary lymphadenitis, perioral numbness, labored respiration/tachypnea, or weakness. Her vitals remained normal and stable. While in the ED she was given a single intravenous dose of cefuroxime, 1.5 g, and oral diclofenac sodium 50 mg. Laboratory investigations including complete blood count and coagulation panel were all unremarkable.

Due to the progressive edema and erythema, the patient was admitted to the medical ward for serial observation. The patient received a single intravenous dose of hydrocortisone, 100 mg and oral chlorpheniramine maleate, 4 mg. There was progressive improvement in the swelling, as well as tenderness, and no expansion of the ecchymosis. She remained afebrile, and was discharged home 3 days after the bite. On follow-up by telephone the patient reported no sequelae.

Case #2. Western beaked snake, *Rhamphiophis oxyrhynchus*

A 24 y/o male amateur private collector was removing a tick that was attached near the head of a captive adult (specific size unclear) *Rhamphiophis oxyrhynchus* when he was bitten on the metacarpal of his left index finger. The snake advanced its jaws and remained attached for approximately 20 s. The victim had a history of multiple bites from several other species of NFFC (e.g., false water cobra, *Hydrodynastes gigas*, Dipsadidae; *Boiga dendrophila*; Asian vine snake, *Ahaetulla prasina*, Colubridae, Colubrinae; lyre snake, *Trimorphodon biscutatus*, Colubridae, Colubrinae; and a few others) that caused only lacerations and slight local transient pruritis, but also had two previous crotaline envenomings from a prairie rattlesnake (*Crotalus viridis*, Viperidae, Crotalinae) and a sidewinder (*C. cerastes*, Viperidae, Crotalinae) and had received six ampoules of Crofab[®] for the *C. viridis* envenoming. The victim noted a sensation compared to that of a “bee sting” that he identified as the penetration of one of the enlarged posterior maxillary teeth. He was concerned about injuring the snake, and declined forcibly removing it; therefore, the snake maintained a protracted tight grip. After successfully removing the snake, the victim reported experiencing pain that was “much worse” than either of his previous rattlesnake bites, or any other previous sting (the victim had a history of having been stung by several taxa of insects and stingrays). Twenty-minutes after the bite, his hand became progressively edematous and erythematous (Fig. 2A). Several hours later, the edema involved the lower forearm (Fig. 2B), and several hours after that he reported

difficulty in moving his arm. By the next morning, the edema began to subside, range of motion returned to normal, and by mid-day only mild edema and erythema remained. On the following day, almost all signs of the bite were resolved aside from mild general tenderness of the affected arm. The victim did not receive formal medical review, and did not take any medications or attempt first aid during the incident. However, the victim reported the bite and medical evaluation of the case was performed by one of the authors (SAW). The victim reported no known atopy, and aside from the previous envenomings, as well as depressive disorder and attention deficit disorder (treated respectively with fluoxetine, 40 mg/d, and dexadrine, 15 mg/d), had no significant medical history/co-morbidities. There was no persistent wound or other sequelae.

Case #3 Rain forest cat-eyed snake, *Leptodeira frenata*

In May 2013, a 35-yo male professional herpetologist (one of the authors, RG) in Laguna del Tigre National Park, northern Guatemala was examining a newly collected 53 cm (total length) female *L. frenata* when the snake seized the middle phalanx of the third digit, right hand. The snake was attached to the victim for approximately one minute, but did not advance its jaws while attached. Within a few seconds of the bite, the victim began to feel pain in the third and fourth digits of the hand. He reported rapid edema of the third digit with the mid-interphalangeal joint particularly affected. The finger became erythematous and two min after the bite ecchymoses appeared on the palmar surface of the affected finger. Approximately 1 h after the bite, the edema progressed to the dorsal surface of the right hand and wrist; the victim described “intense pain” at the mid-interphalangeal joint and noticed blister formation proximal to the bite site (Fig. 3A). He also reported feeling intermittently nauseated during the hour following the bite. Minor bleeding from the bite continued for almost 3 h, and the blisters began discharging serosanguinous fluid some 4 h post-envenoming (Fig. 3B). Shortly thereafter (approximately 5–6 h post-envenoming), he reported throbbing pain so severe that he

