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CASE REPORT

Thrombotic microangiopathy, hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: Rare manifestations of Russell's viper (*Daboia russelii*) envenoming in Sri Lanka

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Abstract

Background: Russell's viper (*Daboia russelii*) of Family Viperidae is a highly venomous snake in Sri Lanka and is responsible for the most snakebite deaths. It commonly causes coagulopathy and neuroparalysis. Thrombotic microangiopathy (TMA) including the triad of acute kidney injury (AKI), thrombocytopenia and microangiopathic hemolysis is a rare complication of its bites. There are two clinical entities of TMA including hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) of which, only few records of TMA and HUS following Russell's viper bites are available in literature.
Case presentation: Two patients presented with TMA following Russell's viper bites. A 36-year-old male who got coagulopathy, respiratory failure, AKI, signs of HUS, and he completely recovered with antivenom and 8 cycles of hemodialysis and discharged on day 19 of snakebite. The other patient was a 66-year-old female who had delayed coagulopathy and persistent drowsiness, the signs of TTP. She required antivenom with 9 cycles of hemodialysis and 6 cycles of therapeutic plasma exchange and got recovered after 30 days in hospital that included intensive care treatments.
Discussion: Russell's viper venom causes activation of Factor V and X which results venom induced consumption coagulopathy and bleeding. The venom also blocks neuromuscular junction and causes neuroparalysis, which are commonly manifested as ptosis and external ophthalmoplegia. It also has direct nephrotoxic effects and there are fibrin depositions in renal microvasculature thereby, causing renal ischemia. In the spectrum of HUS-TTP of TMA, HUS is suggested when there is a severe renal involvement, and TTP is diagnosed when neurological impairment is prominent.
Conclusion: Atypical presentations like TMA and HUS may rarely occur following Russell's viper bites. Further evidence of similar observations is needed to confirm the clinical entity of TTP following *Daboia russelii* bites.

Keywords: snakebites; antivenom; acute kidney injury; blood coagulation disorder; Sri Lanka

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INTRODUCTION

Russell's viper (*Daboia russelii*) is a highly venomous snake in Sri Lanka and responsible for the most snakebite deaths [1]. It is responsible for 30-40% of all snakebites [2], as high as 73% in dry zone in the country (Anuradhapura) [3]. In Sinhala, it is called '*Thith polanga*' (spotted viper) and its envenoming causes systemic effects like neuroparalysis, venom induced consumption coagulopathy (VICC), spontaneous systemic bleeding, AKI and rhabdomyolysis [3],[4],[5],[6]. Atypical features include acute myocardial infarction [7], TMA [8],[9], hypopituitarism [10], capillary leak syndrome [11], pulmonary hemorrhage [12], intracerebral hemorrhages and infarcts [13],[14]. We report rare presentations of HUS and TTP following proven Russell's viper bites manifested with AKI and VICC. Extensive literature confirms that TTP has not previously been reported following Russell's viper bites.

CASE REPORT

Case 1

A 37-year-old previously well male was transferred from a local hospital to intensive care unit (ICU) for mechanical ventilation for respiratory failure following a Russell's viper bite. At about 0130 h on previous day, his left thumb was bitten when he tried to catch the snake in the home garden. At that time, he was under the influence of alcohol. Then he was admitted to a local hospital where he was given 20 vials

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of Indian polyvalent antivenom.

He had hematemesis associated with incoagulable blood that was detected in 20 min whole blood clotting test (WBCT20) with prolonged international normalized ratio of 1.56. One cycle of hemodialysis was performed 33 h after the bite, because he developed anuria associated with elevated serum creatinine (480 μmol/L). He needed endotracheal intubation as he developed respiratory failure and chest x-ray shows pulmonary edema. On admission to ICU, there were mild swelling and necrosis at the site of bite, and bilateral crepitations on lungs, with difficulties in assessing ptosis or external ophthalmoplegia.

