Original Article

Thrombotic Microangiopathy: An Under-Recognised Cause of Snake-bite-related Acute Kidney Injury

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Abstract

Introduction: Thrombotic microangiopathy (TMA) as a cause of snake-bite-induced acute kidney injury (AKI) is rarely reported. Very little is known about the clinical course, optimal management, and prognosis of this entity. We describe a series of snake-bite-induced TMA and compare their outcomes with those without TMA. **Methods:** This was a single-center retrospective study of patients with AKI following snake envenomation admitted between January 2012 and December 2017. Demographic profile, clinical parameters, and outcomes were studied. TMA was diagnosed based on presence of triad of microangiopathic hemolytic anemia, thrombocytopenia, and AKI, and groups with and without TMA were compared. **Results:** Of 103 patients with AKI following snake bite, 19 (18.5%) had clinical evidence of TMA. All patients with TMA had advanced azotemia (mean peak serum creatinine 9.5 ± 3.0 mg/dL), with 18 (95%) requiring renal replacement therapy (RRT). Thirteen (68%) had either complete or partial recovery of renal functions, two (10%) progressed to end-stage renal disease, and one died (three patients were lost to follow-up). Age ≥50 years, presence of oliguria/anuria, anti-snake venom dose ≥10 vials, and urea ≥80 mg/dL at presentation were independently associated with TMA ($P < 0.05$). RRT requirement (95% vs. 57%), mean number of RRT sessions (18 vs. 4.5 sessions), and hospital stay ≥7 days (84% vs. 58%) were higher in patients with TMA ($P < 0.05$), but patient outcomes did not differ. **Conclusions:** In conclusion, TMA was seen in 18.5% of patients with snake-bite-related AKI in our study and was associated with almost universal need for RRT, longer duration on RRT, and hospital stay compared with patients without TMA.

Keywords: *Acute kidney injury, hemolytic uremic syndrome, snake envenomation, thrombotic microangiopathy*

Introduction

Acute kidney injury (AKI) is a common manifestation of snake envenomation and an important cause of mortality and morbidity. The reported incidence varies from 5% to 29% and may occur as early as an hour to as late as days following snake bite.[1] Acute tubular necrosis (ATN) is the most common cause of AKI in this scenario with 75% of cases attributable to ATN,[2] followed by acute interstitial nephritis (AIN) in 5%–15% cases.[3] Thrombotic microangiopathy (TMA) as a cause of AKI following snake envenomation is rarely reported. It has been reported in conjunction with venom-induced consumption coagulopathy (VICC), with the triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and renal failure persisting long after VICC resolves, or in isolation raising the possibility of an acquired hemolytic uremic syndrome (HUS)–like syndrome.[4-13] In this study, we describe a series of snake-bite-induced TMA and compare its outcomes with that of other causes of AKI following snake bite.

Materials and Methods

This was a case-record-based retrospective analysis conducted on patients admitted with snake-bite-related AKI at Kasturba Hospital, Manipal, India, a tertiary-care referral center, over a period of 6 years (January 2012–December 2017). The inclusion and exclusion criteria were as below.

Inclusion criteria

1. Age >18 years
2. Definitive history of snake bite and consistent clinical picture (presence of fang marks, cellulitis, coagulopathy, neuroparalysis)
3. Presence of AKI (as per KDIGO 2012 guidelines)

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Exclusion criteria

1. Preexisting kidney disease
   a. Serum creatinine ≥1.4 prior to snake bite
   b. Ultrasound evidence of chronic kidney disease (bilateral small kidneys, loss of corticomedullary differentiation).

Study definitions

For the purpose of this study, the below study definitions were used.

TMA: Presence of all three of the following criteria in the absence of alternate causes (e.g., sepsis):

1. MAHA [defined as schistocytes >1% in peripheral smear, elevated lactate dehydrogenase >500 with progressive fall of hemoglobin (Hb) by ≥1 g/dL]
2. Thrombocytopenia (platelet count <100,000/mm^3)
3. Presence of AKI (as defined by KDIGO 2012 guidelines).

