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Case report

Partial segmental thrombosis of the corpus cavernosum following Russell's viper bite

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ABSTRACT

Snakebite envenoming (SBE) is common in rural communities living in tropical regions that often have fragile and/or overwhelmed healthcare systems. The complex scenarios around SBE lead to a high number of deaths, disabilities, and long-term consequences in patients. Russell's viper (*Daboia russelii*) is one of the most medically important snake species in India, which causes devastating pathological conditions characterised by a wide range of clinical manifestations. This broad spectrum of symptoms requires additional therapeutic interventions beyond the classical antivenom administration. Hence, positive outcomes for patients affected by SBE can be achieved with a better understanding of previous experiences describing clinical manifestations and various therapeutic interventions including for rare and underreported conditions. Here, we report an SBE victim who developed partial segmental thrombosis in the corpus cavernosum following Russell's viper envenomation and its diagnostic and treatment approaches. The patients received 180 ml of antivenom to resolve the abnormalities in their haematological parameters. Despite antivenom treatment, they developed severe pain in their genital region, and subsequent ultrasound and magnetic resonance imaging confirmed segmental thrombosis in the corpus cavernosum, which required supportive measures. The treatment using low molecular weight heparin, rivaroxaban and non-steroidal anti-inflammatory drugs resolved segmental thrombosis. In conclusion, this case report exemplifies the development of a rare segmental thrombosis in corpus cavernosum and how the medical, scientific, and general community can benefit from documenting clinical manifestations, medically relevant insights into patient care and the management of underreported complications.

1. Introduction

Snakebite envenoming (SBE) primarily affects rural agricultural populations and causes significant morbidity and mortality in South Asia, Africa, and Central and South America (Longbottom et al., 2018). Snake venoms contain a range of toxin components including metalloproteases, serine proteases, three-finger toxins, and phospholipase A_2s which have been recruited into the animal's biochemical arsenal to subdue and digest prey (Calvete et al., 2021; Gutiérrez et al., 2017). Human interactions with snakes can lead to unfortunate consequences for both the snake and the human involved (Uyeda et al., 2022; Williams et al., 2023). Moreover, many snakes are killed after envenoming, while the actions of snake venom toxins in the human body can lead to mortality or near-death experiences (Girish et al., 2019). Additionally, survivors can manifest long-term sequelae such as poor skeletal muscle regeneration and socioeconomic impacts (Waiddyanatha et al., 2019;

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Vaiyapuri et al., 2013). In India, the "Big Four" snakes, which include Russell's viper (*Daboia russelii*), saw-scaled viper (*Echis carinatus*), Indian cobra (*Naja naja*), and common krait (*Bungarus caeruleus*) cause most of the incidents, deaths, and long-term effects (Suraweera et al., 2020). Notably, Russell's viper is responsible for more than half of the SBE incidents and resulting consequences in India. Commonly reported clinical manifestations of Russell's viper bites include pain and swelling at the bite site as well as haemotoxic, myotoxic, nephrotoxic and neurotoxic complications (Gutiérrez et al., 2017). Several rare complications following SBE have been reported previously including priapism, splenic rupture, Hirata's disease, rectus sheath haematoma, and simultaneous bilateral pituitary adrenal haemorrhage (Senthilkumaran et al., 2021, 2022, 2023a, 2023b, 2023c; Arneil and Maclaurin, 1961; Lee and Sung, 2019). The knowledge and dissemination of successful experiences of these rare medical conditions following SBE in low-resource settings allow healthcare professionals to prioritise and anticipate such actions that can shift the patients' outcomes and save lives.

Partial segmental thrombosis of the corpus cavernosum (PSTCC) is an uncommon urologic condition that mainly affects males between the ages of 18 and 59 with symptoms including pain and perineal swelling. PSTCC must be differentiated from priapism and it is most often unilateral and located proximally to the corpus cavernosum (Blaut et al., 2008). Development of this condition has been linked with vigorous sexual activity, bicycle riding, trauma, various haematological conditions, and a hypercoagulable state of the patient's blood (Ilicki et al., 2012). Diagnosis of PSTCC is usually achieved through magnetic resonance imaging (MRI) or ultrasound scan, and conservative treatment with oral anticoagulants usually results in successful resolution of the condition. Mostly, surgical interventions are reserved for PSTCC patients that fail to respond to conservative treatment measures (Lewis et al., 2001). Here, we report a rare case of Russell's viper bite patient who developed partial segmental thrombosis on the left corpus cavernosum despite antivenom treatment. This report highlights the presentation of clinical symptoms for PSTCC in an SBE patient, their diagnosis, and treatment approaches to aid clinicians in the management of such conditions in SBE patients.