Figure 1. Offending snake, Russell's viper (*Daboia russelii*) in case 1 patient

Figure 2. Offending snake in case 2 patient- Russell's viper (*Daboia russelii*), a male snake, 313 mm in total length, head length- 21 mm, tail length-45 mm, snout-vent length (SVL)-268 mm, number of ventrals-172 and number of subcaudals (divided) -53, dorsal view:Note that three transverse rows of bright brownish ovate spots and keeled costal scales (A), ventral aspect (B).

Blood pressure was 97/66 mmHg, pulse rate was 109 beats/min and SpO_2 was 97%.

WBCT20 was prolonged for first 24 hours, done 6 h apart. There were puncture sites bleeding. Furosemide 5 mg/hour infusion and dopamine 10 μg /min/kg infusions were started with intravenous cefoperazone/salbactum 1g twice daily and clindamycin 600 mg thrice daily. Hemodialysis was carried out frequently, up to 8 cycles. Initial blood picture was normal. But on day 5, fragmented red blood cells with acanthocytes were detected in peripheral blood microscopy, suggesting microangiopathic hemolysis. Acute parenchymal kidney disease was suggested on abdominal ultrasound scan after 5 days of snakebite. Other laboratory findings are shown in Table 1. The patient was extubated on day 9 and was transferred to the medical ward. He was discharged on day 19 when his urine output was normal but the creatinine level was elevated and was followed up in nephrology clinic. At the time of bite, the snake was killed, was photographed and was produced to the hospital and was identified as Russell's viper by attending medical officer (Figure 1). One year after the bite, his creatinine was 91 μmol/L, blood urea was 34 mg/dL (normal 10-50), Na^+ 138 mmol/L, K^+ 3.7 mmol/L and Hb-15g/dL.

Case 2

A 66-year-old female patient was bitten by a Russell's viper on her left foot at about 1930 h while she was watching television inside her house. She was a known hypertensive patient and was on a regular treatment with nifedipine with good control of blood pressure. She was admitted to the medical unit around 2015 h with the killed snake which was identified as Russell's viper by the admitting medical officer (Figure 2). On admission, she had severe pain and numbness over the site of bite. On examination, there was a fang puncture on left foot, mild swelling and inguinal lymph node enlargement. But, no bleeding was observed at the site of bite.

Her blood pressure, pulse rate and respiratory rate were 170/90 mmHg, 84 beats/min and 15 breaths/min respectively. Examination of respiratory system, nervous system and abdomen revealed no abnormality. WBCT20 on admission and then at 6 h intervals were normal for 14 hours. At 0930 h following day, the patient vomited once and complained of abdominal pain. At this moment, her WBCT20 was prolonged and she had hematuria too. Then she was administered 20 vials of polyvalent Indian antivenom (Batch No.01AS16035) after giving 200 mg of hydrocortisone and 10 mg of chlorpheniramine intravenously. She developed shivering of the body in halfway of antivenom infusion. Then, antivenom was withheld and she was transferred to ICU for further management. Antivenom was restarted and the patient was given 50 vials in 4 divided doses of 6 hours intervals (20,10,10,10 vials) as she had persistent coagulopathy beyond day 4 of snakebite. Her laboratory findings were shown in Table 2. Ultrasound scans of abdomen (done 26 h after and day 11 of snakebite) revealed features of bilateral acute parenchymal renal changes, suggesting AKI.

