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Case Report

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Thrombotic microangiopathy and hemolytic uremic syndrome following viperidae snakebites in Sri Lanka.

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Abstract

Russell's viper and hump-nosed viper are deadly venomous Viperidae snakes in Sri Lanka. Both these vipers are widely distributed in all climatic zones of the island. Russell's viper causes systemic envenoming such as coagulopathy, neuroparalysis and acute kidney injury (AKI) whilst hump-nosed viper frequently causes local envenoming and rarely causes AKI and coagulopathy. These two snakes may cause atypical syndromes like thrombotic microangiopathy (TMA) and hemolytic uremic syndrome (HUS). We report two cases of HUS, a type of TMA and a rare complication of snakebites including the triad of AKI, thrombocytopenia and microangiopathic hemolysis.

Keywords: snakebites, hump-nosed viper, Russell's viper, thrombotic microangiopathy, hemolytic uremic syndrome

INTRODUCTION

There are four Viperidae snakes in Sri Lanka including Russell's viper (*Daboia russelii*), saw-scaled viper (*Echis carinatus*), hump-nosed viper (*Hypnale spp.*) and Green pit viper (*Craspedocephalus trigonocephalus*). Out of these, Russell's viper (RV) and hump-nosed viper (HNV) are deadly venomous and are widely distributed in all climatic zones of the country. The most snakebite deaths in Sri Lanka occur following Russell's viper bites [1] and is responsible for 30-40% of all snakebites [2]. Multiple systemic manifestations such as venom induced consumption coagulopathy (VICC), neuroparalysis and spontaneous systemic bleeding are common manifestations of RV bites [3]. Hump-nosed vipers are the commonest cause of venomous snakebites (27-77%) in Sri Lanka [2] and they frequently cause local envenoming and rarely cause systemic manifestations like acute kidney injury (AKI) and VICC [4]. Bites by both these snakes may present with atypical manifestations such as thrombotic microangiopathy (TMA), hemolytic uremic syndrome (HUS) and thrombotic

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thrombocytopenic purpura (TTP). We report two cases of HUS, a type of TMA caused by RV and HNV bites.

CASE 1

A 41-year-old known female with epilepsy was admitted to the Emergency Treatment Unit following RV bite (Figure 1) to her left hand around 4.30 pm while she was working in home garden. On admission, she had vomiting, and lower abdominal pain. On examination, she had ptosis, external ophthalmoplegia and mild swelling over the bitten site with a fang puncture. Her blood pressure was 140/80 mmHg, pulse rate was 92 beats per min and the other systems were normal. The 20 min whole blood clotting test (WBCT20) was prolonged on admission and 20 vials of Indian polyvalent antivenom was administered after giving prophylactic treatment. At the ward, she developed haematuria. Twelve hours after the snakebite, she had coagulable blood in WBCT20 and other laboratory findings are shown in Table 1. Peripheral blood picture on day 1 showed microangiopathic haemolytic anaemia (MAHA) and her urine output got reduced on day 1 of admission with increase of creatinine levels. She was started first cycle of haemodialysis on day 3 and subsequently 9 cycles were carried out. First cycle of therapeutic plasma exchange was performed on day 5 and subsequently 3 cycles were done. On and off she was transfused 6 packs of blood. She was discharged on day 23 of snakebite once she was producing normal amount of urine and was followed up in nephrology clinic.

Figure 1: The offending Russell's viper responsible for bite in case 1 patient

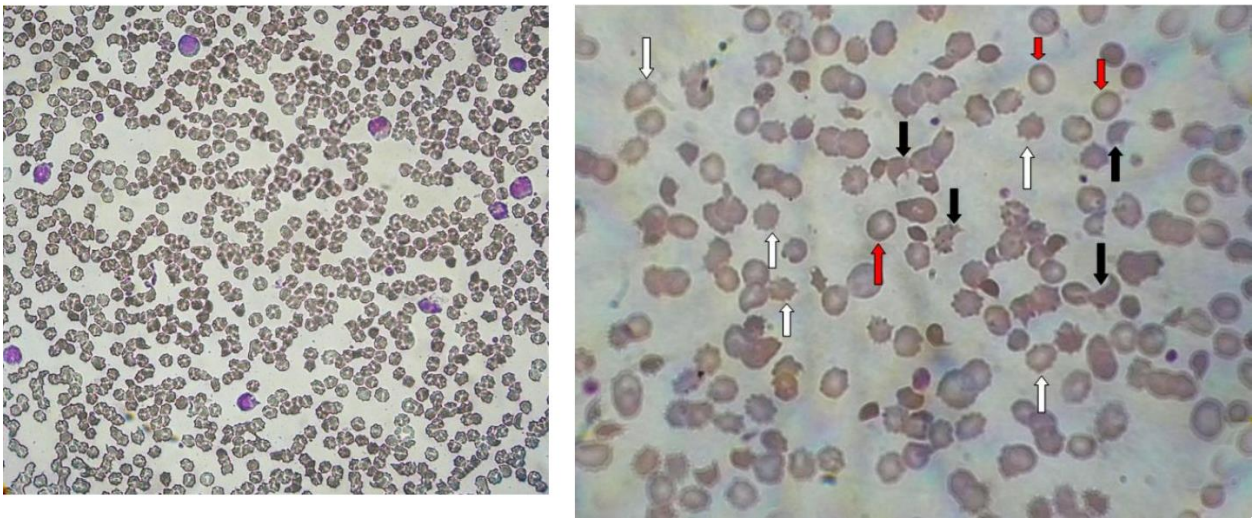
CASE 2

A 72-year-old male patient was transferred from a local hospital for further management of HNV bite with AKI. He was on treatment for hypertension, ischemic heart disease and dyslipidaemia for 10 years. A snakebite happened to his right second finger 3 days back at home garden at about 8.30 am and was admitted to local hospital same day. His WBCT20 was normal. But, he developed AKI for which two cycles of haemodialysis were done at local hospital. On admission to Teaching Hospital, he was anuric. At local hospital, the snake was identified as HNV and photographs were available for the identification (Figure 2).