2. Case report

A 32-year-old male was bitten by a snake on his right great toe while walking in a field. The bite occurred in Semmedu, a village which lies in the Kolli Hills of the Eastern Ghats in the Namakkal district of Tamil Nadu, India. The mountain range consists of areas of dense tropical forests at an altitude of around 1000–1300 m above sea level. The weather and geographical conditions of Kolli Hills provide an ideal habitat for different types of venomous snakes. Immediately following the bite, the snake was killed and it was identified as Russell's viper by a trained herpetologist (Fig. 1A). Within 30 minutes following the bite, the patient was taken to a local hospital where he was found to have a prolonged 20-min whole blood clotting time (WBCT). Therefore, he was initially treated with 10 vials (100 ml) of polyvalent antivenom raised against the 'Big Four' snakes and then 6 h later, another eight vials of antivenom were provided to normalise his coagulation parameters. These parameters became normal 14 hours after the bite. Despite the resolution of his haematological abnormalities, he developed dull pain and swelling in his penis 26 hours after the bite. The treating physician prescribed analgesics, and ice compressions, and provided scrotal support but all of these resulted in only a minimal relief of his symptoms. Therefore, he was subsequently referred to the emergency department of our hospital for additional evaluation and treatment.

A detailed medical history was collected, and it was found to be unremarkable. The patient denied any recent trauma, recreational drug intake, bicycle riding, alcohol use, priapism, or vigorous sexual activity, which are some of the key factors that were previously reported to be the causes of PSTCC. He reported normal sexual activity with his wife and denied the use of any medications or devices to aid in sexual intercourse. Clinical examination revealed a firm, raised area on the left side of the perineum near the base of his penis that was tender to palpation. There was no evidence of penile discharge, haematuria, dysuria, fever, or erectile dysfunction. Both distal corpora and glans were flaccid and there was no difficulty in voiding. His laboratory analysis was unremarkable for any evidence of infection, malignancy, or haematologic abnormalities, including sickle cell disease (Table 1). The urinalysis findings were normal. Doppler ultrasonography revealed no blood flow in the left cavernosum, and the MRI revealed a 10 cm long thrombus in the left corpus cavernosum which appeared expanded with a heterogenous low T2 signal. T1-weighted MRI showed a high T1 signal within the lesion and no enhancement following contrast, findings indicative of an acute thrombus (Fig. 1B–C). There was no pelvic abnormality detected. The radiologist's report suggested PSTCC in this patient.

The urologist-initiated treatment with low molecular weight heparin [Clexane (enoxaparin) 40 mg injection in 0.4 ml twice daily for five days], and oral non-steroidal anti-inflammatory drugs (ibuprofen 400 mg twice daily and aspirin 100 mg/day for four days) and provided other supportive measures such as warm compress. After subsequent