VICC: Presence of prolonged whole blood clotting time >20 min and/or both prolonged international normalized ratio (INR) >1.4 and activated partial thromboplastin time (aPTT)

Clinical and laboratory parameters of all patients with snake-bite-related AKI were recorded and those with clinical evidence of TMA were identified. Outcome parameters such as duration of ICU and hospital stay, duration of renal replacement therapy (RRT), renal recovery, and patient survival were also noted.

Statistical analysis

Continuous data were expressed as mean ± standard deviation and nominal data as frequencies or proportions. Comparison of study groups was done using unpaired *t*-test for continuous variables, and χ^2 test and Fisher's exact test for nominal data. For non-normal data, Mann–Whitney *U* test was used. *P* value of <0.05 was considered statistically significant. Statistical analysis was carried out using SPSS version 18.

The study was approved by the institutional ethics committee.

Results

A total of 103 patients with snake-bite-related AKI were included. Baseline characteristics are tabulated in Table 1. Of these, 19 (18.5%) had clinical evidence of TMA. Only four (21%) had evidence of VICC at presentation, which resolved by 1–3 days (resolving prior to development of nadir Hb and platelet counts). Anemia and thrombocytopenia developed within a median of 3 days [interquartile range (IQR) 2–4 days] of snake bite and resolved over the next 7 days (IQR, 6–8 days). Severe thrombocytopenia (<50,000/mm^3) was seen in 84% and severe anemia (Hb <8 g/dL) in 89% of patients.

Advanced azotemia was noted in all patients (mean peak serum creatinine 9.5 ± 3.0 mg/dL), with 18 (95%) requiring RRT. Patients requiring RRT received intermittent hemodialysis with a mean number of RRT sessions of 18 ± 8.1. Thirteen (68%) had either complete or partial recovery of renal functions, two (10%) progressed to end-stage renal disease, and one died (three patients were lost to follow-up). Plasmapheresis was done in three patients. Two patients underwent three sessions of daily plasmapheresis, while the third underwent two sessions. There was no significant difference between renal outcomes of patients who received plasmapheresis and those who did not. Serum complement levels were available in five patients, of which three had low C3 levels. Tests for ADAMTS13 activity had not been done in any of the patients.

Kidney biopsy was done in two patients. Biopsy was done on day 18 for one patient, which showed evidence of patchy cortical necrosis with fibrin thrombi in glomerular capillary lumen and arterioles. The second patient underwent biopsy on day 31, which showed patchy cortical necrosis with fibrin thrombi in glomerular capillary lumen, along with evidence of AIN. This patient was treated with oral prednisolone at 1 mg/kg/day for 2 weeks, followed by steroid taper (total duration of treatment: 4 weeks). The first patient had complete recovery of kidney functions, whereas the second remained dialysis-dependent.

We then compared groups with and without TMA. It was found that age ≥50 years (P = 0.049), presence of oliguria/anuria (P < 0.001), anti-snake venom dose ≥10 vials (P = 0.015), and urea ≥80 mg/dL at presentation (P = 0.022) were independently associated with development of TMA. Presence of VICC at presentation was not associated with development of TMA (P = 0.391). RRT requirement (95% vs. 57%, P = 0.003), mean number of RRT sessions (18 vs. 4.5 sessions, P < 0.001), and hospital stay ≥7 days (84% vs. 58%, P = 0.041) were higher in patients with TMA (P < 0.05). Renal recovery, either complete or partial (68% vs. 71%, P = 0.752) was similar in both the groups and there was no significant difference in mortality rates (5% vs. 8%, P = 0.602) [Table 2].

Discussion

TMA is rarely reported as a cause of snake-bite-related AKI. In a study by Isbister *et al*. in 2007, 13% of cases with brown snake envenomation were found to have features of TMA, suggesting that TMA could have been overlooked in most of the previous studies.[6] This could be explained by the coexistence of VICC in most cases which makes the diagnosis of TMA challenging, with clinicians erroneously attributing MAHA, thrombocytopenia, and renal injury to disseminated intravascular coagulation (DIC).

