Toxicon 157 (2019) 12–17

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Case report

First reported case of thrombocytopenia from a *Heterodon nasicus* envenomation

Nicklaus Brandehoff[a,c,*], Cara F. Smith[b], Jennie A. Buchanan[a], Stephen P. Mackessy[b], Caitlin F. Bonney[a]

[a] Rocky Mountain Poison and Drug Center – Denver Health and Hospital Authority, Denver, CO, USA
[b] School of Biological Sciences, University of Northern Colorado, Greeley, CO, USA
[c] University of California, San Francisco-Fresno, Fresno, CA, USA

ARTICLE INFO

Keywords:
Envenomation
Colubridae
Heterodon nasicus

ABSTRACT

Context: The vast majority of the 2.5 million annual worldwide venomous snakebites are attributed to Viperidae or Elapidae envenomations. Of the nearly 2000 Colubridae species described, only a handful are known to cause medically significant envenomations. Considered medically insignificant, *Heterodon nasicus* (Western Hognose Snake) is a North American rear-fanged colubrid common in the legal pet trading industry. Previously reported cases of envenomations describe local pain, swelling, edema, and blistering. However, there are no reported cases of systemic or hematologic toxicity.

Case details: A 20-year-old female sustained a bite while feeding a captive *H. nasicus* causing local symptoms and thrombocytopenia. On day three after envenomation, the patient was seen in the emergency department for persistent pain, swelling, and blistering. At that time, she was found to have a platelet count of 90×10^9/L. Previous routine platelet counts ranged from 315 to 373×10^9/L during the prior two years. Local symptoms peaked on day seven post envenomation. Her local symptoms and thrombocytopenia improved on evaluation four months after envenomation.

Discussion: We report the first *Heterodon nasicus* envenomation causing both local toxicity and thrombocytopenia. Potential mechanisms based on *H. nasicus* venom composition are discussed in detail. Treatment is largely supportive. Bites by *H. nascius* should be evaluated by a toxicologist familiar with Colubridae species. This represents the first reported case of hematologic toxicity from envenomation by a North American colubrid snake.

1. Introduction

Venomous snakebites are a significant cause of morbidity and mortality worldwide and were recently designated a neglected tropical disease by the World Health Organization (WHO, 2018). Most of the 2.5 million clinically significant snakebites worldwide are due to elapid, viperid, and atractaspid envenomations (Chippaux, 1998). The largest family of snakes, Colubridae, consists of 2000–2500 species, of which only a handful have been documented to cause fatalities or serious morbidity. In Africa, *Dispholidus typus* (Boomslang), *Thelotornis kirtlandii* (Northern Twig Snake) and *Thelotornis capensis* (Twig Snake) and in Asia, *Rhabdophis subminiatus* (Red-necked Keelback) and *Rhabdophis tigrinus* (Tiger Keelback), are well-documented to cause medically significant envenomations (Weinstein and Keyler, 2009). Other potentially medically important Colubridae include *Boiga irregularis, Malpolon monspessulanus, and Philodryas* sp., though evidence is limited (Weinstein and Keyler, 2009). Despite growing interest in rear-fanged snake venoms, there may be several venomous species in the family Colubridae yet to be identified that could produce venoms resulting in medically important envenomations.

Approximately 9000 venomous snakebites per year occur in the United States (Lavonas et al., 2011). The vast majority of bites are by pitvipers (family Viperidae, subfamily Crotalinae, genera *Crotalus*, *Agkistrodon*, and *Sistrurus*; Lavonas et al., 2011), with less than 100 bites annually from coral snakes (family Elapidae, genus *Micrurus*; Mowry et al., 2013). Approximately 5–12 deaths occur per year and are mainly due to crotaline envenomations (Lavonas et al., 2011). No native colubrid species have been reported to cause medically important envenomations in the United States.