Table 1. Laboratory findings of case 1 patient

		Day from snakebite																	
Investigation	Reference range	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
WBC ($x10^3.\mu L^{-1}$)	4-11	17	22	21	16	9	12	10	11	13	16	17	21	17	12		10	9	10
Neutrophils (%)	50 -70	87	89	88	86	79	71	65	71	77	72	76	73	78	67		71	64	75
Lymphocytes (%)	20 -40	8	5	8	9	13	16	13	12	13	16	14	16	13	20		17	21	17
Neutrophil count ($x10^3.\mu L^{-1}$)	2-7	18.7	19.5	18	13.5	7	8.8	6.7	8	10	11.5	12.8	15.6	13	7.8		6.8	6	7
Lymphocyte count ($x10^3.\mu L^{-1}$)	0.8 - 4		1	1.56	1.4	1.2	2	1.4	1.4	1.7	2.5	2.4	3.5	2.2	2.3		1.6	1.9	1.6
Hb ($g.dL^{-1}$)	11-16	14.6	13.4	11.6	10.5	7.6	9.8	8.4	9.4	8.8	7.8	8.2	8.1	7.6	6.6		7.4	8.1	8.9
Platelets ($x10^3.\mu L^{-1}$)	150-450	117	81	91	91	96	114	132	185	213	245	264	303	362	399		447	468	470
RBC count ($10^6.\mu L^{-1}$)	4-6		4.6	4.2	3.8	3.1	3.5	3	3.4	3.3	2.9	3	2.9	2.8	2.4		2.7	2.9	3
PCV (%)	37-54		39	34	31	26	29	25	28	27	23	25	24	23	20		23	24	27
PT (s)	10-15	18.7	12.1/12	13.7/12	13/12	12.1/12	12.1/12	13/12	14/12	14/12	14/12	11.8/12	13.3/12						
INR	1 - 1.4	1.56	1	1.15	1.08	1	1	1.08	1.18	1.18	1.18	0.98	1.1						
APTT (s)	25 - 30		22/25	27.1/30	28/30	29/30	23/30	27/25	32/30	25/30	14/12	11.8/12	13.3/12						
Na^+ ($mmol.L^{-1}$)	135- 145	141	133	135	138	141	142	142	142	143	136	137	136	135	134	136	134	135	137
K^+ ($mmol.L^{-1}$)	3.5 – 4.5	4.5	6.7	5.2	4.5	3.6	3.9	3.9	3.8	3.6	5.5	3.3	3.4	3.6	3.6	3.9	3.8	3.7	4.2
Creatinine ($\mu mol.L^{-1}$)	60-115	480	478	460	491	443	466	412	347	303	335	461	456	632	604	458	525	438	432
Blood urea ($mmol.L^{-1}$)	7.8-20.1		19		16	15	16	13	11	8									
SGOT(AST) [$U.I^{-1}$]	0 - 35	23	32		22	17	19	25	28	31	42								
SGPT(ALT) [$U.I^{-1}$]	0 - 45	18	23		19	16	19	19	26	28	30								
T.Bilirubin ($\mu mol.L^{-1}$)	5 - 21		43		19	18	17	13	14	11	9								
MCV (fL)	80 - 100		86	83	81	82	81	82	82	81	82	83	83	81	83		85	82	89
MCH (Pg)	27 - 34		29	28	28	24	28	27	27	27	27	27	28	27	27		28	28	29
MCHC ($g.dL^{-1}$)	32 - 36		34	34	34	29	34	34	33	33	33	33	33	34	33		32	34	34
MPV (fL)	7.8 - 11		9.1	9.6	9.9	9.8	10.2	10.5	9.9	9.9	9.5	9.6	9.9	7.9	8.3		7.7	7.5	7.6
CRP ($mg.L^{-1}$)	< 6		115		92	71	75		88		81		42			32		29	
Ca ($mmol.L^{-1}$)	2.1-2.55		1.63				2.3			2.4									
Protein ($g.L^{-1}$)	64-83					53				55									
Albumin ($g.L^{-1}$)	36-48					31				34									