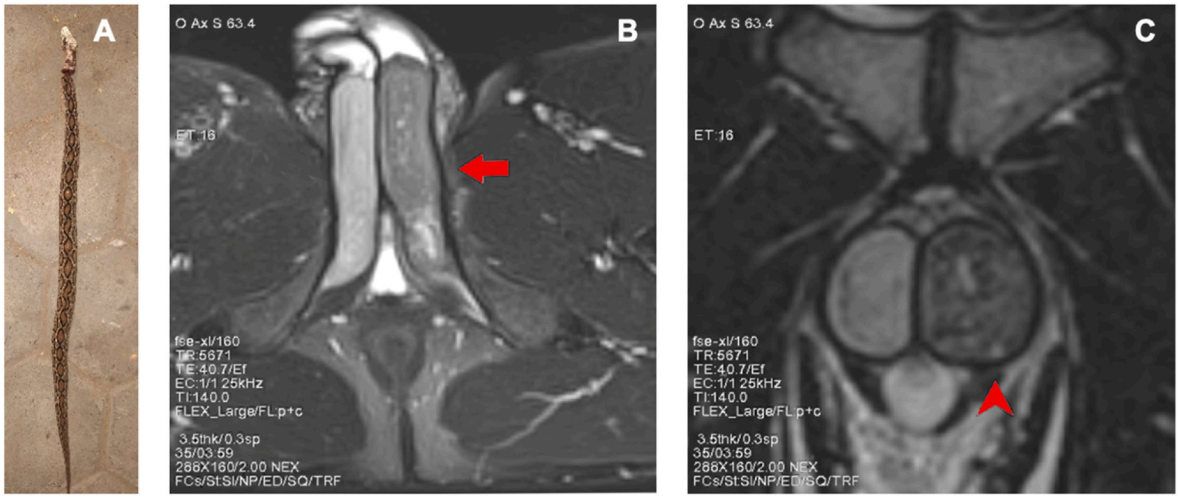

Fig. 1. PTSCC developed in a patient following Russell's viper bite. **A**) the offending snake was identified as Russell's viper by a trained herpetologist. **B**) axial T2/STIR image demonstrating a T2 hypointense signal within the left proximal corpus cavernosum (indicated by an arrow). **C**) an axial T2 sequence demonstrates T2 low signal within the left corpus cavernosum (indicated by an arrowhead).

Table 1
Laboratory investigation report of the patient upon admission to our hospital.

Specimen	Investigation	Results	Unit	Normal range
EDTA Whole Blood	Haemoglobin	10.8	gms%	13.0–16.0
EDTA Whole Blood	Total RBC count	4.67	Millions/μL	4.00–5.00
EDTA Whole Blood	HCT	**39**	%	41.00–50.00
EDTA Whole Blood	MCV	83.5	fl	81.10–96.00
EDTA Whole Blood	MCH	27.4	pg	27.20–33.20
EDTA Whole Blood	MCHC	32.8	%	32–36
EDTA Whole Blood	Total WBC count	6.15	$x10^3$ Cells/μL	4.00–11.00
EDTA Whole Blood	Neutrophils #	6.42	$x10^3$ Cells/μL	2.0 to 7.0
EDTA Whole Blood	Lymphocytes #	**0.93**	$x10^3$ Cells/μL	1.0 to 3.0
EDTA Whole Blood	Monocytes #	0.52	$x10^3$ Cells/μL	0.1 to 0.8
EDTA Whole Blood	Eosinophils #	0.26	$x10^3$ Cells/μL	0.02 to 0.5
EDTA Whole Blood	Basophils #	0.03	$x10^3$ Cells/μL	0.02 to 0.1
EDTA Whole Blood	Neutrophils	**80.3**	%	55–75
EDTA Whole Blood	Lymphocytes	**10.2**	%	15–30
EDTA Whole Blood	Eosinophils	2.8	%	1–5
EDTA Whole Blood	Monocytes	6.4	%	2–10
EDTA Whole Blood	Basophils	0.4	%	Up to 1
EDTA Whole Blood	Platelet Count	320	$x10^3$ Cells/μL	150–450
EDTA Whole Blood	MPV	9.9	fl	6.5–12.0
EDTA Whole Blood	PDW	10.1	fl	9.0–13.0
Serum	Urea	17	mg/dL	15–40
Serum	Creatinine	**0.16**	mg/dL	0.7–1.4
Serum	Uric acid	**3.1**	mg/dL	3.4–7.2
Serum	Bilirubin (total)	**0.17**	mg/dL	0.2–1.2
Serum	Bilirubin (direct)	**0.98**	mg/dL	0–0.2
Serum	Bilirubin (indirect)	0.72	mg/dL	0.2–0.9
Serum	SGOT	30	U/L	5–35
Serum	SGPT	41	U/L	5–45
Citrated plasma	Prothrombin time	15.7	Seconds	11.5–16.0
Citrated plasma	aPTT	39.5	Seconds	26.0–40.0
Citrated plasma	INR	1.01	Ratio	

Result outside the reference range is highlighted in bold. Abbreviations: aPTT, activated partial thromboplastin time; HCT, haematocrit; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PDW, platelet distribution width; RBC, red blood cells; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamate-pyruvic transaminase; WBC, white blood cells.

consultation with a haematologist, the patient was started on oral rivaroxaban 20 mg once daily which resulted in a gradual reduction in his pain. After three months of oral rivaroxaban, the penile lump had diminished in size, and he was able to achieve normal, pain-free erections. Penile curvature did not develop, however, the patient reported difficulty engaging in penetrative sexual intercourse. He scored 21 on the international index of erectile function (IIEF-5), which indicates mild erectile dysfunction. Upon follow-up at six months, the lesion appeared to have decreased further in size and the anticoagulant was discontinued. The patient reported full recovery of his sexual function, and his IIEF-5 score was improved to 25 at his six-month follow-up. During this six-month period, he was not taking any other medications and did not suffer any illnesses. He was engaging in his regular activities during this period. He was not advised to continue any medications after six months of follow-up.