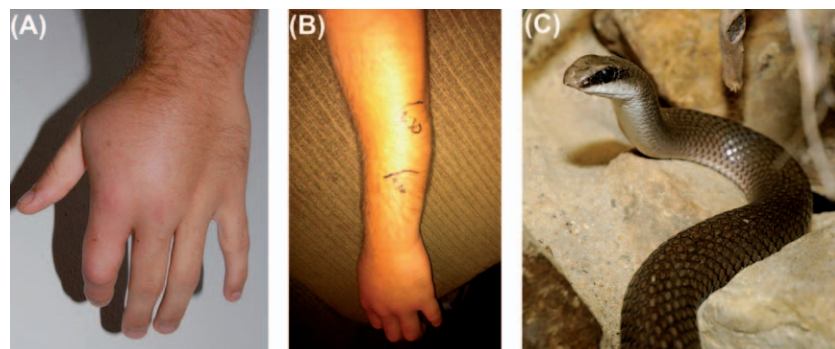


Fig. 2. Local effects of a bite by a captive Western beaked snake, *Rhamphiophis oxyrhynchus* (Case #2). Panel. (A) Dorsal view of left hand, 20 min after bite. Note that the edema rapidly involved the entire thenar aspect of the hand. The bite was inflicted on the metacarpal of the left index finger and the snake was attached for some 20 s (photo courtesy of Zack West, used with permission). Panel (B) Dorsal view of left forearm approximately 3 h after bite. The edema has progressed and involves the mid-forearm. The victim reported severe pain shortly after sustaining the bite (photo courtesy of Zack West, used with permission). Panel (C) A representative specimen of *Rhamphiophis* spp., the rufous beaked snake, *R. rostratus*. There are three taxa of *Rhamphiophis*, an exclusively African genus of active, semi-fossorial snakes. The illustrated species was previously assigned a subspecies (*R. oxyrhynchus rostratus* Broadley and Howell, 1991), but was later given full species status (*R. rostratus* Spawls et al., 2001) [photo courtesy of and copyright to Milan Korinek, www.biolib.cz/en; used with permission].

felt “near to hallucinating”. The edema appeared to subside and the pain decreased after approximately 36 h, although some increased pain was occasionally felt at the bite site. The blisters continued to discharge for about 6 days, and eventually formed a thickened scab that improved over the following 3 days with complete resolution approximately 8 days post-envenoming. From the time of the bite until disappearance of the blistering, treatment consisted only of paracetamol, chlorphenamine (first taken about 5 h after the bite), and

antibiotics (amoxicillin, 875 mg, twice daily for 10 days). There was no formal medical review, but the victim sought medical consultation with one of the authors (SAW). Local wound sensitivity and mild arthralgia of the right mid-IPJ persisted for almost 5 weeks after the bite, and then resolved without sequelae.

In the course of conducting fieldwork, the victim previously had regular contact with snake products (e.g., cloacal gland secretions, excreta, shed skins, etc.), and had a history of inconsequential bites from several taxa of NFFC (including the congener, the Northern cat-eyed snake, *Leptodeira septentrionalis*, Dipsadidae; the speckled racer, *Drymobius margaritiferus*, Colubridae, Colubrinae), as well as one FFC taxon (terciopelo, *Bothrops asper*, Viperidae, Crotalinae). The victim reported no significant medical history.

Discussion

The three cases reported here featured clinical manifestations that ranged from only mild local edema, erythema and pain that were primarily attributable to physical trauma (Case #1, *B. dendrophila*); moderate local edema and pain (Case #2, *R. oxyrhynchus*), to moderate-to-severe local pain, blistering, and progressive local edema resembling that of a mild local crotaline envenoming (Case #3, *L. frenata*). Although the victim in Case #3 reported nausea, likely an autonomic effect, and the sensorial effects of local pain reported as “intense”, there was no reported sign or symptom consistent with systemic envenoming. The critical interpretation of the clinical evolution of Cases #2 and #3 is limited because the victims received no formal medical review, provided self-reported accounts and did not have their symptoms/signs recorded by a medically qualified observer. They also did not have any laboratory investigations. Therefore, although carefully recorded details were provided with supportive photographs, these two cases must be considered reliably reported descriptions, but constitute low-quality evidence. Following the Strength of Recommendation Taxonomy (SORT) described by Ebell et al.⁴, as modified by Weinstein et al.¹, the Evidence Level assigned to Case #1 is “B” (e.g., essentially, a limited case study with formal medical evaluation), while that of Cases #2 and 3 is “C/D” (e.g., essentially, a detailed case reported by a non-medically qualified individual without formal medical review).

