Thrombotic microangiopathy due to *Viperidae* bite: Two case reports

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ABSTRACT

Snake bite is mainly an occupational hazard and causes serious health problems in rural India. Acute kidney injury (AKI) occurs in 5-30% cases. Renal pathologic findings include acute tubular necrosis, cortical necrosis, interstitial nephritis, glomerulonephritis, and vasculitis. Thrombotic microangiopathy (TMA) occurrence after a snake bite is reported rarely. Here, we present two patients who developed TMA after viper bite treated with hemodialysis and plasmapheresis. Renal biopsy showed fibrin thrombi in glomeruli and arterioles with cortical necrosis. One patient progressed to end-stage renal disease and other was lost to follow-up. TMA should be considered as a possible pathogenesis of AKI after snake bite. The role of plasma exchanges in snake bite TMA is yet to be defined.

Key words: Acute kidney injury, plasmapheresis, thrombotic microangiopathy, *Viperidae*

Introduction

Snake bite is an important health problem in tropical countries.[1] Snake bite accounts for 45,900 deaths every year and 3% of total acute kidney injury (AKI) reported in India.[2] AKI complicates the course of viper bite in 5–30%.[3] Here, we report two patients who developed thrombotic microangiopathy (TMA) after viper bite, which is an unusual cause of renal failure.

Case Reports

Patient 1

A 56-year-old male who was a farmer by occupation presented to us with anuric renal failure. He had snake bite (Russells' viper) over his right foot 5 days back for which he received antivenom elsewhere. There was no history of bleeding and neurological deficit. On examination, he had jaundice, edema legs, and right foot cellulitis. Vitals and system examinations were normal. Laboratory investigation revealed urine analysis; 3+ proteinuria, plenty of red blood cells (RBCs); urine protein creatinine ratio 6.8; blood hemoglobin: 9.2 g/dl; total count 15,400/mm^3; platelet count 42,000/mm^3; peripheral smear numerous schistocytes; blood urea 168 mg/dl serum creatinine 8.8 mg/dl; sodium 135 mEq/L; potassium 4.2 mEq/L; total bilirubin 2.5 mg/dl; serum uric acid 8.2 mg/dl; calcium 8.6 mg/dl; phosphorus 6.2 mg/dl; international normalized ratio 0.9; activated partial thromboplastin time 30 s; serum fibrinogen level 225 mg/dl, D-dimer <0.5 mcg/ml; serum lactate dehydrogenase (LDH) 4678 U/L; and creatine phosphokinase 184 U/L. Viral markers, chest X-ray, and electrocardiogram were normal. Ultrasound showed

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normal sized kidneys with increased echogenicity and normal corticomedullary differentiation. Serum complements (C3-95 mg/dl, C4-29 mg/dl) were normal. Thrombotic microangiopathy was considered as a cause of AKI, and he was started on hemodialysis and plasmapheresis.

Renal biopsy showed more than 80% of cortical necrosis with fibrin thrombi involving arteries and glomerular capillaries. Swollen tubular epithelial cells and interstitial edema with hemorrhage were noted. Immunofluorescence showed negative staining for immunoglobulins and complements [Figure 1]. She received a total of six plasma exchanges after which his platelet count and LDH levels were normalized. Despite treatment, he progressed to end-stage renal disease (ESRD).

Patient 2

A 46-year-old female was admitted with snake bite in her left hand, and the snake was identified as a hump-nosed viper. Her whole blood clotting time was normal. She was on the supportive measure for 2 days. The polyspecific antivenom currently available in India is manufactured against cobra, russell's viper, common krait, and saw-scaled viper venom and does not have antibodies against hump-nosed viper venom. Later, she developed oliguria and AKI. Urine showed 2+ proteinuria with numerous RBCs. Investigations revealed anemia with numerous fragmented RBCs in peripheral smear, thrombocytopenia, renal failure with peak serum creatinine of 5.5 mg/dl, and elevated LDH levels. Coagulation profile was normal. She was treated with hemodialysis. Renal biopsy revealed fibrin thrombi in glomeruli and patchy cortical necrosis. She was planned for plasma exchange but her family was not willing for further treatment and went against medical advice.

