CASE REPORT

Venom-Induced Consumption Coagulopathy Unresponsive to Antivenom After *Echis carinatus* *sochureki* Envenoming

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Snakebite envenoming is a serious and life-threatening but neglected problem in the tropics. The focus in the Indian subcontinent is usually on the Indian cobra (*Naja naja*), common krait (*Bungarus caeruleus*), Russell's viper (*Daboia russelii*), and Indian saw-scaled viper (*Echis carinatus*). The Indian polyvalent antivenom contains hyperimmunized horse antibodies against only these 4 species. However, regional intraspecific variations are important in viper envenomings, leading to marked differences in clinical presentation and response to the available polyvalent antivenom. *Echis carinatus sochureki*, a subspecies of *Echis carinatus*, has been linked to serious morbidity in the Thar Desert regions of Rajasthan, although consistent reports are lacking. We report a patient with prolonged venom-induced consumption coagulopathy owing to *Echis carinatus sochureki* envenoming who did not respond to Indian polyvalent antivenom in Jodhpur, India. Features of local and hemotoxic envenoming resolved after a week with supportive care. *Echis sochureki* venom has been shown to be different from *Echis carinatus* in terms of composition and in vitro neutralization by antivenom. Clinicians in the tropical desert regions must suspect *Echis sochureki* envenoming in the setting of nonresponsiveness to Indian polyvalent antivenom. This will help optimize antivenom use in these patients, preventing potentially life-threatening antivenom associated reactions. Because the usefulness of Indian polyvalent antivenom appears to be limited in this setting, there is an urgent need to advocate for region-specific antivenom or monovalent antivenom for this area.

Keywords: snakebite, saw-scaled viper, arid desert

Introduction

Snakebite envenoming is a serious and neglected tropical problem causing considerable mortality and morbidity.¹ In 2019, the World Health Organization launched a global strategy for the prevention and control of snakebite envenoming, which aims to halve deaths and disability by 2030. Prevention and effective first response are the central themes of this program.²

The focus in the Indian subcontinent is usually on 4 common venomous snakes: Indian cobra (*Naja naja*), India krait (*Bungarus caeruleus*), Russell's viper (*Daboia*

russelii), and Indian saw-scaled viper (*Echis carinatus*).³ The Indian polyvalent antivenom is widely used in this region and is available as a freeze-dried powder. It is immunoglobulin purified from the plasma of horses hyperimmunized with the venom of these 4 snakes. Each milliliter after reconstitution neutralizes not less than 0.60 mg of *Naja naja*, 0.45 mg of *Bungarus caeruleus*, 0.60 mg of *Daboia russelii*, and 0.45 mg of *Echis carinatus* venom.⁴ The efficacy of the antivenom depends on the venom used in manufacturing it.⁵ Most of the venom collected for antivenom production in India comes from a small geographic area through the Irula cooperative society, Tamil Nadu, India.⁴

However, apart from these 4 species, several other medically significant venomous snakes are found in India, and there is significant regional intraspecific variation among snakes found in geographically distinct regions, resulting in definite differences in venom composition,

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clinical features, and degree of neutralization by the polyvalent antivenom.^{4,6-9} This appears to be especially important for *Echis carinatus*, common throughout the Indian subcontinent, and its subspecies *Echis sochureki*, which has a geographical distribution including the neighboring regions of Pakistan, Iran, and the Arabian Peninsula.^{5,10} *Echis sochureki* has been linked to serious morbidity in the Thar Desert regions of Rajasthan, Western India, although consistent reports are lacking.^{4,11} We describe a patient with *Echis sochureki* envenoming who did not respond to the polyvalent antivenom.

Case report

A 60-y-old farmer from the Barmer district of the Thar Desert region of Western Rajasthan, India, sustained a snakebite on his right foot when he went to feed his cows just outside his home in the evening in September 2019. His family members who were nearby caught and killed the snake. The family took a photograph of the snake specimen and discarded the snake. He developed swelling and bleeding at the bite site (Figure 1A) and reported severe headache.

