CASE REPORT

Documentation of a proven Mountain Pitviper (*Ovophis monticola*) envenomation in Kathmandu, Nepal, with its distribution ranges: implications for prevention and control of pitviper bites in Asia

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ABSTRACT

We document inadequately diagnosed coagulopathy (potential to be life threatening) due to *Ovophis monticola* bite. Although its bites are common in the hills of Nepal, associated envenomations have not been documented elaborately. Herein, we present the clinical and treatment details of a proven *O. monticola* bite and areas where it may pose the risk of envenomations (suggesting huge populations in Asia to be vulnerable to its bites). Its envenomation was managed symptomatically with several non-evidence-based interventions. Since no specific pitviper antivenom is available in Nepal yet, managing coagulopathy associated to *O. monticola* envenomation is still challenging. This case emphasizes the need of developing the standard protocol for the diagnosis and management of pitviper bites and study of effectiveness of the available pitviper antivenoms until specific pitviper antivenom is available. Further, the demonstrated distribution localities of this species may have implications for snakebite prevention and designing and distribution of the effective antivenoms.

KEYWORDS: Coagulation, coagulopathy, complex regional pain syndrome, hemotoxicity, pain, pitviper, snakebite, venom-induced consumption coagulopathy

INTRODUCTION

The Asian pitvipers of the Crotalinae subfamily are included in nine genera: *Calloselasma*, *Deinagkistrodon*, *Garthius*, *Gloydius*, *Hypnale*, *Ovophis*, *Protobothrops*, *Trimeresurus*, and *Zhaoermia*) (David and Vogel, 2015). The genus *Ovophis* comprises six pitviper species (*O. convictus*, *makazayazaya*, *monticola*, *okinavensis*, *tonkinensis*, and *zayuensis*) found exclusively in Asia (Wallach et al, 2014; David and Vogel, 2015). However, little is known about the *Ovophis* species diversity and the burden and effects of bite envenomations.

Calloselasma rhodostoma (the Malayan pitviper) bite envenomation cause coagulopathy that develops hemorrhagic effects: petechiae, nosebleeds, hematuria, hemoptysis, uterine, gastrointestinal, and central nervous system hemorrhage, disseminated intravascular coagulation, and shock. These effects may result in serious disability and/or death (Wongtongkam et al, 2005). As with American pitviper venoms (Baramova et al, 1989; Maruyama et al, 1992), hemorrhagic metalloproteinases in *C. rhodostoma* venom are responsible for local hemorrhage as a result of degradation of collagen of the vascular basement membrane and destruction of other vascular structures. The *C. rhodostoma* venom contains aggretin that activates platelets by binding to the platelet glycoproteins and promotes platelet aggregation (Navdaev et

al, 2001) inducing thrombocytopenia in envenomed patients (Sanders et al, 1988). Additional venom components — rhodocetin**,** coagulation factor II and factor X activators, and thrombinlike enzymes — inhibit collagen-induced platelet aggregation (Wang et al, 1999) resulting in consumption coagulopathy. The consumption coagulopathy and thrombocytopenia are mainly responsible for systemic bleeding, whereas hemorrhagic metalloproteinases damage vascular endothelial cells, destroy vascular integrity, provoke platelet aggregation, and activate the coagulation cascade leading to disseminated intra-vascular coagulation. *Hypnale* species (Hump-nosed Pitvipers) envenomation usually causes local inflammation only, sometimes coagulopathy, and occasionally kidney injury (Ariaratnam et al, 2008; Wijewantha and Sellahewa, 2010; Herath et al, 2012; Shivanthan et al, 2014; Ehelepola et al, 2019)]. *Trimeresurus* species (Green pitvipers) envenomation often causes swelling and pain, sometimes ecchymosis, blister, wound bleeding and infection, and necrosis, occasionally compartment syndrome, hematoma, and systemic bleeding (Thumtecho et al, 2020). Similar venom effects can be expected from envenomation due to *Ovophis* species as well.