The North American Colubridae genus *Heterodon* consists of four

* Corresponding author. UCSF-Fresno Department of Emergency Medicine, 155 N. Fresno Street, Fresno, CA 93701, USA.
E-mail address: nick.brandehoff@me.com (N. Brandehoff).

https://doi.org/10.1016/j.toxicon.2018.11.295
Received 24 September 2018; Received in revised form 9 November 2018; Accepted 11 November 2018
Available online 19 November 2018
0041-0101/

species: *Heterodon nasicus, H. simus, H. kennerlyi,* and *H. platirhinos. Heterodon nasicus*, commonly known as the Western Hognose Snake, is considered relatively easy to care for in captivity and is a common pet in North America. Specimens are well known for distinctive behaviors, including hissing displays, flattening of the head to appear larger and more threatening, and subsequently playing dead when threatened further. A medium-sized snake, averaging 50 cm in length and often found in loose soils, *H. nasicus* ranges from southern Canada to northern Mexico and from Illinois west to Colorado. It is a rear-fanged venomous snake that feeds mainly on amphibians, insects, lizards and birds. The medical significance of *H. nasicus* envenomations is unclear. Envenomations causing local toxicity including edema, pain, ecchymosis, and hyperpigmentation have been reported (Bragg, 1960; Grogan, 1974; Kroll, 1976; Morris, 1985; Phillips et al., 1997; Weinstein and Keyler, 2009). There are no previously reported cases of hematologic toxicity. Here we report the first case of hematologic toxicity from a *H. nasicus* envenomation.

2. Case report

A 20-year-old woman with a history of iron deficiency anemia, taking iron supplementation, presented to the emergency department (ED) three days after being bitten on the second inter-digit web of her left hand by her captive-born two-year-old pet albino Western Hognose Snake *(Heterodon nasicus*; Fig. 1). Just prior to the bite, the patient had handled a warmed dead neonate mouse before placing it in a separate container used for feeding. She then proceeded to transfer the snake to the feeding container by hand. During transfer, the snake bit the patient at the second interdigit space on her left hand. She was unable to remove the snake for approximately two minutes, after which the snake spontaneously released. Several minutes after the bite, the patient began to experience pain and irritation at the bite site. Over the next three days, the patient experienced progressive pain, swelling, and ecchymosis extending from her left hand to left forearm associated with the development of several large fluid-filled blisters proximal to the bite site (Fig. 2A–D).

Due to progression of symptoms, the patient sought medical care at a local emergency department on day three post-envenomation. The patient was found to have a swollen left hand and forearm, four out of ten pain on the Wong-Baker FACES pain scale, ecchymosis, and multiple bullae with clear fluid. There was no documented tenderness or bleeding, and sensation and capillary refill remained intact. Her documented vital signs included a heart rate of 86 beats per minute, systolic blood pressure of 110 mm Hg and diastolic blood pressure of 68 mm Hg, respiratory rate of 15, oxygen saturation 100%, and an oral temperature of 37.1 °C. Laboratory tests were notable for a white count of 12.7×10^9/L, hemoglobin of 10.7 g/dL, and a platelet count of 90×10^9/L. Her International Normalized Ratio (INR) and prothrombin time (PT) were 1.1 and 12.9 seconds, respectively. Laboratory tests one year prior showed a hemoglobin of 9.3 g/dL and platelet count of 315×10^9/L (Table 1). Electrolytes and liver function tests were within normal limits. A left upper extremity ultrasound was negative for a deep vein thrombosis. Toxicology was consulted for management and potential treatment. The snake was positively identified as *H. nasicus* via a video provided to the consulting toxicologists by the patient (Fig. 1). Her complete physical exam was normal other than reported findings. Supportive care with close follow-up was recommended. Cephalexin was prescribed by the treating emergency medicine physician at discharge.

On a follow-up visit four days after envenomation, the patient was prescribed clindamycin and amoxicillin/clavulanic acid in addition to continued cephalexin for presumed cellulitis. Repeat laboratory tests (complete blood count with differential, partial thromboplastin time, and PT with INR) were ordered but specimens were not collected. On day seven, her physical exam was notable for an increase in the number of fluid-filled bullae, expansion of the surrounding erythema, and extension of skin changes beyond the antecubital fossa (Fig. 3). Cephalexin was discontinued, and the patient was prescribed diphenhydramine in addition to her ongoing clindamycin and amoxicillin/clavulanic acid regimen. She was referred to dermatology. On day eleven, the bullae on the left forearm were significantly reduced in size and more flaccid, and the surrounding erythema had resolved. Her upper extremity was non-tender to palpation. Sixteen days after envenomation, bullae were noted to be less taut and less erythematous. Clindamycin, amoxicillin/clavulanate, and diphenhydramine were continued. A new macular and erythematous rash over her upper chest and back was noted, for which 1% hydrocortisone lotion was prescribed for suspected allergic dermatitis. At a visit thirty days after the bite, the upper extremity bullae and erythema had resolved. She was noted to have hyperpigmentation at the prior locations of the bullae. Betamethasone dipropionate 0.05% ointment and vitamin E lotion were prescribed for hyperpigmented dermatitis. At this visit she complained of arthralgias, joint swelling, and myalgias. During multiple visits, follow-up laboratory tests were ordered by her primary care doctor and

Fig. 1. Left: photograph of albino *Heterodon nasicus* involved in the reported case after swallowing a neonatal mouse. A second neonate is located in bottom right of picture (still from video provided by patient). Right: normal patterned *Heterodon nasicus* from northeastern Colorado.