3. Discussion

Russell's viper envenomation often manifests bleeding complications, although, it can rarely induce thrombosis in patients (Senthilkumaran et al., 2023d). This case report describes the development of PSTCC following Russell's viper bite. The patient developed pain and swelling on the perineum near the base of his penis 26 hours after the bite despite antivenom treatment. PSTCC is a rare urologic condition that most often occurs in men between 18 and 59 years old (mean age of 30 years old) (Blaut et al., 2008; Ilicki et al., 2012). It results in extreme pain and swelling in the perineal area and is often due to an occlusion near the proximal part of the corpus cavernosum (Lewis et al., 2001). The causes of PSTCC are not fully understood, however, studies have suggested the hypercoagulable state of patients, haematological disorders, trauma, bicycling, prolonged intercourse or vigorous sexual activities and abuse of cocaine and marijuana as potential causes for this condition (Ilicki et al., 2012; Lewis et al., 2001). However, SBE has not been reported as a cause for PSTCC. Diagnosis of PSTCC is usually made based on clinical presentation and ultrasound and/or MRI imaging. Both imaging methods were used in this patient to ascertain the development of PSTCC. Various strategies have been employed to treat this condition including surgical procedures, intra-cavernosal injections of vasoactive medications, and both parenteral and oral anti-coagulation therapy (Lewis et al., 2001; Horger et al., 2005). Here, this patient was successfully treated only with anti-coagulants such as low molecular weight heparin and rivaroxaban without the need for surgical intervention. The patient displayed mild erectile dysfunction and reported painful intercourse at their three-month review, however, these were resolved at six months. The development of erectile dysfunction following PSTCC of other causes has been reported previously, and it resolved after varying time periods (Lewis et al., 2001). This case suggests that Russell's viper envenomation can act as a potential cause for PSTCC although this could be rare, and diagnostic and therapeutic approaches that are normally practised for this condition can be used to tackle this issue in Russell's viper and other SBE patients.

The patients bitten by several viper species and some elapids as well as a small number of rear-fanged colubrid snakes, are likely to present various coagulopathies with bleeding as a frequent clinical symptom. Russell's viper venom is well known to contain procoagulant toxins such as factor X (a metalloprotease) and V (a serine protease) activators, both of which may result in a hypercoagulable state in certain individuals (Tans and Rosing, 2001; Yadav et al., 2017). The rapid activation of coagulation factors often results in a consumption coagulopathy leading to a deficiency of clotting factors and therefore, subsequent bleeding effects. While endogenous thrombin can act as a protease for multiple substrates including factors V, VIII, XI, XIII and protein C, snake venom serine proteases (thrombin-like enzymes) are normally limited to specific substrates or factors (McCleary and Kini, 2013). For example, some thrombin-like enzymes can only cleave the A or B chain of fibrinogen and some specifically activate one or two coagulation factors. The incomplete cleavage of fibrinogen impairs the production and cross-linking of fibrin clots and leads to the formation of an unstable clot which may be more susceptible to degradation with the development of subsequent hypofibrinogenemia (Kini and Koh, 2016). The reasons for some patients developing overt bleeding and others developing thrombosis with ischemia and infarction have not been fully determined.

To the best of our knowledge, PSTCC in SBE patients has not been reported previously. However, previous case studies have described thrombosis in SBE patients in areas that are distant from the bite site as well as a case of priapism after Russell viper bite (Senthilkumaran et al., 2021). Recently, our research group reported peripheral arterial