Ovophis monticola (the Mountain Pitviper) is a monotypic species (Malhotra et al, 2011) reported from across the hills of Nepal (Pandey, 2015; Pandey and Thapamagar, 2019) (Figure 1), Bangladesh, northeastern India, northeast, central and western Bhutan, west and southwestern China, northern Myanmar, northern Thailand, southern Laos, northeast and southwest Cambodia, Vietnam, and Malaysia (Grismer et al, 2010; Wallach et al, 2014), where it may cause local and systemic envenomation resulting in throbbing pain, local swelling, blister formation, necrosis, coagulopathy (Wall, 1908; Parajuli et al, 2017), and chronic pain (abnormal neurohumoral and inflammatory syndromes were reported to occur due to a suspected *O. monticola* envenomation in the hills of eastern Nepal by Bhattarai et al (2008). However, little is known about circumstances of the confirmed *O. monticola* bites, evolution of its venom effects, treatment of local and systemic envenomations, and associated burden in its distribution ranges (Wall, 1908; Tillack et al, 2003; Pandey, 2015; Bhatt et al, 2020) although it poses the risk of envenomations throughout the hills of Nepal. Herein, we present circumstances of bite and prehospital care, clinical manifestations and management practices involving several non-evidence-based interventions and using no antivenom, for a confirmed *O. monticola* envenomation in the central hills of Nepal. We also illustrate its distribution ranges where it may cause life threatening coagulopathy. This report can have significant implications for the prevention and improvement of pitviper bite management (particularly to design and distribute effective antivenom) in its distribution ranges.

CASE REPORT

A 42-year-old, female from Kirtipur Municipality, Kathmandu District was bitten by *O. monticola* at 1600h on 24 August 2018 while cutting grasses in the yard of Tribhuvan University Central Library (TUCL), Kirtipur,

central hills of Nepal (27.681949° N, 85.28533° E, elevation 1330 m asl, Figure 1). The snake involved in envenomation (Figure 2) was identified by the author-DPP.

Prehospital: She did not wear boots or gloves while cutting grasses as usual. She felt sharp pain (i.e., pinning like sensation, tingling pain), and saw bleeding and bite marks on the base of thumb of the left hand and a snake beside her (Figure 2). After her cry, TUCL staffs rushed to the site nearly 30 m from the TUCL main entrance (Figure 2). One of the TUCL staffs killed the involved snake and next applied single ligature using shawl just above the wrist and carried her immediately on a motorcycle about 1.5km to Tribhuvan University Hospital (TUH). After knowing history of snakebite, TUH referred her to Sukraraj Tropical and Infectious Disease Hospital, Teku, Kathmandu (Teku Hospital) located about 4.3km from TUCL where she was carried in the same motorcycle within 0.6 h post-snakebite.

First admission: Teku Hospital noticed two distinct fang marks with slight local bleeding from the bite site, pain, tenderness, and swelling of the wrist and fingers without neurological deficit and with all other systemic examination within normal range. She was discharged from Teku Hospital the same day when blood coagulation profile was normal.

Second admission: After 19.5h post-snakebite, the swelling extended up the wrist to the elbow and arm. Then she was readmitted in Teku Hospital for altered clotting profile and local swelling with pain (see supplementary data). The repeated tests showed rise in clotting time. Then she was treated (see supplementary data) for swelling, pain, and abnormal blood coagulation assuring hemotoxic snakebite. In laboratory investigations (see supplementary data), the PT was reduced on subsequent testing in the 3rd, 5th, 6th, and 7th post-snakebite days. She did not develop bleeding disorder (*e.g.,* bleeding from gums, urine, etc.). She was investigated for renal function test only in the first day by performing urine routine examination. The swelling gradually subsided and PT and CT profiles were within the normal ranges after 3d 17.7h post-snakebite. Then, she was discharged with advice of oral medicines, measuring PT, INR, and CT for next three consecutive days to assure the stability in blood clotting profiles (Supplementary data), and with follow-up checks until complete recovery of the envenomation effects. She was treated symptomatically with pre-emptive systemic antibiotics and analgesia (Supplementary data).

Follow-up visits: At her follow up visit on 7th post-snakebite day, her coagulopathy was corrected, and her medications were ceased.

She developed local swelling, lymphadenopathy, and mild-coagulopathy. There was no abdominal pain, and no bruise developed. Although swelling disappeared by 14d 21h post-snakebite, she had paraesthesia on bite site, sensation of heaviness and continuous deep pain in the bitten hand, and inability to grab and lift a

water-jug with the affected hand. She was unable to lift the normal weight even after the five weeks post-snakebite. So, in Oct 2018 (38d 20.5h post-snakebite), she visited National Academy of Medical Sciences Bir Hospital (aka Bir Hospital), Kathmandu where author-BRS observed and evaluated the progress on recovery of venom effects.