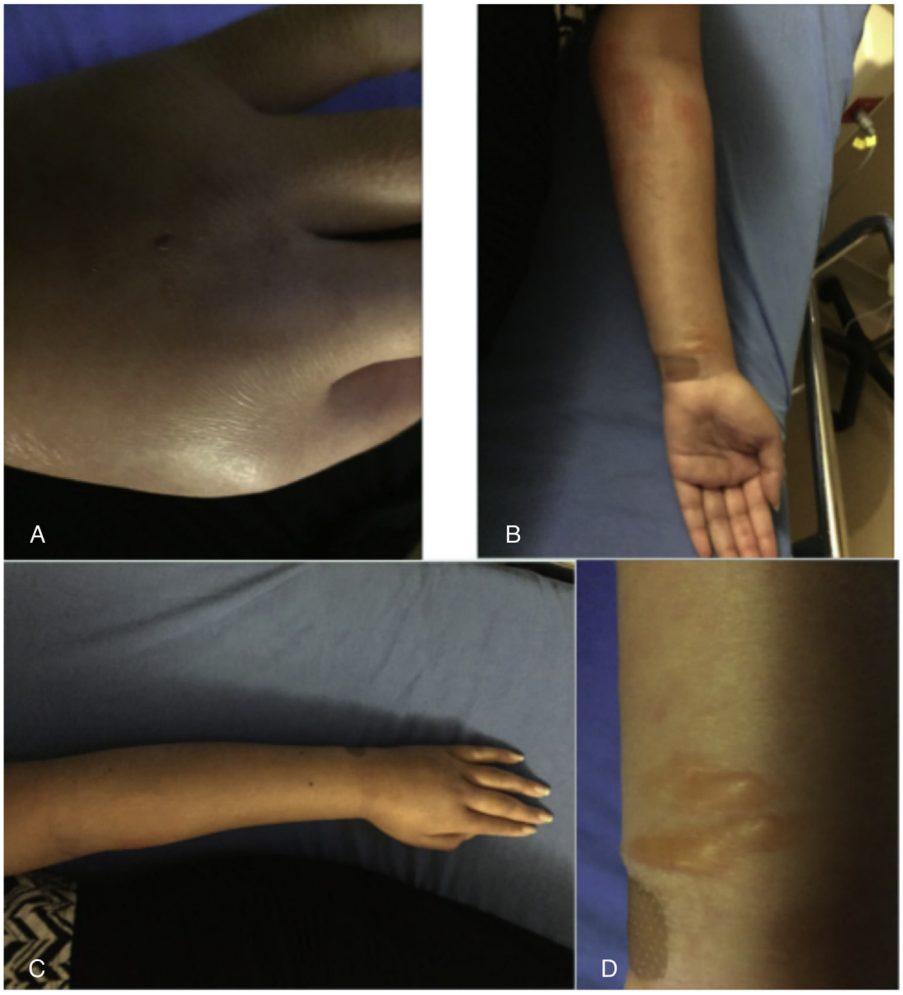

Fig. 2. A-D. Bitten left upper extremity 3 days post envenomation. Note swelling of the hand (A & C) and the presence of several bullae in the vicinity of the wrist (B & D).

Table 1
Complete blood count of patient.

	3 years prior	1 year prior	Day 3	Day 130
White blood cell count (x10^9/L)	5.2	6.8	12.7	6.4
Hemoglobin (g/dL)	9.9	9.3	10.7	10.4
Hematocrit (%)	29.2	29.5	31.2	29.2
Platelet count (x10^9/L)	373	315	90	315

dermatologist but the patient did not follow up at the laboratory. The patient was lost to follow up over the next several months. Four months after the bite, the patient was evaluated by the primary author. She had normal function of her left arm and hand, with complete resolution of her swelling and pain (Fig. 4). She continued to have hyperpigmentation of the affected areas. A complete blood count showed a white blood cell count of 6.4 × 10^9/L, hemoglobin of 10.4 g/dL, and platelet count of 315 × 10^9/L (Table 1). She finished her antibiotic course as previously prescribed. She continues to keep the snake as a pet.