He was transported to a nearby district hospital by a hired vehicle within an hour of bite, and he did not receive any native treatments before this. Ten vials of Indian polyvalent antivenom were given at the district hospital. He was then referred to our emergency department, a tertiary care teaching hospital, 6 h after the bite.

A whole blood clotting test was performed using 2 mL of freshly sampled venous blood in a dry test tube left undisturbed for 20 min at ambient temperature. Unclothed blood after tilting once at the end of 20 min was considered positive. Because the test was positive at 6 h, 10 vials of antivenom (Premium Serums and Vaccines Private Limited, Nagpur, India; batch number 28A104) was administered (Figure 1B). A single loose tourniquet tied just above the wound was removed slowly at presentation while antivenom was being given. A further 10 vials of antivenom were administered because the whole blood clotting test was persistently uncoagulable after the next 6 h. The coagulation profile revealed prolonged prothrombin time and activated partial thromboplastin time (testing performed with Sysmex CA1500 Hemostasis System and Thromorel S kit—reagent and control plasma from Siemens Healthcare Diagnostics). These remained prolonged (>120 s, limit of detection) until 7 d after the bite. Local bleeding subsided in 24 h. Platelet counts and renal function were normal throughout.

The photograph of the snake taken by the patient's family and the patient's unresponsiveness to polyvalent antivenom strongly suggested *Echis carinatus sochureki* envenoming. The photograph was identified as *Echis carinatus sochureki* by a herpetologist (Figure 1C). The patient received supportive care. No transfusions were required. Coagulation parameters normalized completely by day 10 (Table 1).

Discussion

Saw-scaled viper envenoming presents with local tissue swelling, vascular involvement, bleeding manifestations, and rarely with atypical features of renal dysfunction and thrombotic microangiopathy leading to considerable morbidity and mortality.^{4,12} A recent nationally representative snakebite mortality study classified Rajasthan state as a high-burden region.¹ Regional intraspecific variation appears to be especially important in vipers, leading to different clinical manifestations. Severe envenoming from *Echis sochureki* has been reported from the United States and Eastern Europe in snake handlers.^{8,9} Despite its widespread distribution in Northern India, Pakistan, Afghanistan, Iran, and the Arabian Peninsula, *Echis sochureki* has received considerably less attention in comparison to the other common subspecies, *Echis carinatus*. A series of 12 patients with *Echis sochureki* envenoming causing serious morbidity was reported from the Thar Desert region of Rajasthan in 2007. This report described persistent coagulopathy and use of large doses of Indian polyvalent antivenom.¹¹

Prolonged venom-induced consumptive coagulopathy (VICC) with poor or partial response to polyvalent antivenom has been a prominent feature in various reports of *Echis sochureki* envenoming.^{11,13-15} This unresponsiveness to antivenom and the length of the snake (>30 cm) as assessed from the photograph of the snake brought by the patient's relatives were key points in suspecting *Echis sochureki* envenoming. Although the photograph was useful for snake identification in our case, it is pertinent to note that any handling of the snake by the family or killing of offending snakes must be strongly discouraged because it places those individuals at risk for bites and does not support snake conservation efforts from an ecologic perspective.

Our patient experienced no clinical bleeding, but the persistent coagulation abnormalities were a cause for concern. Local bleeding with prolonged persistent VICC in most of the reported cases suggests that apart from poor neutralization by polyvalent antivenom, the pharmacokinetics of *Echis sochureki* venom may differ from other vipers. Several studies examining venomics

Figure 1. (A) Local swelling with bite mark over right foot. (B) Whole blood clotting test showing uncoagulable blood at 24 h. (C) Photograph of the snake provided by the patient's family.

and proteomics of different *Echis* species have confirmed this. Caswell et al highlighted the difference in the interspecific changes in the number of toxin genes, their transcription in the venom gland, and their translation into proteins secreted in the venom of various *Echis* species, including *Echis sochureki* (collected from United Arab Emirates (UAE)). They demonstrated that *Echis* venoms exhibit significant interspecific variation in their ability to cause hemorrhage in murine in vivo models.⁵