She suffered from residual slight hypoesthesia at the bite site and persistent deep pain on bitten limb. There was no swelling and scar on bitten body part. All systematic examinations were normal including sensation and power (no clinical neurological deficit was noted). After the diagnosis, she was treated for post-snakebite peripheral neuropathy with Pregabaline. In 68th day post-snakebite, her pain syndrome was markedly reduced. In the last follow up on 11 April 2019 (7 months 18d post-snakebite) in TUCL, she reported negligible pain on the bitten hand while lifting a pile of books.

DISCUSSION

Definitive *O. monticola* bites have been rarely documented in the central hills of Nepal and elsewhere, although bites may occur in its distribution ranges at 450–2680 m asl in Nepal (Tillack et al, 2003; Nepali and Singh, 2019) and at 500–3000 m elsewhere in Asia (Wallach et al, 2014), resulting in mild coagulopathy. Herpetologists stipulated up to five envenomations due to its bites per village/year in the hills of Nepal (Tillack et al, 2003) without clinical and treatment details. Bhattarai et al (2008) reported an envenomed case identified by a non-expert as a pitviper bite. From eastern Nepal, at least six confirmed *O. monticola* bites have been reported without clinical and treatment details: Pandey (2015) mentioned a single diurnal bite in Ilam District (at 1683 m asl), Sharma et al (2016) identified five *O. monticola* bites, and Parajuli et al (2017) documented the highest responses of locals claiming it to be the common cause of envenomation in Ilam District. From far-western hills of Nepal, Bhatt et al (2020) mentioned three expert identified *O. monticola* envenomations. Therefore, this is probably the second report of expert-identified *O. monticola* envenomation in the central hills of Nepal.

Although she did not develop any systemic bleeding manifestations as is reported from India (Wall, 1908) and far-western Nepal (Bhatt et al, 2020), there was the risk of life-threatening bleeding, because clinical symptoms of coagulation disorder may not be present even in the case of severe hypofibrinogenemia (Maduwage and Isbister, 2014). The pronounced swelling, prolonged PT and CT, and chronic pain on bitten body parts (Supplementary data) indicated, however, moderate to severe local envenomation with mild systemic involvement. Venous clotting time ranging 20 min to more than 20 min between 19 h and 6 d 19 h post-snakebite (Supplementary data) indicated the mild depletion of fibrinogen resulting in mild consumption coagulopathy (Wedasingha et al, 2020). However, *O. monticola* caused much pain, extensive swelling, and profuse bleeding (Wall, 1908) and a death (Tillack et al, 2003). Due to thrombin-like

compounds in its venom (Menon and Joseph, 2015), there is the risk of systemic bleeding due to its envenomations. This risk is even greater without using proper antivenom. However, she was inadequately investigated to assess the progress of coagulopathy probably due to the assessment of the case by untrained healthcare professionals. Although thrombocytopenia is a hallmark of hematological disorder due to pitviper envenomation (Soogarun et al, 2003), platelets were not measured (Supplementary data) to determine potential coagulation disorder. Since thrombocytopenia is a common hematological effect due to pitviper bites, the trend of platelet counts should be evaluated (in addition to PT, INR, CT, and other the hematologic tests) serially until normal hematology for the proper diagnosis and treatment of pitviper bites.

Kidney function testing was carried out only for the first day following snakebite. Urine output was not measured. Since oliguria or anuria may occur due to Asian pitviper venom effects and kidney function may be impaired (Menon and Joseph, 2015; George et al, 2019), the urine output checklist should be maintained along with the periodic kidney function tests for all pitviper bite cases.

Besides coagulopathy, the *O. monticola* bite caused distinctive swelling extended proximally to the upper arm. The swelling pattern was similar to the report of edema of a patient envenomed by this species elsewhere (Wall, 1908; Bhatt et al, 2020). Similar swelling patterns were also noticed in other Asian pitviper bites (Pandey et al, 2019; Bhatt et al, 2020). The pronounced chronic pain experienced by the patient was likely to be complex regional pain syndrome type-1 (Bhattarai et al, 2008) because the edema and chronic pain experienced by her was not associated with the loose-fitting tourniquet that was removed in about 0.6 h post-snakebite in Teku Hospital. The local edema might be caused by venom phospholipases A_2, metalloproteases, and proteases (Menon and Joseph, 2015). Our case did not develop local blistering and tissue necrosis. However, these enzymes can cause blistering and tissue damage (Gowda et al, 2018), chronic pain on bitten body part persisting more than seven months, and permanent sequelae or death if untreated.