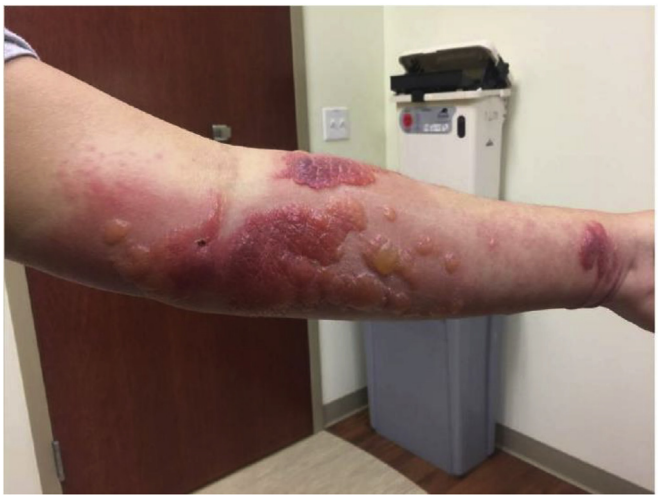

Fig. 3. 7 days post envenomation of left upper extremity. Note extensive formation of bullae and hyperpigmentation, extending into the median brachial surface.

3. Discussion

Edema, ecchymoses, blistering, and discoloration are known sequelae of significant *H. nasicus* envenomations. Bragg (1960) noted pain and swelling one-third up his arm lasting for approximately 2 weeks after being bitten on his thumb. Kroll (1976) documented pain to the elbow after a bite to the thumb, and Weinstein and Keyler (2009) documented whole arm swelling, ecchymoses, and blistering similar to our patient's presentation. While the local toxicity experienced by the patient in this report is consistent with previously reported *H. nasicus* bites, concomitant thrombocytopenia is previously unreported.

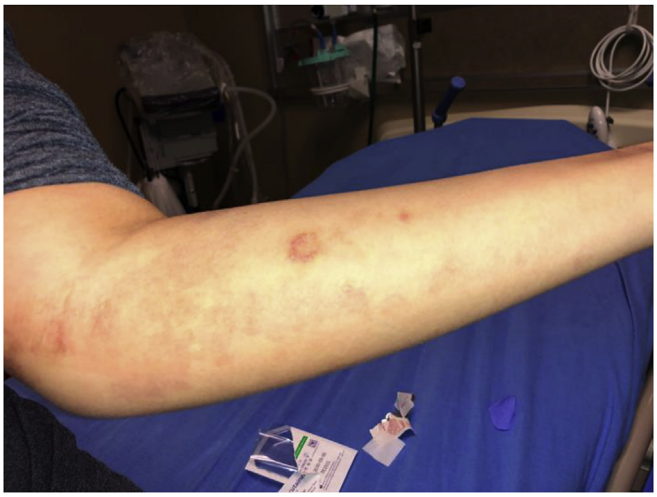

Fig. 4. 130 days post envenomation of left upper extremity. Effects of the bite have largely resolved, with minimal scarring apparent.

Limited data exist on venom components of *Heterodon* sp. that may be responsible for local or hematologic effects. Hill and Mackessy (2000) analyzed the venom and saliva secretions of 12 Colubridae species including *H. nasicus*. *Heterodon nasicus* venom exhibited moderate snake venom metalloprotease (SVMP) activity, high phosphodiesterase (PDE) activity, and no phospholipase A_2 (PLA_2) activity. Saliva from the same *H. nasicus* displayed moderate SVMP activity and moderate levels of PLA_2 activity. Thrombin-like, hyaluronidase, and kallikrein-like activities were not found in venom or saliva.

These findings are consistent with protein gel electrophoresis (previously unpublished) that the authors performed using crude venom extracted from a wild-caught *H. nasicus* (Fig. 5). Our data shows the presence of phosphodiesterases (~66 kDa), P-III snake venom metalloproteinases (P-III SVMPs, ~53 kDa), and cysteine-rich secretory proteins (CRiSPs; ~23 kDa). No PLA_2 enzymes were detected in the venom of our sample; moderate PLA_2 activity has previously been reported only in the saliva of *H. nasicus* (Hill and Mackessy, 2000). We did not collect saliva from the snake used in this sample and therefore were unable to analyze it for PLA_2 activity.