His peripheral blood microscopy showed fragmented red cells, polychromatics and acanthocytes suggestive of MAHA (Figure 3) and the other laboratory findings are shown in Table 1. Third cycle of haemodialysis was started on day 5 of snakebite and subsequently 8 cycles were performed. The patient was discharged on day 17

when he produced normal amount of urine and arranged nephrology clinic follow up.

Figure 2: The offending hump-nosed viper responsible for bite in case 2 patient



(A) x 40 **(B) x 100**

Figure 3: Microangiopathic haemolysis in blood picture of case 2 patient. Note that fragmented red blood cells (indicated in black arrows), acanthocytes (indicated in white arrows) and polychromatics (indicated in red arrows). (A) x 40, (B) x 100

Table 1: Laboratory findings of the patients

		Case 1 patient-Day from the snakebite										Case 2 patient-Day from the snakebite						
Investigation	**Reference range**	**1**	**2**	**3**	**4**	**5**	**8**	**10**	**14**	**18**	**21**	**1**	**4**	**6**	**10**	**12**	**14**	**17**
WBC ($x10^3.\mu L^{-1}$)	4-10	19	26	20	18	15	22	19	12	7			14	11	10	8	7	8
Neutrophils (%)	50 -70	96	93	92	89	90	81	83	78	75			80	71	73	73	73	61
Platelets ($x10^3.\mu L^{-1}$)	150-400	197	128	76	62	37	62	136	288	215	147	194	98	97	138	192	245	325
Hb ($g.dL^{-1}$)	11-16	9.2	8.8	7.9	10	8.5	7.9	7.8	8.5	8	8	11	8.3	9.1	8	7.4	7.6	7.8
PT (sec.)	10-15	19/ 12	22/ 12	17/ 12	13.3/ 12	14/ 12	13.6/ 12	12.5/ 12		12.4/ 12				18/12				
INR	1 - 1.4	1.6	1.85	1.4	1.1	1.17	1.14	1.04		1.03		0.95		1.5				
APTT (sec.)	25 - 30		36/ 30		31/ 30	25/ 30	28/ 30							30/30				
Na^+ ($mmol.L^{-1}$)	135- 145		139	136	135	133	134	137	138	128	134	130	133	132	136	130	136	136
K^+($mmol.L^{-1}$)	3.5 – 4.5		4.3	4.4	4.3	4.4	4.5	4.2	4	3.4	3.3	3.9	4.5	4	4	3.6	4.3	4.2
Blood urea ($mmol.L^{-1}$)	2.2-8.2	5.2	6.8	18	16	28	26	20	15	13	10		14	17	10	8	9	7
Creatinine ($\mu mol.L^{-1}$)	60-115	140	270	440	391	617	658	688	722	610	370	373	594	568	644	674	546	616
SGOT(AST) [$U.I^{-1}$]	0 – 35	44	191	291	55	32	39					38						
SGPT(ALT) [$U.I^{-1}$]	0 – 45	53	201	289	129	57	45					38						
Total bilirubin ($\mu mol.L^{-1}$)	5-21			39		26	20	15				77	12					
CRP ($mg.L^{-1}$)	< 6	< 6	64	187	158	57		39				22						
LDH U/I	< 250	2090		5124	4255	1644			731				2140					

DISCUSSION

Hemolytic uremic syndrome, a rare complication of snakebites has previously been reported in Sri Lanka following envenoming by HNV and RV [4][5]6]. The spectrum of HUS and TTP are two clinical entities of TMA which includes AKI, thrombocytopenia and MAHA. Acute kidney injury occurs due to direct or indirect effects of Viperidae snake venoms. In-vitro studies showed that RV venom causes direct nephrotoxicity [7] and indirect effects are due to renal ischemia caused by the venom. Both venoms contain snake venom metalloproteinases that may function as direct nephrotoxins.

In our case 1 patient, she had neuroparalysis, short lived VICC and predominant AKI. She also had hepatotoxicity because her liver enzymes (SGOT/SGPT) mildly elevated in first 2-4 days. Case 2 patient only developed TMA without VICC. Both patients had severe form of kidney injury which is consistent with diagnosis of HUS together with MAHA associated with low haemoglobin which is due to intravascular haemolysis caused by phospholipase A_2 found in both venoms. This was further evidenced from the elevated bilirubin and LDH levels (Table 1). Therapeutic plasma exchange (TPE) is one of management options in the treatment of snakebites complicating TMA [4],[5],[6]. It is thought that auto-antibodies against ADAMTS 13 are removed in the process of TPE. Antivenom, haemodialysis and TPE are the mainstay of treatments in snakebite complicating TMA. However, no antivenom is currently available for HNV bites in Sri Lanka. These index cases are medically important because reports of HUS following Viperidae snakebites are rare in literature and physicians should be aware of how these patients should be managed promptly in order to prevent irreversible renal damage causing chronic kidney disease. Therefore, these patients should be closely monitored in order to diagnose TMA early.

Author declaration

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Author contributions:
RMMKNR and PEANR: conception, literature search and management of patients.
RMMKNR, PEANR and SAMK drafted the first manuscript and wrote the case histories.

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The authors declare no competing interests.

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All the data generated and analyzed for this case report have been included in this article.

Consent:
Written consent for publication of these case histories and photographs was obtained from the relevant patients.

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