Like the green pitviper bite management in central Nepal (Pandey et al, 2019), a non-evidence-based intervention (i.e., use of proteolytic enzyme, antibiotics, and vitamin K of uncertain benefits) was used with our patient so as to reduce the swelling of the bitten body part. Antibiotics are not normally used prophylactically because they may potentiate proteolytic snake venom toxins (Kerrigan et al, 1997; Sørensen et al, 2020). However, any signs of bacterial infection known after careful evaluation should be treated with broad-spectrum antibiotics. The pre-emptive use of antibiotics (in this case, Ciprofloxacin) without clinical and laboratory evidence is not justified. During entire treatment process, the use of tetanus vaccination was unclear. However, we advise using tetanus prophylaxis (Suankratay et al, 2002), but after

serial clotting time/INR tests and normal blood clotting profile. Administration of tetanus toxoid is unnecessary if the patient was recently vaccinated and completed the antitetanus course.

Similarly, ranitidine was provided to this case to prevent/reduce the stress owing to gastritis likely to be induced by the Chymosin (Supplementary data). There is no evidence to support the use of vitamin K for envenomation. However, unlike treating *T. albolabris* bite (Pandey et al, 2019) or suspected pitviper bites (Koirala et al, 2013), our case did not receive fresh frozen plasma (FFP) to correct coagulation abnormalities because the clinical indications for FFP use was not defined. Without using pitviper antivenom, there may occur complications in treatment while using FFP. Overall, improper assessment, lack of follow up, and no available snakebite management guidelines for the management of this pitviper bite suggest the need of intensive training for healthcare professionals involved in snakebite management in Nepal.

Due to unavailability of pitviper antivenoms in Nepal (Shrestha et al, 2017), this case was treated without using antivenom. Similar conservative treatment of pitviper envenomations without using antivenom was practiced elsewhere in Nepal (Pandey et al, 2019; Bhatt et al, 2020). Since envenomation by this species can be serious because it can result in severe coagulopathy, keeping the patient at the risk of systemic bleeding and death, there is a need for available pitviper antivenom to reverse coagulopathy. Before designing effective polyspecific antivenom against Nepalese snakebite envenomations (Shrestha et al, 2017), it is recommended to know the effectiveness of Thai green pitviper antivenom to prompt recovery of its envenomation effects.

Prompt action to seek professional healthcare and transporting patients quickly to health facilities providing proper medical care were notable in this case, although the patient used ligature due to out-of-date knowledge of the best practices for first aid of snakebites. This shortcoming may be due to improper school education and public perception for snakebite treatment in Nepal (Pandey and Khanal, 2013; Pandey et al, 2016; Pandey et al, 2020). To confine the venom to the affected extremity and/or reduce systemic absorption of venom, reduce local swelling, and minimize local tissue damage, we recommend using the local compression pad immobilization method (Tun-Pe et al, 1995), and keeping the bitten body part elevated (Lavonas et al, 2011), for all pitviper envenomations. Encounters of this snake with humans in areas of increasing human activity suggest improving prevention strategies against pitviper bites. Using snake resistant boots and gloves while working in grassy areas in and around residential areas can be the best measure to prevent snakebites.

CONCLUSION

O. monticola poses risk of life threatening coagulopathetic envenomation in its distribution ranges. In Nepal, no availability of pitviper antivenoms, use of antibiotics without proper evaluation for microbial infections, inadequate diagnosis and monitoring of the patient, use of other non-evidence-based interventions, and poor knowledge on the patient's part of snakebite first aid all increase the complexity for the management of the effects of envenomation. This indicates the need for an evidence-based national guideline/protocol for the diagnosis and treatment of pitviper bites, for which additional clinical and laboratory studies of confirmed *O. monticola* bites are essential. All *O. monticola* bite patients should be periodically evaluated for platelet counts, prothrombin time, thrombin time, international normalized ratio, activated partial thromboplastin time, blood concentration of fibrinogen, fibrinogen degradation product, plasminogen, and D-dimer level, renal functions (urine creatine kinase, serum creatinine levels, blood urea, daily urine amount measurements, albumin and blood cells in urine), and liver functions until the recovery of coagulopathy.