Phosphodiesterases are commonly found in snake venoms, yet few studies have looked at their clinical effects or biological roles. Once thought to be largely nontoxic, phosphodiesterases are now known to release purines endogenously, which may act in synergism with other venom toxins to disrupt normal physiological processes (Aird, 2002, 2005). Previous murine models found that intravenous injection of PDEs caused hypotension and decreased locomotor activity by reducing cyclic adenosine monophosphate (cAMP) concentrations, causing disruption of cellular signaling (Russell et al., 1963), Interestingly, 5′ nucleotidases and adenosine diphosphatases (ADPases), which have been shown to have overlapping substrate affinities with phosphodiesterases, inhibit platelet aggregation and blood coagulation (Dhananjaya et al., 2010). However, the role of phosphodiesterases in this case presentation is unclear.

Snake venom metalloproteinases, especially subtype P-III, are known to cause both local and systemic effects, including coagulopathy, hemorrhage, edema, pain, and blistering. These effects are due to hydrolysis of the basement membrane, increased vascular permeability, release of pro-inflammatory cytokines, and destruction of the dermal-epidermal junction (Gutiérrez et al., 2005, 2010b; Kamiguti et al., 1996). P-III SVMPs are also much more likely to have hemotoxic and hemorrhagic effects than other SVMP subtypes. Most SVMPs are classified as Group A and do not require a cofactor to cause procoagulant effects, while Group B SVMPs require Ca^{2+} for activity. These procoagulant effects are achieved by consumptive hydrolysis of fibrinogen

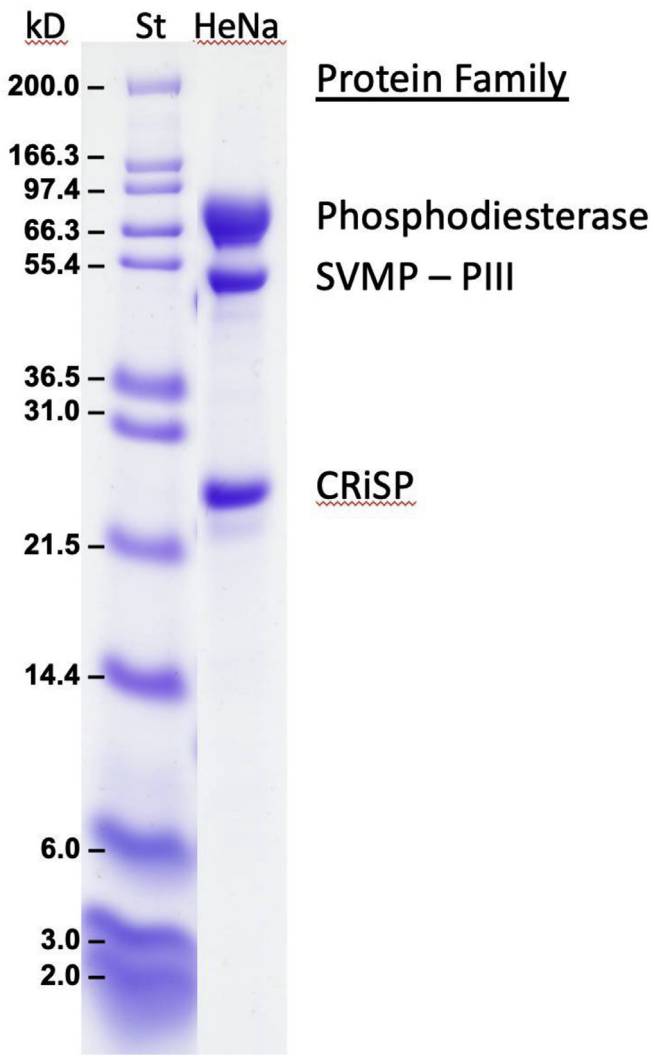

Fig. 5. Gel electrophoresis of venom from a wild-caught adult male *Heterodon nasicus* (NE Colorado). Crude venom (20 μg) was analyzed on a NuPAGE Novex Bis-Tris 12% acrylamide mini gel as described previously (Smith and Mackessy, 2016). kD = kilodaltons; St = molecular weight protein standards; HeNa = *H. nasicus* crude venom; SVMP P-III, snake venom metalloproteinase, class P-III; CRiSP, cysteine-rich secretory protein.

or interfering with platelet aggregation. The group or groups of SVMPs in *H. nascius* venom or saliva has not been characterized (Gutierrez et al., 2010a). It is likely that SVMPs play a significant role in the local toxicity of *H. nasicus* envenomations (Morris, 1985; Weinstein and Keyler, 2009).