Table 2. Laboratory findings of case 2 patient

		Day from the snakebite														
Investigation	Reference range	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
WBC ($x10^3.\mu L^{-1}$)	4-11	10	13	14	15	13	10	9	7	8	7	14	15	13	14	16
Neutrophils (%)	50 -70	68	78	93	87	84	85	79	72	70	72	85	85	82	82	79
Lymphocytes (%)	20 -40	22	11	4	7	7	13	11	15	13	16	9	9	11	11	11
Neutrophil count ($x10^3.\mu L^{-1}$)	2-7	7	11	12	13	11	9	7	5	5	5	12	13	11	12	13
Lymphocyte count ($x10^3.\mu L^{-1}$)	0.8 - 4	2.1	1.5	0.5	1	0.9	1.3	1	1.2	1.1	1	1.3	1.4	1.4	1.5	1.8
Platelets ($x10^3.\mu L^{-1}$)	150-450	191	93	86	37	37	42	48	49	64	67	70	61	74	78	73
Hb ($g.dL^{-1}$)	11-16	8.6	8.6	7.3	6.2	6.2	7.2	6.9	7.1	6.2	7	8.3	7.9	7.1	6	8.7
RBC count ($10^6.\mu L^{-1}$)	4-6	4.7	4.7	4.5	3.5	3.1	3.4	3	3.2	2.8	3	3.5	3.1	3	2.5	3.4
PCV (%)	37-54	29.3	27.8	27.7	19.9	19.1	21.9	18.4	21.4	18.2	20.9	25	23.1	21.4	18.9	26
PT (s)	10-15	14/13	27.5/13	18/12	19/12	13/12	15/12	14.4/12	14/12	12.3/12	14/12	16/12	12.5/12	12/12	12/12	
INR	1 - 1.4	1.08	2.08	1.53	1.6	1.08	1.26	1.21	1.1	1.03	1.18	1.34	1.04	1	1	
APTT (s)	25 - 30	34.7/25	39.5/25	88/25	35/25	23/25	26/25	26/25	26/25	24.5/25	26/25	28/25	25/25	22/25	26/25	
Na^+ ($mmol.L^{-1}$)	135- 145	145	144	146	146	147	145	141	139	144	144	143	143	132	140	144
K^+ ($mmol.L^{-1}$)	3.5 – 4.5	3.7	3.6	3.4	4.8	3.8	3.9	3.7	4	3.8	4.6	3.9	4	4.5	4.5	4.8
Blood urea ($mg.dL^{-1}$)	7.8-20.1	3.1	5.8	11.6	17.2	15.5	14.7	21.5	8.6	18.3	6.6	6.3	8.5	13.6	15.8	13
Creatinine ($\mu mol.L^{-1}$)	60-115	75	156	188	116	374	240	343	299	306	249	216	182	298	361	263
SGOT(AST) [$U.I^{-1}$]	0 - 35	23		523	184	71	64	56	48	37	36	34	53	23	19	22
SGPT(ALT) [$U.I^{-1}$]	0 - 45	16		247	159	74	64	44	43	36	32	30	34	26	24	26
T.Bilirubin ($\mu mol.L^{-1}$)	5-21	19	89	156	115	157	179	184	209	165	111	96	90	63	56	49
D.Bilirubin ($\mu mol.L^{-1}$)	0- 3.4	15.5	82	153	97	142	174	178	202	157	101.5	86	77	49	51	43
Indirect bilirubin ($\mu mol.L^{-1}$)	5- 21	3.5	7	3	18	15	5	6	7	8	9.5	10	13	14	5	6
ALP ($U.I^{-1}$)	30 - 120			202				133	117	140	154		165			
MCV (fL)	80 - 100	67	60	60	58	55	64	61	67	66	71	72	74	72	75	77
MCH (Pg)	27 - 34	18	18.5	18.5	18	18	21	20	22	22	23	24	25	24	24	26
MCHC ($g.dL^{-1}$)	32 - 36	29	31	31	32	32	33	33	32	34	33	33	34	33	32	33
MPV (fL)	7.8 - 11	10.7	9.8		7.7	7.8	10	7.7	7.7	8	8.6	7.8	11.7	8.8	10	11
CRP ($mg.L^{-1}$)	< 6	< 5			103						11				10	
Blood picture		MAHA	MAHA	MAHA		MAHA	MAHA	MAHA	MAHA	MAHA			MAHA			