The composition of NFFC venoms/Duvernoy’s secretions is similar to that of venoms of viperids, elapids and *Atractaspis* spp.^{5–14} and recent proteomic, genomic, and transcriptomic investigations have further characterized or identified a rich array of biologically active constituents including multiple enzymes and isozymes, cysteine-rich secretory proteins (CRISPs), myotoxins, and post-synaptic neurotoxins.^{10–18} Although it is likely that some of these (e.g., proteolytic hemorrhagins) contribute to the local pathology observed after some medically significant NFFC bites, to date, there is no information that facilitates direct assignment of a defined molecular species to the well-documented effects of *B. dendrophila* bites, or to the reported bites by the other two taxa described here.



Fig. 3. Local effects of a bite by a rainforest cat-eyed snake, *Leptodeira frenata* (Case #3). Panel (A) Ventral view of third digit, right hand approximately 1 h after bite. Note the hemorrhagic blistering of the bitten digit. The victim reported that he experienced intense pain at the time the photo was taken (photo copyright to Rowland Griffin, used with permission). Panel (B) Ventral view of third digit, right hand approximately 3–4 h after bite. Note that the hemorrhagic blistering of the bitten digit has increased in volume and the blister located on the metacarpal has gained volume. Mild mottling erythematous changes are evident, as is edema involving the proximal palmar surface. The digital appearance is reminiscent of a mild to moderate local crotaline envenoming. The victim reported short-term sequela consisting of arthralgia of approximately 5 weeks duration (photo copyright to Rowland Griffin, used with permission). Panel (C) The *L. frenata* specimen (photographs archived in the Colecciones Biológicas de la Universidad del Valle de Guatemala, specimen #UJVG-0003) responsible for the bite described in Case #3. There are approximately 12 taxa of *Leptodeira* and the genus has a wide distribution extending from extreme southern Texas essentially throughout Central America and is found at elevations up to 2000 m; some occur in semi-arid habitats, while others are found in tropical rain forest. There is limited information about the biochemistry and pharmacology of venoms of *Leptodeira* spp. (photo copyright to Rowland Griffin, used with permission).

As all victims had prior repeated exposure to ophidian buccal secretions and products of captive husbandry (e.g., shed skins, excreta, etc.), all that may contain shared antigens, it is possible that they may have become sensitized to venom and/or other oral secretion antigens. There are several documented cases of bites from NFFC (e.g., from a Western hog-nose snake, *Heterodon nasicus*; Dipsadidae)¹⁹ that contained some features suggestive of secondary effects resulting from hypersensitivity. Local effects from Type I hypersensitivity may include erythema, edema, induration, blistering, ulceration, and excoriation/desquamation, all similar to that of mild-to-moderate local envenoming from many viperids and some elapids. There is a great deal of uninformed, inaccurate speculation, and medically unsupported interpretation on the Internet, in popular media, and even in some biomedical literature about the nature of medically significant effects from NFFC bites.^{1,2} Characteristics of some documented cases have recently been comprehensively analyzed.^{1,2} Assessment of IgE levels in those who have unfortunately received medically significant NFFC bites could help determine the possible role of atopic responses in some of these cases.^{1,19} However, as noted previously, the presence in some NFFC oral products of toxins capable of inducing local effects in a bitten human certainly suggests that in many cases the observed effects are caused by the direct actions of components present in NFFC venoms and/or other secretions.

Case #1 is concordant with the few (<4) well-documented reports of bites by *B. dendrophila*,¹ and like the few other well-studied members of the genus *Boiga* (containing approximately 33 species), has a serous low-pressure venom gland (or, Duvernoy's gland) and associated enlarged, deeply grooved posterior maxillary teeth that conduct the secreted venom by capillary action along the dental surface.¹

Undoubtedly, there have been many unreported *B. dendrophila* bites (particularly from captive specimens) but as noted above, only a handful has been documented. There are several anecdotal cases reporting more severe local effects that are commonly discussed, and occasionally illustrated, on the Internet. While it is likely that larger specimens of *B. dendrophila* can inflict more medically significant bites, all significant cases require careful qualified medical review, evaluation and documentation before being utilized in hazard index assessment for the species.^{1,2}