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COMPETING INTERESTS

None declared.

LIST OF ABBREVIATIONS

asl = Above sea level
CT = Clotting time
d = Day
FFP = Fresh frozen plasma
h = Hour
INR = International normalized ratio
min = Minutes
PT = Prothrombin time
TUCL = Tribhuvan University Central Library
TUH = Tribhuvan University Hospital

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391 **FIGURE LEGENDS**

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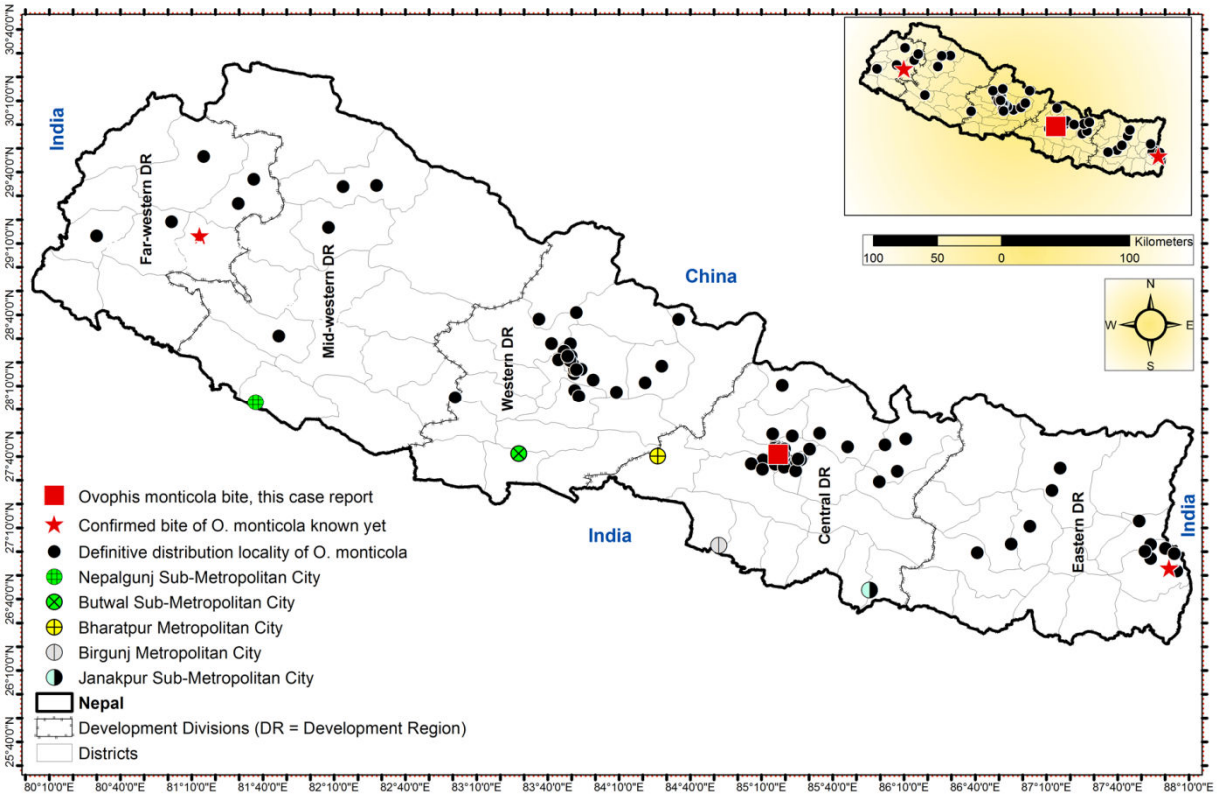

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394 **Figure 1.** Distribution localities of the Mountain Pitviper (*Ovophis monticola*) in Nepal (black circle shows its
395 definitive distribution localities, red star shows locality where *O. monticola* bite occurred definitely, and red
396 square represent the location of *O. monticola* bite that is described in this case report).

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Figure 2. The Mountain Pitviper (*Ovophis monticola*) (top right, photo by I P Adhikari) responsible to bite Tribhuvan University Central Library (TUCL) staff (top left, black circle shows bite site on her left hand at the base of thumb) while cutting grasses aside TUCL main entrance (bottom, victim showing the actual location where pitviper bite occurred). The bitten body part and location were portrayed at 14th day post-snakebite.