Cysteine-rich secretory proteins in *H. nasicus* venom were not investigated in the Hill & Mackessy study (2000), and their roles in envenomation, if any, are poorly defined (Heyborne and Mackessy, 2010). Smaller, nonenzymatic proteins, CRiSPs have no known toxic effects; however, previous research has investigated their effects on various neuronal ion channels (Brown et al., 1999, 2003; Yamazaki et al., 2002; Yamazaki and Morita, 2004) as well as on Ca^{2+} gradients in cardiac and skeletal muscle (Morrissette et al., 1995). However, the role of CRiSPs in *H. nasicus* bite pathology remains unclear (Heyborne and Mackessy, 2010; Yamazaki and Morita, 2004).

Snake venom PLA_2 enzymes from many different species exhibit a wide array of pathologies, despite maintaining a relatively conserved molecular structure, and they have been implicated in pre- and post-synaptic neurotoxicity, cardiotoxicity, local edema, myoglobinuria, and hematotoxicity. PLA_2 can cause hematotoxicity by several mechanisms,

including factor X inhibition and platelet aggregation. While PLA_2s have been implicated in venom-induced thrombocytopenia (White, 2005) it is unclear if it is the cause of thrombocytopenia in this case. PLA_2 is present in the saliva but not the venom of *H. nasicus* (Hill and Mackessy, 2000), and it is likely that this patient was exposed to both saliva and venom during the prolonged duration of the bite.

Type 1 hypersensitivity reaction has been proposed as a mechanism (Weinstein and Keyler, 2009) of the local reaction caused by a *H. nasicus* bite. The quick onset of pain, swelling, and blistering may be a result of local IgE-mediated hypersensitivity due to the protein components found in *H. nasicus* saliva and/or venom. Previous studies have illustrated increased risk of Type 1 hypersensitivity reactions from people who keep captive venomous snakes (Hogan and Dire, 1990; Reimers et al., 2000), likely due to sensitization (de Medeiros et al., 2008), though these reported cases are of systemic or anaphylactic reactions from Viperidae or Elapidae bites. Other types of hypersensitivity, such as antibody-dependent (Type II), immune complex-mediated (Type III), or delayed-type (Type IV), are possible but less likely given their mechanisms and clinical course.

Vipers and elapids produce venom that is secreted and stored in ductules and a basal lumen of the venom gland and delivered through hollow fangs, assisted by compression of a modified adductor muscle that creates a high-pressure injection system. In contrast, rear-fanged snakes produce venom in Duvernoy's glands, which secrete venom by exocytosis through a system of secretory tubules. Venom, which is not stored in a lumen prior to injection, is then delivered along elongated or grooved rear maxillary teeth without the aid of a compressor glandulae muscle. To compensate for this low-pressure system, rear-fanged snakes deliver venom through a series of bites, prolonged attachment, and/or chewing behavior. Nevertheless, the volume of venom delivered by rear-fanged snakes and the protein content of the venom that is delivered is significantly lower than that delivered by front-fanged snakes, and symptomatic human envenomations by rear-fanged snakes typically require long contact time (Mackessy and Saviola, 2016). This mechanism provides an explanation why all previous reported cases of *H. nasicus* envenomations were by captive snakes during feeding with prolonged bite exposures. While there have been reported cases of envenoming by “rapid” bites from other species of rear-fanged snakes (Warrell, 2004), there are no reported cases of *H. nasicus* “rapid” bites or envenomings in the wild.

4. Limitations

The patient had several appointments in the first two weeks of her presentation but unfortunately never followed up with the laboratory to reassess her platelet count. After several attempts at contacting her, four months after the bite she allowed the primary author to assess her and obtain laboratory tests. We do not know at what point her platelet count returned to her normal baseline. Furthermore, laboratory tests prior to the bite were obtained one year before her presentation. It is unclear if the thrombocytopenia was due to direct venom toxicity. Sequestration of platelets in the affected local tissue several days after envenomation has been proposed as a mechanism for delayed thrombocytopenia (Offerman et al., 2003). Given that the first set of hematalogic testing was three days after envenomation, we cannot confirm if thrombocytopenia was an acute or delayed effect.