VICC is the most common coagulopathy seen in snake envenomation and is often confused with DIC since

Table 1: Baseline characteristics of patients with snake-bite-related AKI

Baseline parameter	Without TMA (*n*=84)	With TMA (*n*=19)	*P*
Demographic characteristics			
Age, years (mean±SD)	48.1±13.35	52.7±11.14	0.167
Gender			0.962
Male, *n* (%)	57 (68%)	13 (68%)	
Female, *n* (%)	27 (32%)	6 (32%)	
Site of snake bite			0.979
Upper limb, *n* (%)	16 (19%)	4 (21%)	
Lower limb, *n* (%)	68 (81%)	15 (78.9%)	
Time to hospital admission, h [median (IQR)]	24 (24-72)	48 (48-72)	0.585
Clinical characteristics			
VICC at presentation, *n* (%)	26 (31%)	4 (21%)	0.391
Time to resolution of VICC, h [median (IQR)]	22 (13-30)	48 (25-72)	0.08
Time to TMA, days [median (IQR)]	NA	3 (2-4)	NA
Bleeding manifestations, *n* (%)	8 (9.1%)	3 (15.8%)	0.657
Hypotension, *n* (%)	11 (13.1%)	0 (0%)	0.091
Neuroparalysis, *n* (%)	2 (2.4%)	0 (0%)	0.497
Cellulitis, *n* (%)	52 (61.9%)	11 (57.9%)	0.604
Myocarditis, *n* (%)	3 (3.57%)	2 (10.5%)	0.203
ARDS, *n* (%)	11 (13.1%)	3 (15.8%)	0.757
Oliguria/anuria, *n* (%)	47 (55.9%)	18 (94.7%)	<0.001
Laboratory parameters			
Hb, g/dL (mean±SD)	11.9±3.2	10.1±2.5	0.029
Platelet count (mean±SD)	157±103	96±87	0.019
Serum creatinine, mg/dL (mean±SD)	5.3±4.2	6.1±3.5	0.447
INR (mean±SD)	2.4±2.4	2.8±2.7	0.731
aPTT, s (mean±SD)	34.8±10.1	33.6±8.8	0.642
LDH, U/L (mean±SD)	711±484	2381±1035	<0.001

AKI: Acute kidney injury, TMA: Thrombotic microangiopathy, SD: Standard deviation, IQR: Interquartile range, VICC: Venom-induced consumption coagulopathy, ARDS: Acute respiratory distress syndrome, Hb: Hemoglobin, INR: International normalized ratio, aPTT: Activated partial thromboplastin time, LDH: Lactate dehydrogenase

Table 2: Outcomes in patients with and without snake-bite-induced TMA

	Patients with TMA (*n*=19)	Patients without TMA (*n*=84)	*P*
Need for RRT (%)	18 (94.7%)	48 (57.1%)	0.003
No. of RRT sessions	18±8.1	4.5±3.1	<0.001
Hospital stay, days (mean±SD)	13.32±7.6	11.45±9.1	0.702
Hospital stay >7 days (%)	16 (84.2%)	49 (58.3%)	0.041
Renal recovery (%)	13 (68.4%)	60 (71.4%)	0.752
Mortality (%)	1 (5.3%)	7 (8.3%)	0.602

TMA: Thrombotic microangiopathy, RRT: Renal replacement therapy, SD: Standard deviation

elevated D-dimer, prolonged aPTT, abnormal INR, and hypofibrinogenemia are all features seen in both.[14] The following characteristics distinguish the two: (1) *time course* – VICC appears within hours of envenomation and resolves, often spontaneously, by 24–48 hours; (2) *pathogenesis* – in VICC, activation of coagulation pathway is mediated by the procoagulant effect of snake venom (e.g., Factor X in Russell's viper venom, thrombin-like enzymes in many vipers, and prothrombin activators in *Echis* spp.), rather than by tissue factor/factor VIIa pathway as seen in DIC; (3) *clinical presentation* – evidence of systemic microthrombi and end-organ failure are not seen in VICC, unlike DIC. This is because in DIC, depression of fibrinolysis leading to reduced fibrin removal is seen, whereas no such defect is seen in VICC. As a consequence of this, patients with VICC present with bleeding manifestations or may remain asymptomatic, unlike those with DIC who develop both bleeding manifestations and end-organ damage or organ failure due to systemic microthrombi.[14]

