Case Report

Atypical Hemolytic Uremic Syndrome in Snake Bite : An Often Missed Entity

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Snake envenomation is an important and common cause of Acute Kidney Injury(AKI) in India. AKI can occur following bites from snakes belonging to various families, due to multiple mechanisms. Hemolytic Uremic Syndrome (HUS) is an unusual cause of AKI following snake envenomation. We are reporting the case of a patient who developed HUS following envenomation by an unknown snake, presumed to be vasculotoxic. The patient presented with oligouria within 12 hours of the bite and having grossly deranged KFT, was promptly started on hemodialysis with improvement being noticed after 4 episodes of hemodialysis. The patient finally improved with hemodialysis and supportive treatment alone, obviating the need for plasma exchange, which is generally the standard treatment modality for HUS, making the case rare. HUS complicating snake bite has been reported earlier but recovery with hemodialysis is not common.

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Snakebites are a major occupational hazard in tropical countries like India, particularly in the rural areas. There are more than 5.4 million snake bites per year worldwide with 81,000-138,000 deaths all over the world[1], and an average of 58,000 deaths per year in India[2]. Snake envenomation is an important occupational injury, which affect a multitude of workers including farmers, fishermen, herders and plantation workers.The case in discussion is about a farmer who was bitten by an unknown snake while working on the field and developed rapidly progressing renal failure and was ultimately diagnosed to be a case of atypical HUS. It has been noted that there are spikes of snakebites during rainy seasons and during harvesting seasons and the incident in our case too happened during the mid monsoon.

There are roughly 236 species of snakes in India of which 13 are venomous[3]. There are four families of poisonous snakes: Elapidae, Viperidae, Hydrophidae and Colubridae. Most often the clinical effects of venom of vipers are vasculotoxic whereas that of Elapids are neurotoxic and hydrophids or sea snakes are mostly myotoxic. In India viper bites are most common and incidence of AKI following Russell's viper and E carinatus bites is 13-32%[4-6]. Although the snake in our case was not identified by the patient, in all likelihood, it was a viper, considering the gross nephrotoxicity and vasculotoxicity the venom was seen to induce.

Editor's Comment :

- Atypical hemolytic uremic syndrome often complicates snake bite which needs plasma exchange coupled with hemodialysis
- Awareness of this condition is important while managing a case of acute kidney injury in snake bite for therapeutic decision

The complications of snakebite can be local or systemic and our case displays predominantly a systemic manifestation with minor local changes. Local changes are part of an acute inflammation process causing local edema, pain, ecchymosis, blisters, bleeding, bruises, lymphangitis, lymph node enlargement, skin necrosis and may lead on to infection and cellulitis. Systemic complications include manifestations of hemotoxicity, neurotoxicity, rhabdomyolysis and Acute Kidney Injury (AKI)[4].

AKI, one of the most common and important manifestations of snake envenomation, particularly vasculotoxic envenomations, in turn, occurs by numerous mechanisms such as hemodynamic disturbances, direct tubular toxicity, hemoglobinuria, myoglobinuria, coagulopathy and thrombotic microangiopathy[4]. Our case was diagnosed to be a case of HUS, one of Thrombotic microangiopathy, which recovered with multiple episodes of Hemodialysis alone and there was no need of plasma exchange or any targeted therapy like Eculizumab. It is extremely uncommon for a case of Atypical HUS with such severe kidney injury to recover without any specific intervention, thereby necessitating a case report.

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Case Report

A 60-year-old male, farmer by profession, hailing from a rural area in West Bengal, was bitten by an unknown snake on the right leg. The patient presented to our Tertiary Care hospital, 4 days after the bite, with complaints of swelling of the right foot along with decreased urine output and generalised swelling of the whole body. According to the patient and his relatives, within 3 to 4 hours of the bite, the patient's right leg and foot became swollen. He was taken to a district hospital, where he was not given any Anti snake venom due to uncertainty of bite by poisonous snake. Over the 24 hours after the bite, the urine was dark brown and the urine volume was less than 100 ml in 24 hours with progressively increasing generalised body swelling. He remained anuric over the next few days and on the fourth day after the bite, he was referred to our tertiary care referral centre in view of renal dysfunction. He also complained of mild pain at the bite site. There was no history of fever, bleeding at bite site or any distant site, breathing difficulty, perioral tingling or blurring of vision. There was no history suggestive of neurological involvement. There was no history of intake of any nephrotoxic drugs.The patient was not known to be diabetic, hypertensive, smoker or to have any other comorbidities.