To date, all well-documented cases of *B. dendrophila* bites have only required local wound care. In the case presented here, the patient was given i.v. hydrocortisone and p.o. chlorpheniramine. There is currently no evidence that supports using these, or parenteral calcium, in any snakebite, although their use in snakebite management persists in some rural hospitals in Asia, Latin America, and Eastern Europe.¹ However, as discussed above, clinical evidence of Type I hypersensitivity should prompt provision of appropriate pharmacotherapy depending on the severity: in the setting of anaphylaxis, epinephrine should be given according to protocol, while oral anti-histamines are reasonable for mild reactions. Intravenous corticosteroids provide delayed action and probably present more adverse side effects in this setting than benefit, and are thus contraindicated.¹ Likewise,

the provision of any non-steroidal anti-inflammatory drug (e.g., diclofenac, as provided to the patient in this case) is contraindicated because in the possible event of coagulopathy this can promote active bleeding and renal dysfunction.

In Case #2, the victim sustained a firm bite by a *R. oxyrhynchus* that included "pterygoid walking", the process by which a snake advances its jaws by alternating bilateral maxillary mobilization. This process increases venom/oral secretion release when extracting these from captive specimens (SAW, personal observations) and may conceivably enhance venom/oral secretion during prey capture, as well as in bites inflicted on humans. The victim reported distressing pain, which reportedly exceeded that experienced during a crotaline envenoming, and he exhibited locally progressive edema (Fig. 2A and B). Many of the considerations noted for Case #1 also apply here, especially the possible role of Type I hypersensitivity, as the victim had extensive previous exposure to FFC and NFFC products, as well as the two previous FFC (crotaline) envenomings in which he was treated on one occasion with antivenom. However, as in Case #1, the descriptive course of the bite and its effects do suggest that the primary effects were caused by the inoculation of locally toxic components present in the introduced venom/oral products.

There are no previously well-documented bites by *Rhamphiophis* spp., but Spawls et al.²⁰ opined that large adults could deliver a "powerful bite" and that their venom "does not appear to be particularly toxic to humans". *R. oxyrhynchus* has serous low-pressure venom glands (Duvernoy's glands) associated with grooved, enlarged posterior maxillary teeth.²¹ To date, there has been limited investigation of the venom/oral secretion properties of *Rhamphiophis* spp., and only a single toxin has been characterized.^{22,23} Currently, there is no information that supports any possible clinical importance of this toxin. However, it is noteworthy that another psammophine lamprophiid, the Montpellier snake (*Malpolon monspessulanus*) is the only NFFC that has inflicted a verified and well-documented neurotoxic envenoming.²⁴

The medically significant local effects that developed in Case #3 have also been described after protracted bites by several other NFFC taxa.^{1,19} Review of the few (<4) previously reported bites by *Leptodeira* spp. indicated only mild local effects.¹ Studied members of the genus have serous low-pressure venom glands (Duvernoy's glands) associated with enlarged posterior maxillary teeth that often contain ventrolateral grooves.^{25,26} It is speculative to consider the specific basis for the pathophysiology that occurred after this bite, but hypothetically the victim's presentation is at least partly consistent with the local effects of rhexic proteolytic hemorrhagins introduced into the relatively rigid compartments of the interphalangeal joint. Venom of the congener, *Leptodeira annulata ashmeadi* (Ashmead's banded cat-eye snake), contained proteolytic and hemorrhagic activities; the minimal hemorrhagic dose was 7.8 g.²⁷ In some cases, the severity of local effects may be enhanced by attempted inappropriate first aid and/or non-sterile interference with the wound. Although there is no evidence supporting routine antibiotic prophylaxis in snakebites, any bite featuring

pronocrotic effects or exhibiting signs suggestive of an evolving secondary infection should prompt initiation of a broad-spectrum antibiotic regimen covering anaerobic and facultative anaerobic organisms.¹

It must be emphasized that the lack of available information about the medical hazards by little-studied species should not be incorrectly interpreted as synonymous with “harmless”, or “dangerous”, as there are insufficient data about the possible medical significance of the majority of NFFC taxa. The vast majority of NFFC bites occur as a consequence of intentional manual handling of a specimen. Handling should be avoided unless absolutely necessary and should never occur after contact with food items/potentially natural prey, as this has caused several well-documented medically significant NFFC bites.^{1,3,19} Therefore, as the effects of many NFFC bites have been anecdotally reported, and the majority not reported at all, an evidence-based approach to risk analysis is mandatory, but caution is strongly advised. Review by a physician, or other available medical professional, of any bite distressing to the victim is strongly recommended.

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Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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