Patra et al performed proteomic analysis of *Echis* spp. from India and demonstrated that the proteome composition of venom correlated well with its in vitro coagulant action and clinical manifestations.⁶ Senji Laksme et al showed notable differences in the relative abundance of various toxins, such as phospholipase A2, snake venom metalloproteinase, and small molecules such as cysteine-rich venom secretory proteins, between *E. carinatus* and *E. sochureki*.¹⁶ An important finding by

both Patra et al and Senji Laksme et al relates to small-molecular-weight proteins (<30 KDa), which are more abundant in *E. sochureki* compared to *E. carinatus*.^{6,16} This was confirmed by Bhatia and Vasudevan in their recent report; they found low-molecular-weight components such as phospholipase A2 and cysteine-rich venom secretory proteins were abundant in *E. sochureki* venom obtained from Rajasthan when compared to *E. carinatus* from Tamil Nadu or Goa states of India.⁷ Snake venom serine proteases, which catalyze the coagulation pathway, showed 5-fold variation in snakes from the 3 regions, suggesting that the clinical profile of coagulopathy may significantly differ in these envenomings.

Another interesting speculation relates to the low abundance of L-aminoacid oxidases, responsible for tissue edema and platelet apoptosis in *E. sochureki* venom.⁷ Thus, absence of significant local swelling

Table 1. Coagulation and other laboratory parameters after envenoming

Test/Parameter (normal range)	Day 1	Day 1 (after ASV)	Day 2	Day 3	Day 4	Day 5	Day 10
PT (s) (10–15)	>120	25	68	>120	>120	>120	13
INR (<1.1)	Not calculated	2	9	Not calculated	Not calculated	Not calculated	1
aPTT (s) (25–35)	38	–	57	>120	–	>120	26
WBCT 20 (min)	>20	>20	>20	>20	–	>20	clotted
Hemoglobin (g·dL ⁻¹) (12.1–15.1)	13	–	13	–	–	–	–
Platelet (10 ⁹ ·L ⁻¹) (150–400)	278	–	249	251	–	–	250
Serum fibrinogen (mg·dL ⁻¹) (180–350)	13	–	–	–	–	–	–
Blood urea (mg·dL ⁻¹) (8–20)	27	–	–	–	26	–	–
Serum creatinine (mg·dL ⁻¹) (0.5–1.1)	0.8	–	–	–	0.9	–	–
Serum sodium (mmol·L ⁻¹) (135–145)	129	–	–	–	132	–	–
Serum potassium (mmol·L ⁻¹) (3.5–5.2)	4.4	–	–	–	4.2	–	–
Serum lactate dehydrogenase (U·L ⁻¹) (130–280)	186	–	–	–	–	–	–

aPTT, activated partial thromboplastin time; ASV, Indian polyvalent antivenom; INR, international normalized ratio; PT, prothrombin time; WBCT 20, 20-min whole blood clotting test.

(usually reported in *Echis* envenomings from Tamil Nadu) and absence thrombocytopenia in *E. sochureki* envenoming may be explained by this relative reduction in L-aminoacid oxidases abundance.^{7,12,16} It is pertinent to note that these small molecules were poorly neutralized by Indian polyvalent antivenom.⁶

Recently, camelid immunoglobulins have been explored and found to work successfully against *Echis sochureki* venom from Rajasthan in a preclinical setting.¹⁷ The in vitro neutralization efficacy of camelid IgG for venom-induced coagulant effects, hemorrhage, and necrosis were comparable to equine antivenom against other *Echis* sp. outside India.

Because the usefulness of Indian polyvalent antivenom appears limited, such innovations need to be translated rapidly into clinical practice to effectively address *Echis* envenoming in the region. We suggest that early suspicion of *Echis sochureki* envenoming can help clinicians limit the use of polyvalent antivenom in these

patients, thus avoiding unnecessary exposure to potentially life-threatening antivenom-associated reactions.

Conclusions

We document a case of clinical antivenom failure after *Echis sochureki* envenoming. There appears to be limited value of Indian polyvalent antivenom in neutralizing VICC caused by *Echis carinatus sochureki*.

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