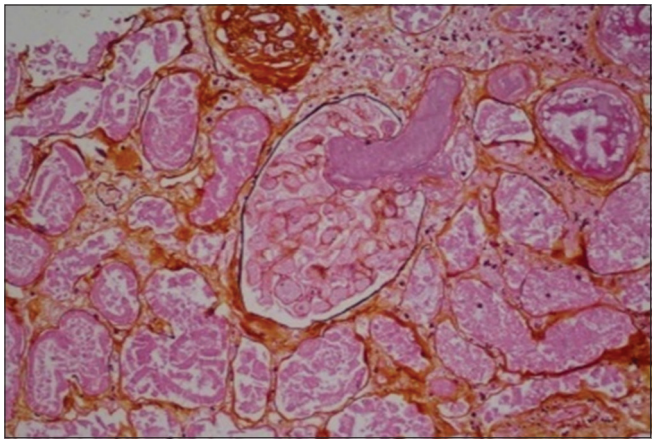

Figure 1: Renal biopsy showing glomeruli without cellular architecture (ghost glomeruli) and fibrin thrombi (arrow) in afferent arteriole (trichrome)

Discussion

Four important venomous snake families[4] include neurotoxic *Elapidae* (cobra and krait), hemotoxic *Viperidae* (russell's viper and saw-scaled viper), myotoxic hydrophiidae (sea snakes), and colubridae (bird snakes). Most of the Indian patients who developed AKI are victims of russell's viper and saw-scaled viper. The pathogenesis of AKI in snake envenomation includes hypotension, hemolysis, rhabdomyolysis, disseminated intravascular coagulation (DIC), direct cytotoxic effect of the venom, sepsis, hemodynamic alterations, and cell injury induced by the release of proinflammatory cytokines and vasoactive mediators.[3] Renal pathological changes include glomerular lesions such as mesangiolysis, proliferative glomerulonephritis, renal limited vasculitis, and tubulointerstitial lesions such as acute tubular necrosis (most common), cortical necrosis, and rarely acute interstitial nephritis and renal infarction.[5]

Cortical necrosis can be patchy or diffuse, and pathomechanism includes DIC, TMA secondary to venom mediated endothelial injury, and alternate complement pathway activation. In a cohort of seventy patients,[4] 94% developed oliguric renal failure. Hemodialysis was done in 53 (72%) patients. Renal biopsy done in 56 patients showed acute tubular necrosis as the most common pathology (73%), followed by diffuse cortical necrosis (18%) and patchy cortical necrosis (9%). Complete recovery was seen in 66%, persistent renal failure in 6%, and death in 28%. TMA in snake bite was rarely reported as given in Table 1.[6-13]

Traditionally coagulopathy in snake bite has been referred to as DIC. Recently, venom-induced consumption coagulopathy (VICC) has been described because it better explains the clinical features and the absence of other features of DIC. VICC is characterized by bleeding without obvious fibrin deposition, microvascular thrombotic obstruction, or nonrenal end organ failure and is due to the action of snake toxin in the coagulation pathway, not the tissue factor/factor VIIa pathway. VICC is characterized by prolonged clotting times due to activation of the coagulation cascade by thrombin-like enzymes, prothrombin, and factor X activators in the venom. TMA occurs in the subset of patients in snake bite envenomation with or without VICC. The proposed mechanism is venom or its vascular endothelial toxins may act as von Willebrand factor activators or vascular endothelial growth factor–type factors and initiate TMA by inducing endothelial damage. The role of ADAMTS-13, a von-Willebrand factor-cleaving protease in snake bite is unclear and requires further investigation.[14]