WBC, white blood cells; Hb, hemoglobin; RBC, red blood cells; PCV, packed cell volume; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; SGOT, serum glutamic-oxaloacetic transaminase; AST, aspartate aminotransferase; SGPT, serum glutamic-pyruvic transaminase; ALT, alanine aminotransferase; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MPV, mean platelet volume; CRP, C-reactive protein; MAHA, microangiopathic hemolytic anemia

Blood picture (12 h of snakebite) showed microangiopathic hemolysis (Figure 3) and the first cycle of plasmapheresis was performed on day 3 of snakebite (60 h after the snakebite) and then subsequent 6 cycles were performed (Figure 4A). Since day 2 of snakebite, the patient developed AKI and she was producing less urine. Her blood urea and serum creatinine levels gradually increased. But, serum K^+ levels were maintained in normal range throughout the hospital stay. Hemodialysis was started on day 3 and subsequent 9 cycles were performed, until she produced normal amount of urine. Her blood pressure was controlled with nifedipine and prazosin. The patient was icteric since the day 3 of snakebite and her plasma bilirubin level (total and direct) was gradually increased (Figure 4B, 4C). As she had persistent drowsiness on day 1, non-contrast computed tomography (NCCT) scan of brain was done on day 5 of snakebite which was normal. She was transferred to the medical ward on day 13 of snakebite with continuous hemodialysis and plasmapheresis, until she was discharged on day 30 of snakebite with arrangements of following up in nephrology clinic. Three months following the snakebite, creatinine level was 173 µmol/L (normal 35-115) and K^+ was 4.9 mmol/L (normal 3.4-5.1), but urine output was normal. Her creatinine was 136 µmol/L and K^+ was 5 mmol/L at 1 ½ years after the bite.

DISCUSSION

Three common clinical manifestations of Russell's viper bites are VICC, neuroloparalysis and AKI [3],[4],[5],[6]. Neurotoxic manifestations are generally confined to eye muscles causing ptosis and external ophthalmoplegia, and paralysis may involve bulbar group of muscles and neck flexors. Respiratory muscle paralysis is very rare [5],[15],[16]. Even though, envenoming of Russell's viper bite affects many systems of the body, three systems will be affected in the majority of patients causing VICC, neuroparalysis and renal dysfunction. But, occasionally, only one system may also be affected, and it is the mono-systemic effect or mono-systemic involvement [6]. This phenomenon could be due to different venom compositions in the same species of snakes depending on the age of the snake (ontogenic) and its geographical habitat. Our patients had VICC that was confirmed by positive WBCT20, prolonged INR and hematemesis. In the patient case 2, VICC started 14 h after the snakebite and prevailed till day 4, which was associated with gross hematuria. Coagulopathy in case 1 patient was short lasting and occurred within 30 min following the bite, whereas in case 2, it was late onset. Usually VICC appears within 30 min to 12 h after the Russell's viper bites [5]. But in case 2 patient, she was free of any systemic manifestations within the first 14 h and her WBCT20 became prolonged after about 14 h of the snakebite associated with nausea, vomiting, abdominal pain and hematuria. Therefore, first cycle of antivenom had to be administered after 14 h of snakebite. Russell's viper venom contains four main protein families including phospholipase