While the patient's local reaction is consistent with prior reported *H. nasicus* envenomations, there is the possibility the patient had thrombocytopenia due to another cause. Prior to the envenomation, she reported no viral illnesses, change in medications, drug use, easy bleeding, rashes, or other prodromes, making the likelihood of drug-induced thrombocytopenia, infection, myelodysplastic or bone marrow suppression, or other causes less likely. Idiopathic thrombocytopenia purpura cannot be ruled out but is unlikely given platelets counts are often below 20×10^9/L and the spontaneous remission without treatment.

We requested to obtain venom samples from her pet *H. nasicus* to compare venom components to previous reported *H. nasicus* samples, but the patient declined.

5. Conclusions

Here we have described the first reported case of thrombocytopenia from a *Heterodon nasicus* envenomation. Local effects are consistent with previous reports. *H. nasicus* venom and saliva contains multiple components that could contribute to hematologic effects including thrombocytopenia. Though antivenom is not produced for this species (or for any other North American colubrid) and treatment is largely supportive, we recommend *Heterodon* bites be assessed in a medical facility to evaluate the patient for local and systemic signs, including thrombocytopenia. Laboratory tests including a complete blood count, comprehensive metabolic panel, coagulation panel, and creatine kinase should be considered, and cases with local or systemic signs of envenomation should be discussed with a toxicologist familiar with Colubridae species. Prophylactic antibiotics are not indicated, though if secondary infection is present, the patient should be treated with a beta-lactamase inhibitor such as amoxicillin/clavulanic acid to cover Colubridae oral flora(Weinstein and Keyler, 2009). Close follow-up is imperative to document the trajectory of the clinical course. Instances of Colubridae envenomation are rare, but likely are underreported. Cases of local, hematologic, or systemic effects from rear-fanged venomous snake bites should be reported in the literature.

Ethical statement

All subjects gave their informed consent for inclusion before this case report was written.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.toxicon.2018.11.295.

References

Aird, S.D., 2002. Ophidian envenomation strategies and the role of purines. Toxicon 40, 335–393.

Aird, S.D., 2005. Taxonomic distribution and quantitative analysis of free purine and pyrimidine nucleosides in snake venoms. Comp. Biochem. Physiol. B Biochem. Mol. Biol. 140, 109–126.

Bragg, A.N., 1960. Is *Heterodon* venomous? Herpetologica 16, 121–123.

Brown, R.L., Haley, T.L., West, K.A., Crabb, J.W., 1999. Pseudechetoxin: a peptide blocker of cyclic nucleotide-gated ion channels. Proc. Natl. Acad. Sci. U. S. A. 96, 754–759.

Brown, R.L., Lynch, L.L., Haley, T.L., Arsanjani, R., 2003. Pseudechetoxin binds to the pore turret of cyclic nucleotide-gated ion channels. J. Gen. Physiol. 122, 749–760.

Chippaux, J.P., 1998. Snake-bites: appraisal of the global situation. Bull. World Health Organ. 76, 515–524.

de Medeiros, C.R., Barbaro, K.C., Lira, M.S., Franca, F.O., Zaher, V.L., Kokron, C.M., Kalil, J., Castro, F.F., 2008. Predictors of *Bothrops jararaca* venom allergy in snake handlers and snake venom handlers. Toxicon 51, 672–680.

Dhananjaya, B.L., Vishwanath, B.S., D'Souza, C.J.M., 2010. Snake venom nucleases, nucleotidases, and phosphomonoesterases. In: Mackessy, S.P. (Ed.), Handbook of Venoms and Toxins of Reptiles. CRC Press/Taylor & Francis Group, Boca Raton, FL, pp. 155–171.

Grogan, W.L., 1974. Effects of accidental envenomation from the saliva of the eastern hognose snake, *Heterodon platyrhinos*. Herpetologica 30, 248–249.

Gutiérrez, J.M., Rucavado, A., Escalante, T., Diaz, C., 2005. Hemorrhage induced by snake venom metalloproteinases: biochemical and biophysical mechanisms involved in microvessel damage. Toxicon 45, 997–1011.

Gutiérrez, J.M., Ruvacado, A., Escalante, T., 2010a. Snake venom metalloproteinases: biological roles and participation in the pathophysiology of envenomation. In: Mackessy, S.P. (Ed.), Handbook of Venoms and Toxins of Reptiles. CRC Press/Taylor & Francis Group, Boca Raton, FL, pp. 115–138.

Gutiérrez, J.M., Williams, D., Fan, H.W., Warrell, D.A., 2010b. Snakebite envenoming from a global perspective: towards an integrated approach. Toxicon 56, 1223–1235.

