CASE REPORT

Naja species Bite Injury- Pathophysiology of Envenomation and Multidisciplinary Approach in Management.

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ABSTRACT

Cobra bite envenomation is one of the commonest causes of snake related injuries in Malaysia. Local tissue injury following a cobra bite is a complex sequalae of envenomation that is attributed to various peptides and enzymes including cytotoxin, metalloproteases, phospholipase A2 and hyaluronidase. This case involves a young construction worker who was bitten by an unidentified snake on the dorsum of his left foot. He presented with typical features of local and systemic envenomation of a *Naja* species. Remote Envenomation Consultancy Services was consulted and the appropriate antivenom was administered. The patient underwent wound debridement and subsequent skin grafting. Follow up at outpatient clinic showed good skin graft uptake and recovery. Managing a significant *Naja* species bite envenomation can be a lengthy process requiring expertise from various subspecialties. Timely and seamless multidisciplinary approach in managing a *Naja* species envenomation ensures a favorable outcome with minimal complication..
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INTRODUCTION

Snake bite injury is a potentially serious health threat that leads to significant morbidity and mortality. In a tropical developing country where rural urbanization takes place, venomous snake bite is often a neglected hazard for outdoor workers (1). Most snake bite occurs when the snake is stepped on either in the dark or undergrowth (2).

In Malaysia, significant numbers of snake related injuries (SRI) in urban setting are from the *Naja* species and the reticulated python (1,2). Bite envenomation from the Naja species can cause local and/or systemic effects, depending on the amount of venom injected (1-3). Systemic effects include cardiotoxicity and neurotoxicity (1-3). Local effects vary from mild pain and swelling of the affected bitten area to significant tissue injury and necrosis (1-5).

Managing envenomation from a *Naja* species requires a timely and appropriate treatment and intervention across clinical disciplines. We describe a case of a *Naja* species envenomation causing significant tissue injury necessitating surgical intervention, a lengthy hospital stay, prolonged wound care and rehabilitation.

CASE REPORT

A 32-year-old construction worker was bitten on the dorsal aspect of his left foot by an unidentified snake in the late afternoon. Further search at patient's workplace by his co-workers revealed a *Naja* species, hiding near the site of incident and believed to be the snake that caused the bite. He was brought to an emergency department approximately one hour after the incident and presented with drowsiness and profuse sweating. His heart rate was 65/min, blood pressure 105/79mmHg, respiratory rate 18/min, and SpO_2 97% on air. Intramuscular adrenaline 0.5mg was given twice for suspicion of anaphylaxis. Intramuscular anti-tetanus toxoid 0.5mL (10 Lf), intravenous morphine 2 mg and fentanyl 50 mcg were given. Examination of the bite site showed a broken-off fang still embedded on the skin (Fig. 1A) with a few punctured wounds and surrounding skin discoloration (Fig. 1B). Other systemic examination was unremarkable. Initial investigations did not reveal