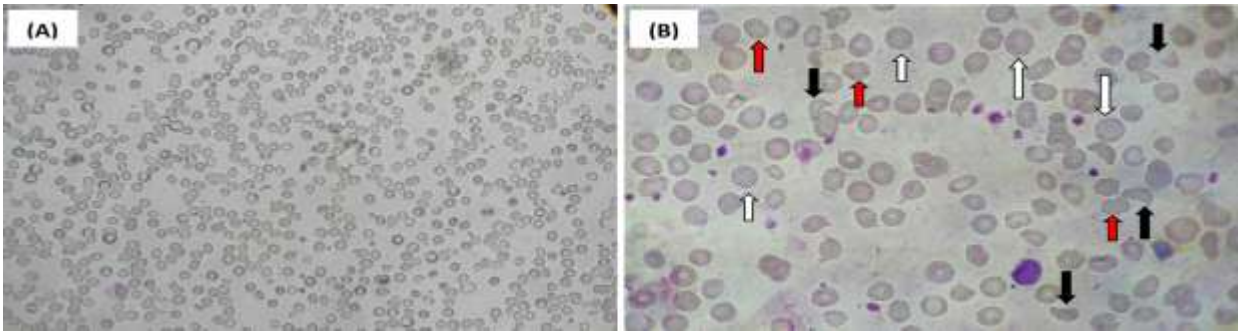

Figure 3. Microangiopathic hemolysis seen in peripheral blood picture 12 h after the snakbite in case 2 patient. Note that black arrows indicate fragmented red blood cells (schistocytes), white arrows indicate polychromatics and acanthocytes are indicated in red arrows. x 40 (A), x 100 (B)

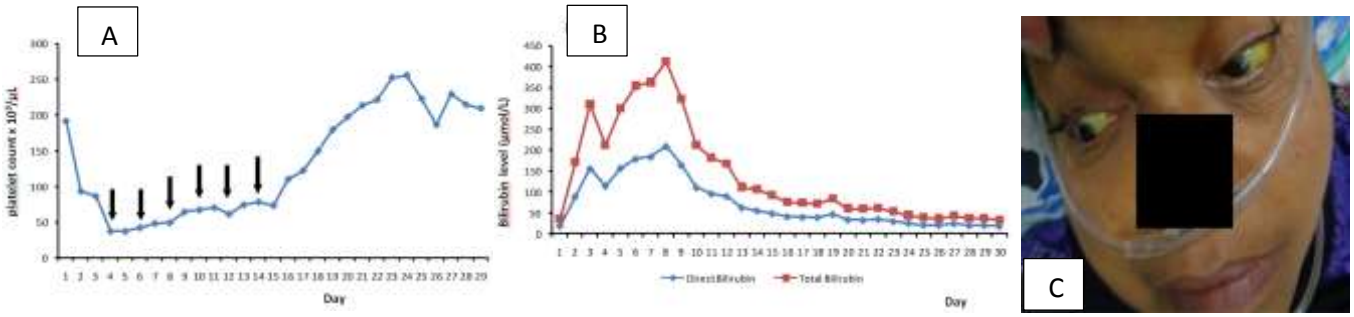

Figure 4. Daily changes of platelet counts with therapeutic plasma exchange (indicated in arrows) (A) Daily changes of serum bilirubin levels (B) icterus of bilateral eyes on day 5 of snakebite in case 2 patient (C)

A_2, snaclec, snake venom serine proteinase and snake venom metalloproteinase [17]. Factor V and factor X are procoagulants which cause VICC and bleeding. Venom may also cause vascular endothelial damage resulting hemorrhage [16].

In-vitro studies showed that Russell's viper venom causes direct nephrotoxicity [18] and indirect renal effects are due to renal ischemia [19]. There are fibrin depositions in renal microvasculature which cause renal ischemia in *Daboia russelii* envenoming [20]. Red blood cells get distorted when they flow through these blocked vessels and can be visualized in blood picture as schistocytes (fragmented red blood cells). When these cells present in peripheral blood smear together with other indicators of hemolysis (low hemoglobin, elevated lactate dehydrogenase or high indirect bilirubin), the condition is called microangiopathic hemolytic anemia (MAHA) which is a type of hemolytic anemia diagnosed by the presence of fragmented red blood cell associated with low hemoglobin level, elevated indirect bilirubin or elevated lactate dehydrogenase level. Usually in hemolytic anemias, indirect (unconjugated) bilirubin is high. But in case 2 patient, direct (conjugated) bilirubin levels were elevated more than indirect bilirubin throughout. This might be due to some kinds of cholestasis caused by the snake venom as supported by the high levels of alkaline phosphatase (Table 2). Hepatic injury following snakebites is very rare. However, severe fatty changes with hepatocellular necrosis have been observed in a Sri Lankan bitten by a Russell's viper [21].