Table 1 — *Lab values at the time of presentation and at the time of discharge*

Parameters	At Presentation	At Discharge
Urea (mg/dL)	292	79
Creatinine (mg/dL)	10.8	2.9
USG KUB	RK: 10.5 cm X 5 cm, CMD maintained LK: 11.2 cm X 5.5 cm, CMD maintained	RK: 10.7 cm x 5.1 cm, CMD maintained, Cortical echo mildly raised. LK: 11.5 cm X 5.3 cm, CMD maintained, cortical echo mildly raised.
Urine R/E, M/E	Protein +, RBC 4-5, Pus cells 2-3/HPF.	Protein +, Pus cells: 1 -2/HPF, epithelial cells: 3-4/HPF, RBC: 1-2/HPF.
Hemoglobin (g/dL)	7.1	8.2
WBC (/mm3)	12800	5400
Platelet Count (/mm3)	90000	2,20,000
LDH (U/L)	814	290
Total Bilirubin (mg/dL)	2.0	0.6
Indirect Bilirubin (mg/dL)	1.6	-
SGPT / SGOT / ALP (U/L)	19/21/65	12/10/83

The patient presented on day 4 of bite. At presentation, patient was conscious, alert and oriented. His blood pressure was 134/ 84 mm Hg and the pulse rate was 92 beats/min, temperature 98.2 F, and respiratory rate was 18/min. Physical examination revealed moderate pallor, bilateral pitting pedal edema. Jaundice was absent. Examination of the cardiovascular, respiratory, gastrointestinal and central nervous system was unremarkable. The right leg and foot were swollen more than left side without any redness or other signs of local inflammation. There was no active bleeding from the fang mark site. There were no signs and symptoms suggestive of neurotoxic bite. There was no weakness in any of the extremities and no respiratory muscle weakness (single breath count was 35).

His investigation reports are given in Table 1. He was diagnosed to have acute kidney injury AKIN Stage-3 and was found to have evidence of Thrombotic Microangiopathy (TMA). His peripheral blood smear showed >3 schistocytes per high power field (Fig 1). He did not have clinical or laboratory features of sepsis. His urine routine examination had few pus cells and RBC in high power fields. Corrected Reticulocyte count 2.1 The coagulation tests such as Prothrombin Time (PT) & activated Partial Thromboplastin Time (aPTT) were normal. Serum haptoglobulin level was low and d-Dimer and FDP levels were normal. His serum vitamin B12, folate and iron studies were normal. Direct Coombs test was negative. The ultrasound and MRI of both the kidneys did not reveal any significant abnormality. In view of evident Microangiopathic Hemolysis with thrombocytopenia and normal coagulation profile associated with Acute Kidney Injury, a diagnosis of snake bite induced Atypical HUS was entertained[3]. Unfortunately, we could not measure ADAMTS-13 levels due to logistic reasons. A renal biopsy to confirm HUS and other causes of AKI could not be performed.

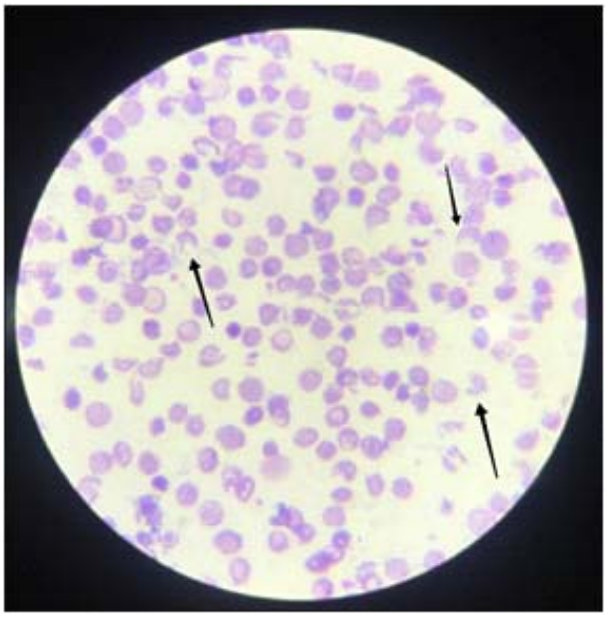

Fig 1 — Peripheral blood smear of the patient showings chistocytes (shown by arrows)

So in view of AKI, hemodialysis was started and considering HUS, he was planned for treatment with

therapeutic plasma exchange. While undergoing hemodialysis, he improved in terms of urine output, platelet count and renal function. He received 9 sessions of hemodialysis during his hospital stay. By 26 days after admission his renal function recovered with good urine output. He was discharged with a serum creatinine level of 2.9 mg/dl at the time of discharge and was expected to reduce further to near normal value. He was asked to follow up in nephrology OPD.