Table 1: Thrombotic microangiopathy in snakebite reported in literature

Author (year)	Number of patients	Age	Sex	Snake species	Clinical presentation	Renal biopsy	Treatment	Outcome
Date *et al*. - India (1986)[6]	16	NA	NA	Russell's viper	HUS	Fibrin thrombi in glomeruli in 5 patients	HD/PD	NA
Cobcroft *et al*.- Australia (1997)[7]	1	33	Male	Taipan	HUS	Fibrin thrombi of interlobular artery	HD/PE	Died
Isbister *et al*. - Australia (2007)[8]	6	NA	NA	Brown snake	HUS	Fibrin thrombi in glomeruli	HD/PE	All recovered
Casamento *et al*. - Australia (2011)[9]	2	55,46	Female-1, male-1	Tiger snake	HUS	Not done	HD/PE	Partial recovery
Karunatilake *et al*. - Sri Lanka (2012)[10]	1	35	Male	Hump-nosed viper	HUS	Not done	HD	NA
Herath *et al*. – Sri Lanka (2012)[11]	7		Female-4, male-3	Hump-nosed viper	HUS	Fibrin thrombi in glomeruli	HD	Complete recovery-3 chronic kidney disease 2, died-2
Mitrakrishnan *et al*. – Sri Lanka (2013)[12]	1	70	Male	Hump-nosed viper	HUS	Not done	HD/PE	Complete recovery
Withana *et al*. – Sri Lanka (2014)[13]	1	55	Female	Hump-nosed viper	TTP	Not done	HD/PE	Complete recovery

NA: Not available, HUS: Hemolytic-uremic syndrome, TTP: Thrombotic thrombocytopenic purpura, PE: Plasma exchange, HD: Hemodialysis, PD: Peritoneal dialysis

Most of the reports of TMA after snake envenomation were from Sri Lanka and Australia. In many of the reports, there were features of DIC/VICC later went on to develop TMA. Hence, it was not clear whether thrombocytopenia and microangiopathic hemolytic anemia (MAHA) occurred as a part of DIC. Date *et al*.[6] from India reported 16 cases of snake bite developing HUS and renal biopsy was available in five patients which showed fibrin thrombi in glomeruli. Casamento *et al*.[9] presented two cases of TMA caused by envenomation of common tiger snake (*Notechis scutatus*). Normal ADAMTS-13 (*a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13*) activity was found in one patient and so plasmapheresis was not tried.

The hump-nosed pit viper (*Hypnale* species) is distributed in South India and Sri Lanka.[5] Hump-nosed pit viper causing TMA was reported from Sri Lanka and there were no reports from India till date. Here, we describe two patients with snake bite-induced TMA. The first patient was a male patient bitten by Russell's viper. He received antivenom therapy and plasma exchanges for renal TMA. Despite all supportive measures, he progressed to ESRD which was probably due to late presentation and extensive cortical necrosis. Our second patient who was a female, developed TMA following hump-nosed pit viper. She received supportive therapy and lost follow-up. Unfortunately, we could not measure ADAMTS-13 levels in both the patients due to logistic reasons.

The clinical indication and efficacy of plasma exchange in snake bite envenomation are unclear. Though immune-complexes and toxins were removed during plasma exchange, studies showed no difference in timing of renal recovery, anemia, and platelet count between treated with or without plasmapheresis.[14] In patients refractory to conventional therapy with anti-snake venom, plasma exchange can be considered. In addition to removal of toxins, mediators of inflammatory and coagulopathic pathway invoked by snake toxins can be removed and may be lifesaving in severely ill patients. American society for Apheresis has placed the role of plasmapheresis in envenomation as Grade 2C, Category 3 (weak recommendation, optimum apheresis therapy not established, decision should be individualized) evidence.[15,16]

In conclusion, in patients with snake bite presenting with AKI, thrombocytopenia, MAHA and normal coagulation profile the possibility of TMA should be considered. Prompt diagnosis and early dialysis and plasmapheresis may improve the renal outcome.

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Conflicts of interest
There are no conflicts of interest.

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