TMA is a recognized uncommon complication of snake envenoming in Viperidae including Russell's viper [8],[9] and hump-nosed viper (*Hypnale hypnale*) [22]. It includes the triad of thrombocytopenia, MAHA and AKI. Further, TTP and HUS are two clinical syndromes of TMA. In TTP, there is a neurological impairment whereas in HUS, the renal impairment is prominent [23]. HUS has previously been reported following Russell's viper envenoming in Sri Lanka [24] and in India [25]. At the same time, TTP has previously been documented in Sri Lanka following hump-nosed viper bites [22]. In primary or congenital cases of TTP, there is a deficiency of ADAMTS 13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13/von Willebrand factor-cleaving protease [VWFCP]) which is a metalloprotease enzyme that cleaves the large von Willebrand factor (vWF), an inhibitor of spontaneous activation of platelet aggregation. In case 2 patient, she had central nervous system (CNS) depression as manifested by persistent drowsiness (up to day 7 of snakebite). And at this time, her NCCT scan of brain was normal. Depression of CNS is somewhat unusual in snakebites since neurotoxins block only neuromuscular junction, causing neuroparalysis [26]. In addition, this cerebral depression or drowsiness cannot only be explained by the venom components of Russell's viper too. Therefore, this can be considered as one of secondary clinical effects of the venom. Severe hypertension itself is associated with TTP as a confounding morbidity. But according to the patient's past medical records, her blood pressure was well controlled with an antihypertensive drug (nifedipine) and she had no previously detected complications of hypertension. Therefore, it is presumptive that TTP was due to *D. russelii* envenoming. As she is a chronic hypertensive patient, prophylactic subcutaneous adrenaline was not administered before the antivenom therapy. On the other hand, 50 vials of antivenom have been administered to case 2 patient because she had persistent VICC which was unresponsive to antivenom. This implies that there is some kind of therapeutic failure in Indian polyvalent antivenom on Sri Lankan snakes. According to snakebite management guidelines, up to 40 vials of antivenom can be given for VICC caused by Russell's viper [27].

In case 1 patient, he had severe microangiopathic hemolysis associated with renal impairment for which 8 cycles of hemodialysis were carried out. This favors the diagnosis of HUS. There are evidences that therapeutic plasma exchange (TPE) is performed for TMA in snakebites [28],[29]. It is thought that auto-antibodies against ADAMTS 13 are removed in the process of TPE. Our case 2 patient was offered 6 cycles of TPE according to her clinical and laboratory response. During this procedure her platelet count did not further drop but there was a slight increase (Figure 4A). Russell's viper bite is an occupational hazard of rice farmers and it is frequently found in paddy fields in the harvesting period. However, case 2 patient was bitten inside the house (living room) which was also an unusual epidemiological incident. There are enough research evidences that Russell's viper causes clinical syndromes of TMA and HUS in Sri Lanka [8],[9],[24] and India [25]. But, presentation with TTP is extremely rare and this is the first report of Russell's viper bite causing TTP. These two clinical presentations highlight the complex nature of the viper venom which should be further studied in laboratory settings.

CONCLUSION

Atypical presentations like TMA, HUS and TTP may rarely occur following Russell's viper bites. However, further evidence of similar observations is needed to confirm the clinical entity of TTP following *Daboia russelii* bites. Also, hemodialysis and therapeutic plasma exchange are beneficial for these patients, in addition to antivenom.

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