In a majority of reported cases so far, TMA occurs in conjunction with VICC, hence leading to the mistaken diagnosis of DIC.[4-11] However, given the finding that

Table 3: Available literature on snake-bite-related TMA

Author	Year	No. of cases	TMA spectrum	PLEX	Outcome
Date *et al*.[4]	1986	16	HUS	No	ND[a]
Herath *et al*.[5]	2012	7	HUS	No	Complete recovery - 2, ESRD - 2, died - 2
Isbister *et al*.[6]	2007	6*	HUS	Yes	Complete recovery
Casamento *et al*.[7]	2011	2	HUS	Yes	Partial recovery
Dineshkumar *et al*.[8]	2017	2	HUS	Patient 1 - yes Patient 2 - no	Patient 1 - ESRD Patient 2 - ND
Cobcroft *et al*.[9]	1997	1	HUS	Yes	Died
Karunatilake *et al*.[10]	2012	1	HUS	No	ND
Mitrakrishnan *et al*.[11]	2013	1	HUS	Yes	Complete recovery
Withana *et al*.[12]	2014	1	TTP	Yes	Complete recovery
Ying Mao Gn *et al*.[13]	2017	1	HUS	No	ESRD

Source: Original, *TMA accounted for 13% of cases of snake-bite-related AKI, TMA: Thrombotic microangiopathy, PLEX: Plasmapheresis, HUS: Hemolytic uremic syndrome, ND: No data, ESRD: End-stage renal disease, TTP: Thrombotic thrombocytopenic purpura

MAHA and thrombocytopenia continue to worsen despite normalization of coagulation parameters, it is now believed to be a distinct entity. A few reported cases of TMA occurring in the absence of VICC further support the possibility of an acquired-HUS-like syndrome.[12,13] The exact mechanism of TMA following envenomation is unclear, but it has been proposed that a toxin in the venom may initiate TMA by inducing endothelial damage.[2,6]

In this study, we found an incidence of TMA in 18.5% (19/103) cases. To the best of our knowledge, this is the largest reported series of snake-bite-related TMA to date [Table 3]. Only 21% (4/19) had coexistent VICC at presentation, which resolved by 1–3 days. Since ours is a tertiary referral center with most patients presenting after 48–72 hours following snake bite, it is possible that VICC had resolved by the time of arrival at our hospital. The clinical presentation appears to be consistent with an acquired-HUS-like syndrome, given the prominent renal involvement. All 19 patients had oliguria/anuria with advanced azotemia, and 95% (18/19) required hemodialysis.

A majority of patients (68%) had either complete or partial recovery of renal function. Two (10%) patients progressed to end-stage renal disease, of which one patient had evidence of renal cortical necrosis secondary to TMA on kidney biopsy, while the second did not consent for the procedure. Three patients were lost to follow-up and one died. On comparison of patients with and without TMA, although RRT requirement and mean number of RRT sessions were significantly higher in patients with TMA, renal and patient outcomes did not differ.

The role of plasmapheresis in snake envenomation is unclear. In our study, only three patients received plasmapheresis. Consistent with previous studies, we found no difference in outcomes between those who were treated with or without plasmapheresis, although the small sample size in this study makes it difficult to draw a definite conclusion.

Conclusion

TMA is a fairly common cause of snake-bite-related AKI, with an incidence of 18.5% in our study. It is possibly overlooked because of coexistent VICC, which often leads to a mistaken diagnosis of DIC. Although it is associated with almost universal need for RRT and longer duration of RRT requirement, outcomes appear to be comparable to those without TMA. Role of plasmapheresis is unknown.

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Conflicts of interest

There are no conflicts of interest.

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