Heyborne, W.H., Mackessy, S.P., 2010. Cysteine-rich secretory proteins in reptile venoms. In: Mackessy, S.P. (Ed.), Handbook of Venoms and Toxins of Reptiles. CRC Press/Taylor & Francis Group, Boca Raton, FL, pp. 325–336.

Hill, R.E., Mackessy, S.P., 2000. Characterization of venom (Duvernoy's secretion) from twelve species of colubrid snakes and partial sequence of four venom proteins.

Toxicon 38, 1663–1687.
Hogan, D.E., Dire, D.J., 1990. Anaphylactic shock secondary to rattlesnake bite. Ann. Emerg. Med. 19, 814–816.
Kamiguti, A.S., Hay, C.R., Theakston, R.D., Zuzel, M., 1996. Insights into the mechanism of haemorrhage caused by snake venom metalloproteinases. Toxicon 34, 627–642.
Kroll, J.C., 1976. Feeding adaptations of hognose snakes. Southwest. Nat. 20, 537–557.
Lavonas, E.J., Ruha, A.M., Banner, W., Bebarta, V., Bernstein, J.N., Bush, S.P., Kerns 2nd, W.P., Richardson, W.H., Seifert, S.A., Tanen, D.A., Curry, S.C., Dart, R.C., Rocky Mountain, P., Drug Center, D.H., Hospital, A., 2011. Unified treatment algorithm for the management of crotaline snakebite in the United States: results of an evidence-informed consensus workshop. BMC Emerg. Med. 11, 2.
Mackessy, S.P., Saviola, A.J., 2016. Understanding biological roles of venoms among the Caenophidia: the importance of rear-fanged snakes. Integr. Comp. Biol. 56, 1004–1021.
Morris, M.A., 1985. Envenomation from the bite of *Heterodon nasicus* (Serpentes: Colubridae). Herpetologica 41, 361–363.
Morrissette, J., Krätzschmar, J., Haendler, B., el-Hayek, R., Mochca-Morales, J., Martin, B.M., Patel, J.R., Moss, R.L., Schleuning, W.D., Coronado, R., 1995. Primary structure and properties of helothermine, a peptide toxin that blocks ryanodine receptors. Biophys. J. 68, 2280–2288.
Mowry, J.B., Spyker, D.A., Cantilena Jr., L.R., Bailey, J.E., Ford, M., 2013. 2012 annual report of the American association of poison control centers' national poison data system (NPDS): 30th annual report. Clin. Toxicol. (Phila) 51, 949–1229.
Offerman, S.R., Barry, J.D., Schneir, A., Clark, R.F., 2003. Biphasic rattlesnake venom-induced thrombocytopenia. J. Emerg. Med. 24, 289–293.
Phillips, S., Rose, B., Kulig, K., Brent, J., 1997. Envenomation from the bite of the Western hognose snake. J. Toxicol. Clin. Toxicol. 35, 532.
Reimers, A.R., Weber, M., Müller, U.R., 2000. Are anaphylactic reactions to snake bites immunoglobulin E-mediated? Clin. Exp. Allergy 30, 276–282.
Russell, F.E., Buess, F.W., Woo, M.Y., 1963. Zootoxicological properties of venom phosphodiesterase. Toxicon 1, 99–108.
Smith, C.F., Mackessy, S.P., 2016. The effects of hybridization on divergent venom phenotypes: characterization of venom from *Crotalus scutulatus scutulatus* x *Crotalus oreganus* helleri hybrids. Toxicon 120, 110–123.
Warrell, D.A., 2004. Snakebites in Central and South America: epidemiology, clinical features, and clinical management. Venom. Reptiles West. Hemisph. 2 709- 671.
Weinstein, S.A., Keyler, D.E., 2009. Local envenoming by the Western hognose snake (*Heterodon nasicus*): a case report and review of medically significant Heterodon bites. Toxicon 54, 354–360.
White, J., 2005. Snake venoms and coagulopathy. Toxicon 45, 951–967.
WHO, 2018. Global Snakebite Burden. Seventy-first World Health Assembly. World Health Organization.
Yamazaki, Y., Brown, R.L., Morita, T., 2002. Purification and cloning of toxins from elapid venoms that target cyclic nucleotide-gated ion channels. Biochemistry 41, 11331–11337.
Yamazaki, Y., Morita, T., 2004. Structure and function of snake venom cysteine-rich secretory proteins. Toxicon 44, 227–231.