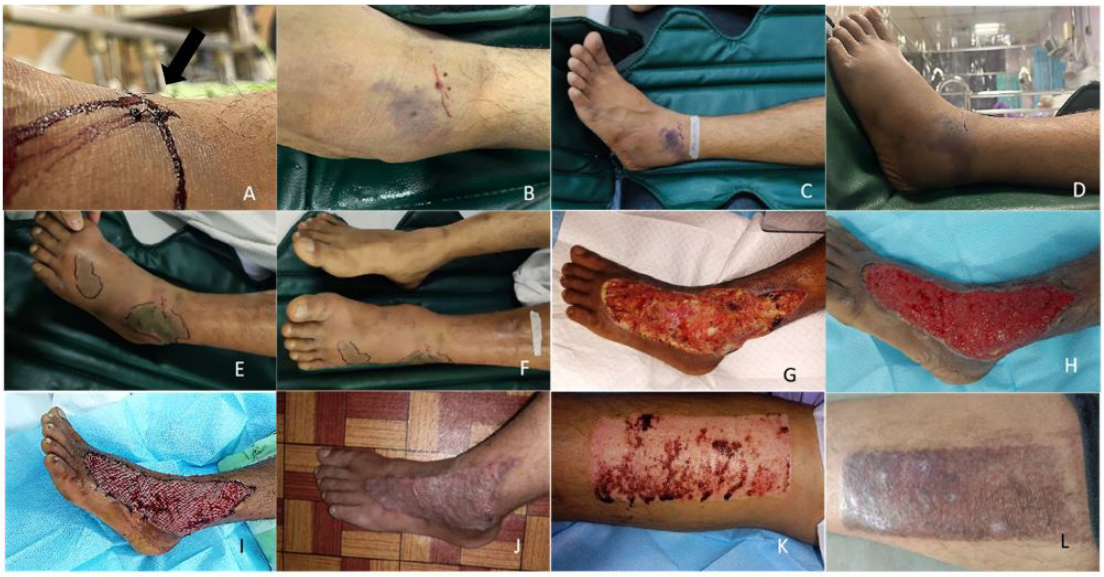

Figure 1: A: Retained broken off fang embedded on skin. B: Wound at 1 hour post snake bite. C: Progression of dermonecrosis at 6 hours. D: Progression of proximal swelling and dermonecrosis at 12 hours. E: Worsening swelling and redness on day 2 with presence of skip lesion. F: Comparison with normal limb on day 2. G: Wound condition on day 5 prior to wound debridement. H: Wound inspection pre SSG. I: SSG done on 23 days post wound debridement. J: SSG 6 weeks post grafting showing good uptake of the skin graft. K: Wound inspection of donor site at day 5. L: Wound inspection of donor site at 6 weeks.

any significant abnormality. 6 hourly serial blood tests were performed (Table I).

The Remote Envenomation Consultancy Services (RECS) was consulted for patient management 40 minutes after patient's arrival to the emergency department. An initial dose of 10 vials of *Naja kaouthia* antivenom from Queen Saovabha Memorial Institute Thailand (NKAV QSMI) was indicated and decided following close serial monitoring of patient's progress. The antivenom was administered as per Malaysia Ministry of Health Guideline on the Management of Snakebite. The patient developed chills 30 minutes after completion of the antivenom with a recorded temperature of 37.6°C. He responded to antipyretics and no further reactions occurred.

The patient was admitted for continuation of care. He was monitored for the rate of proximal progression (RPP), pain score progression (PSP), lymph nodes and progression of local tissue injury such as dermonecrosis and blisters. He developed a temperature spike 12 hours post incident with the expansion of dermonecrosis and further progression of the swelling proximally. The distal circulation of the limb remains intact with capillary refill time less than 2 seconds. He was started on intravenous Amoxycillin/clavulanic acid 1.2g 8 hourly and subsequently changed to intravenous Ampicillin/sulbactam on day 2 due to persistent temperature spike. Swelling and redness of the limb progressed up to mid shin level and the dermonecrosis expanded distally over the dorsum of the foot (Fig. 1D, Fig. 1E and Fig. 1F). This was accompanied by a rise in his white blood cell count, C-reactive protein and creatine kinase (Table I). Blood cultures did not grow any organism. His pain was well controlled with regular intravenous tramadol 50mg 8 hourly.

The orthopaedic team performed wound debridement on day 5. Intraoperatively there was liquefactive necrosis of subcutaneous tissue over the anteromedial aspect of the left ankle extending to dorsum of his forefoot. Necrotic tissue was debrided and 50cc of pus drained. He was transferred to an Orthopaedic ward post operatively to continue wound care management. Cultures of the wound revealed a growth of Morganella morganii sensitive to Cefepime and antibiotic therapy was changed accordingly. He had three cycles of vacuum dressing with repeated tissue culture (Fig. 1G and Fig. 1H). Following a normal flora skin growth on repeated culture, he had split thickness skin grafting on day 27. He was discharged well 5 days post skin grafting