Discussion

Acute kidney injury following snake envenomation can occur due to multiple mechanisms. Hypotension and circulatory collapse occurs due to numerous mechanisms such as vasodilatation, increased capillary permeability, bleeding due to coagulation abnormalities and myocardial depression, ultimately culminating into ischemic AKI. Intravascular hemolysis due to phospholipase A2 and direct lytic factor (found only in elapid venom), present in snake venom can release myotoxins and cause hemoglobinuria and myoglobinuria leading to AKI. Direct action of toxin enzymes, especially phospholipases and metalloproteases can also cause renal injury. A number of proinflammatory cytokines and mediators such as Tumor Necrotic Factor (TNF), interleukins 1,6,10, interferon-Y and nitric oxide are released following exposure to toxin enzymes.

Venom Induced Consumptive Coagulation (VICC) is a very well known consequence of viper snake bites. It is caused by activation of coagulation pathway, mediated by the procoagulant effect of snake venom (eg, Factor X in Russell's viper venom,thrombin like enzymes in many vipers and prothrombin activators in Echisspp).VICC is characterized by rapid onset coagulopathy within hours after the snake bite with elevated D-dimer levels, prolonged prothrombin time and low fibrinogen levels which at times is associated with thrombocytopenia[7,8]. This resolves within 24 to 48 hours. It is not associated with systemic microthrombi and end organ failure. This is in contrast to Disseminated Intravascular Coagulation (DIC) which appears much later, its pathogenesis involves tissue factor/factor VIIa pathway with depression of fibrinolysis leading to reduced fibrin removal and is characterized by evidence of systemic microthrombi, bleeding from multiple sites and end organ failure.

Acquired/ Atypical HUS has been described as a complication of snake envenomation. HUS is characterized bypresence of thrombocytopenia, micro angiopathic hemolytic anemia and renal dysfunction with normal prothrombin time and activated partial thromboplastin time. HUS comes under constellation of Thrombotic Microangiopathy (TMA) which also includes Thrombotic Thrombocytopenic Purpura (TTP), which in addition of above features also has neurological involvement and fever. 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[9]. Snake 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[10]. Microangiopathic haemolytic anemia is suggested by drop in hemoglobin, high Lactate Dehydrogenase (LDH), reduced serum haptoglobin levels, indirect hyperbilirubinemia and presence of schistocytes in peripheral blood smear. TMA/ HUS is also seen in other conditions such as viral and bacterial infections, toxins, pregnancy, HELLP syndrome, bone marrow transplantation, drugs (mitomycin, cyclosporin A, ticlopidine) therapy and cancer. The diagnosis of HUS is mainly indirect as there are no definite tests to prove and renal biopsy is not always feasible.

Our patient had evidence of Thrombotic Micro-Angiopathy in the absence of disseminated intravascular coagulation (DIC)as PT & aPTT were within normal limits,serum haptoglobulin level was low and d- Dimer and FDP levels were normal without malignanthy pertension and without any use of drugs or other causes known to cause HUS. The secondary causes of HUS were ruled out in our case. Table 1shows trend in creatinine, hemoglobin, platelet count and other investigations and laboratory parameters of our patient at the time of admission and discharge. We could not do the renal biopsy and ADAMTS-13 levels due to logistic reasons. There was no hypotension, rhabdomyolysis or clinical and laboratory evidence of sepsis inour patient. So, the diagnosis of AKI secondary to snake envenomation induced Acquired/ Atypical HUS was made. We treated our patient with renal replacement therapy/ hemodialysis. Following treatment his renal function recovered with stable levels of creatinine of around 2.9 mg/dl and urine output also improved to normal daily amount.

TMA is rarely reported as a cause of snake bite related AKI. In a study by Isbister *et al*[11] 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. This could be explained by the coexistence of VICC in most cases which makes the diagnosis of TMA challenging, with clinicians erroneously attributing MAHA, thrombo-cytopenia, and renal injury to disseminated intravascular coagulation (DIC)[9]. So the presence of HUS in snake envenomation should besought as timely intervention earlyinterventions in the form of hemodialysis and therapeutic plasma exchange can aid in recoveryof renal function as well as increase the survival probability.

Our patient recovered with hemodialysis alone, without any plasma exchange therapy. Some published cases of snakebite-associated TMA with acute kidney injury (AKI) have reported successful treatment with plasmapheresis. Other published cases of snakebite-associated TMA with AKI report that the renal end organ damage resolves with renal replacement therapy alone[12].