thrombosis in various locations in different Russell's viper bite patients (Senthilkumaran et al., 2023d). Non-invasive computed tomography angiography was mainly performed to assess thrombi in peripheral arteries and their precise locations in these patients. In addition to antivenom therapy, mechanical retrieval (thrombectomy) was successfully employed as a strategy to remove thrombi identified in the peripheral arteries of the patients. *In vitro* experiments revealed the acute thrombotic nature of Russell's viper venom by inducing plasma clotting while inhibiting agonists-induced platelet activation. In line with these findings, our *in vivo* assessments using experimental mouse models demonstrated the development of thrombi in the microvasculature, muscle injury and pulmonary veins (Senthilkumaran et al., 2023d). Another case report highlights the clinical aspects of a female patient in India envenomated by Russell's viper with the development of systemic bleeding. She subsequently manifested a cerebral venous thrombosis which was diagnosed on MRI. The patient was successfully treated with antivenom as well as enoxaparin and made a complete recovery (Ghosh et al., 2022). One additional example of thrombosis events associated with Russell's viper envenomation was also reported previouslyDas et al. (2013) (Das et al., 2013). Here, the patient developed a cortical venous thrombosis, which was identified by magnetic resonance venography. Interestingly, thrombosis occurring in other parts of the body has also been reported following envenomings from other snake species. For example, thrombosis was reported in victims of *Bothrops lanceolatus* (Thomas et al., 1995; Resiere et al., 2010, 2018), an unknown viper in China (Lu et al., 2021) and Southern Pacific rattlesnake (*Crotalus oreganus helleri*) in California (Bush et al., 2014).

The patient in our case did not present with any of the factors associated with PSTCC other than a possible transient hypercoagulable state which might have occurred as a result of envenomation. The bite occurred on the toe, yet the thrombosis occurred at a site distant from the bite site. These findings suggest that the systemic effects of the venom contributed to the thrombus formation as similar to peripheral arterial thrombosis in limbs (Senthilkumaran et al., 2023d). Many explanations have been proposed for the development of thromboses following SBE. It has been suggested that some snakes, even within the same species, may contain variable levels of procoagulant versus anticoagulant toxins, thus tipping the balance in favour of blood clotting in some cases (Mukherjee, 2020; Rodríguez-Vargas et al., 2022; Suntravat et al., 2010). It cannot be ruled out that ontogenetic, dietary, and environmental factors play a role in variable venom composition. Since this patient was bitten in a high-altitude mountain range, the venom composition of Russell's vipers living there might be different from the species living in terrestrial regions at low altitudes. Variable amounts of snake venom metalloproteases within a species may cause some specimens to promote excessive damage to the endothelium which may expose or release pro-coagulant molecules such as collagen or tissue factor (Baldo et al., 2010). Patient-specific factors may also play a role in susceptibility to thrombosis. For example, minor genetic differences may cause sub-clinical mutations in any of the coagulation factors rendering them more susceptible to venom toxins-induced coagulopathy. While some case reports have measured various coagulation parameters such as protein C and S levels, factor V Leiden, and antithrombin III levels and found no abnormalities, other cases have not tested for these specific parameters. Therefore, it was not possible to compare these factors with others. We cannot rule out the possibility of antivenom-inducing hypercoagulable state and therefore, thrombosis in some cases.

Overall, this case report highlights a rare complication of PSTCC in Russell's viper bite patient and adds this to an expanding portfolio of Russell's viper bite-induced unusual complications. It provides the required knowledge for clinicians dealing with these patients to increase their awareness for better management of SBE. Additionally, these types of unusual cases provide the impetus for additional scientific research to unravel the complexities that define the interactions between venom toxins and modulators of haemostasis in humans.

Ethical statement

This research was conducted according to the Declaration of Helsinki and the ethical guidelines of the Indian Council of Medical Research. The data collection, consent form, and information sheets were approved by the Institutional Ethics Committee at Toxiven Biotech, Tamil Nadu, India (Reference number: ICMR-Toxiven Ethics, 2022/1) and the University of Reading Research Ethics Committee (Reference number: UREC 23/05). Written informed consent was obtained from the patient to collect and publish the data presented in this article.

Credit author statement

Subramanian Senthilkumaran: Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Visualization, Supervision; **Sasikumar Sampath** - Conceptualization, Validation, Investigation; **Stephen W Miller -** Writing - Original Draft, and Visualization; **José R. Almeida**: Writing - Original Draft, Writing - Review & Editing, Visualization; **Jarred Williams**: Writing - Original Draft, Writing - Review & Editing, Visualization; **Harry F. Williams**: Formal analysis, Resources, Writing - Review & Editing; **Ponniah Thirumalaikolundusubramanian**: Formal analysis, Validation, Investigation, Writing - Review & Editing; **Ketan Patel**: Formal analysis, Writing - Review & Editing; **Sakthivel Vaiyapuri**: Formal analysis, Validation, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All the data associated with this article are presented within this article.

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