TABLE I: Serial blood investigation

Investigation	Reference range	Duration from snake bite										
		1 Hour	7 Hours	13 Hours	25 Hours	Day 2	Day 3	Day 4	Day 8	Day 10	Day 14	Day 17
White blood cell	(4-10) x10	14.8	16.7	14.5	13.6	14.5	11.5	10.3	9.1	11.9	9.8	11.1
Hemoglobin	13-17 g/dL	15.2	13.8	13.8	14.0	14.3	12.8	12.8	11.2	12.3	12.6	12.0
Platelet	(150-400) x10	358	282	289	273	229	222	243	553	647	715	580
C-reactive protein	<0.5 mg/dL			2.32	24.04				2.26	1.31	0.43	0.44
Creatine Kinase	30-200 U/L	221	146	152	107	679	1513	497				

(Fig. 1I) with daily wound dressing of recipient site at a nearby health clinic and weekly wound inspection at orthopaedic clinic (Fig. 1J, Fig. 1K and Fig. 1L).

DISCUSSION

Cobra bite injury is known to cause local tissue damage with or without systemic envenomation (1,2). Three-fingered toxins (*α-cobratoxins*) causes muscle paralysis by competitively binding to post-synaptic nicotinic acetylcholine receptors at neuromuscular junction. The outcome may lead to bulbar and respiratory muscle paralysis and death due to asphyxiation. Dysrhythmias and hemodynamic instability may result from cardiotoxins. Local tissue injury following a cobra envenomation, may not be life threatening but often leads to significant morbidity i.e. septicaemia and loss of limb (1,2). The extent of tissue injury depends on local (amount of venom injected, time of antivenom administration) and host factors (nutrition, age, pre-existing medical co-morbidities).

Cobra venom, containing proteins like enzymes and toxins, triggers diverse envenomation reactions. Venom constituents vary geographically. Local tissue damage from cobra bites results from cytotoxins (CTXs)- a non-enzymatic, highly basic polypeptides made up of 60-70 amino acids (3-5), forming 20-80% of total venom protein. Metalloproteases and phospholipase A2 (PLA2) are linked to tissue injury by affecting vascular endothelium, nerves, and muscles (3,4). Dermonecrosis in cobra bites damages cell membranes, heightens vascular permeability, and prompts inflammatory mediator release (4). Hyaluronidase, an enzyme, facilitates venom spread, causing swelling, blisters, and necrosis at the bite site (1,4).

Specifically for *N. kaouthia, N. sumatrana* and *N. atra*, cytotoxin induced cytotoxicity has been observed in-vitro. *N. kaouthia* has a lower abundance of cytotoxins (~28% of total venom proteins) compared to *N. sumatrana* and *N. atra* (50% of total venom proteins), reflecting a lower cytotoxicity activity of *N. kaouthia* venom (3-5). Other variables affecting cytotoxicity level of different Asian cobra species include its target cells and the subtypes of its cytotoxin. *N. kaouthia* venom is further subtyped to the S-type while *N. sumatrana* and *N. atra* belong to the P-type cytotoxin (3). In general, the S type cytotoxin is relatively less potent than the P-type due to its lower lipid binding activity and shallower tissue penetration.

The cornerstone treatment of local tissue injury following a snake bite envenomation is neutralization of the cytotoxic venom constituent (1-5). Appropriate and timely administration of antivenom is crucial in reducing the occurrence of severe tissue injury. Subsequently, up to 60% of cobra envenomations require additional surgical intervention due to dermonecrosis and associated bacterial infection.

Secondary bacterial infection may lead to further tissue necrosis. *Enterococcus spp*. and *Morganella morganii* are the most encountered organisms following cobra bite envenomation (1,4). The combination of bacterial load in the mouth of the snake and cytotoxic effects of snake venom constituents potentiates local tissue injury leading to necrotising soft tissue infection (3-5). Early decontamination of the wound, and antimicrobial treatment aids tissue salvageability, and function reducing morbidity and mortality (1,2).

CONCLUSION

Snake bite envenomation can be associated with morbidity and mortality if not managed appropriately. Public awareness on safety and prevention of SRI needs to be enhanced. A Multidisciplinary approach in managing SRI is required for appropriate and timely clinical management.

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