However, the mechanism for which is not known and various in-vitro studies may point to its pathogenesis. The potential role of plasmapheresis in the treatment of snake bite associated TMA treatment is also unknown. Any association with respect to the pathophysiology or long- term outcomes of snakebite TMA with either a HUS or TTP is not established. When the existing gap in the knowledge of mechanism and pathophysiology of snakebite induced a HUS will be known, then we would have some clear idea of what the preferable option for snakebite associated a HUS would be.

Conclusion

Atypical HUS should always be kept in mind whenever a patient presents with the triad of haemolytic anemia, thrombocytopenia and AKI following a snake bite; while it may be rare, it is albeit a distinct entity and plasma exchange in addition to hemodialysis, is often life saving if the diagnosis is made early.The paucity of case reports, particularly from India, pertaining to this rare systemic manifestation of snake bite, that too one where the patient completely recovered without any use of AVS, should make this case an interesting and informative addition to existing literature.

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Conflicts of Interest : The authors declare that there are no conflicts of interest regarding the publication of this paper.

References

1 Snakebite envenoming :Global situationhttps://www.who.int/news-room/fact-sheets/detail/snakebite-envenoming#:~:text=About%205.4%20million%20snake%20bites,Africa%2C%20Asia%20and%20Latin%20America

2 Suraweera W, Warrell D, Whitaker R — Trends in snakebite deaths in India from 2000 to 2019 in a nationally representative mortality study. *Elife* 2020; **9:** e54076. Published 2020 Jul 7. doi:10.7554/eLife.54076

3 Philip AM — *Thrombocytopenia, Microangiopathy and End Organ Damage in Snakebites: A Descriptive study.* Masters thesis, Christian Medical College, 2019. Vellore.http://repository-tnmgrmu.ac.in/11197/1/200101119anil_mathew_philip.pdf

4 Hemolytic Uremic Syndrome — An unusual complication of snake envenomation, KSV GODAVARI, University Journal of Medicine and Medical Sciences http://14.139.191.179/index.php/medicine/article/viewFile/521/118

5 Chugh KS — Snake-bite-induced acute renal failure in India. Kidney Int. 1989 Mar;35(3):891-907. doi: 10.1038/ki.1989.70. PMID: 2651763.

6 Chugh KS, Pal Y, Chakravarty RN, Datta BN, Mehta R, Sakhuja V, *et al* — Acute renal failure following poisonous snakebite. *Am J Kidney Dis* 1984; **4(1):** 30-8. doi: 10.1016/s0272-6386(84)80023-2. PMID: 6741936.

7 Isbister GK — Snakebite doesn't cause disseminated intravascular coagulation: coagulopathy and thrombotic microangiopathy in snake envenoming. Semin Thromb Hemost 2010; **36(4):** 444-51. doi: 10.1055/s-0030-1254053. Epub 2010 Jul 7. PMID: 20614396.

8 Withana M, Rodrigo C, Gnanathasan A — Presumptive thrombotic thrombocytopenic purpura following a hump-nosed viper (*Hypnalehypnale*) bite: a case report. *J Venom Anim Toxins Incl Trop Dis* 2014; 26: https://doi.org/10.1186/1678-9199-20-26

9 Rao IR, Prabhu AR, Nagaraju SP, Rangaswamy D — Thrombotic Microangiopathy: An Under-Recognised Cause of Snake-bite-related Acute Kidney Injury. *Indian J Nephrol* 2019; **29(5):** 324-8. doi:10.4103/ijn.IJN_280_18

10 Dineshkumar T, Dhanapriya J, Sakthirajan R — Thrombotic microangiopathy due to *Viperidae* bite: Two case reports. *Indian J Nephrol* 2017; **27(2):** 161-4. doi:10.4103/0971-4065.196936

11 Isbister GK, Little M, Cull G, McCoubrie D, Lawton P, Szabo F, *et al* — Thrombotic microangiopathy from Australian brown snake (Pseudonaja) envenoming. *Intern Med J* 2007; **37(8):** 523-8. doi: 10.1111/j.1445-5994.2007.01407.x. PMID: 17640187.

12 Noutsos T, Currie BJ, Isbister GK — Snakebite associated thrombotic microangiopathy: a protocol for the systematic review of clinical features, outcomes, and role of interventions. *Syst Rev* 2019; **8:** 212. https://doi.org/10.1186/s13643-019-1133-2.