BRIEF REPORT

Acute Interstitial Nephritis Following Snake Envenomation: A Single-Center Experience

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Objectives.—To identify the clinical and histopathological characteristics of patients who develop acute interstitial nephritis (AIN) following snake envenomation.

Methods.—A retrospective analysis of patients diagnosed with snake envenomation-induced AIN from October 2013 to November 2014.

Results.—After snake envenomation, 88 patients developed acute kidney injury (AKI). Biopsies were performed on 7 patients due to nonrecovery of kidney function. Among these, 5 patients had AIN. Thus, AIN accounted for 5.7% of snakebite-related acute kidney injury. All patients had severe envenomation at presentation and had prolonged renal failure. Kidney biopsy found a mixed infiltrate composed of predominantly lymphocytes, with variable proportions of other cells including eosinophils neutrophils and plasma cells. The response rate to corticosteroids was 80%.

Conclusions.—AIN after snake bite is not uncommon. AIN needs to be considered in patients with persistent renal failure after snake envenomation. Identifying this complication is of utmost importance because of the potentially reversible nature.

Key words: Renal failure, viper bite, tubulo-interstitial inflammation

Introduction

Snakebite is an important occupational hazard in countries of Southeast Asia, especially India. The most medically significant snake species in India include Russell's viper (*Daboia russelii*) and saw-scaled viper (*Echis carinatus*). Acute kidney injury (AKI) is the leading cause of death in *D russelii* envenoming in India.¹ In addition to increased morbidity and mortality, it can lead to progressive kidney failure in the long term.² Acute tubular necrosis (ATN) and cortical necrosis account for the majority of renal lesions after viper bites.^{3,4} Information on acute interstitial nephritis (AIN) after envenomation is limited. So far only 1 case series and a few single case reports have been published, including 1 case report from our group.⁵ Due to paucity of data, the optimal management strategies and long-term outcomes of snake venom-induced AIN is not known. Here we report our experience and treatment outcomes of AIN after presumed *D russelii* envenomation.

Materials and Methods

We identified the total number of patients admitted with snake envenomation-related AKI between October 2013

and November 2014 from hospital records. AKI was diagnosed according to Kidney Disease Improving Global Outcomes 2012 criteria. The details of the patients who underwent kidney biopsy were collected from the renal biopsy registers maintained in the Departments of Nephrology and Pathology at our institution. A total of 88 patients were admitted during the period. As per hospital policy, kidney biopsies are performed if the serum creatinine remains greater than 2 mg/dL 4 weeks post-envenomation. Seven patients with snake envenomation and AKI underwent kidney biopsy during this period. Five patients were reported to have acute interstitial nephritis. The discharge summaries and case records during the hospital stay were retrieved and a chart review was performed using a predefined data collection proforma. Two pathologists who were blind to clinical data reviewed the biopsy slides. Follow-up information was collected from outpatient records.

Results

During this period, 88 patients were admitted with AKI after snake envenomation. Among the 7 patients who underwent kidney biopsy, 5 patients (4 males and 1 female) were reported to have AIN. AIN accounted for 5.7% of snake envenomation-related AKI.

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All patients sustained bites in lower limbs. Species identification was not possible in 2 patients, and the rest were presumed to be due to *D russelii* (as reported by the patients). Fang marks were visible in all patients. Three patients sustained bites during farming-related activities. All patients developed severe local reaction with systemic envenomation and had evidence of disseminated intravascular coagulation at presentation. After admission, all patients were started on prophylactic broad spectrum antibiotics after taking blood and local site cultures. Polyvalent snake antivenom (*Naja naja* [cobra], *E carinatus* [saw-scaled viper], *Bungarus caeruleus* [common Krait], *Daboia russelii* [Russell's viper]) was administered to 4 patients within 6 hours of

envenomation. One patient received antivenom from the referring hospital; further doses were not given as the whole blood clotting time had already normalized at the time of admission. Patients 1, 3, and 4 had minor infusion reactions (chills and rigor), which were treated by slowing the antivenom infusion, intravenous hydrocortisone, and antihistamines. The reactions were not severe enough to warrant discontinuation of further antivenom doses. Oliguric renal failure was documented within 24 to 72 hours after the bite; all patients were supported with haemodialysis. Urine sediment was unremarkable at the time of admission. The time frame for recovery of disseminated intravascular coagulation varied from 5 to 16 days. Antibiotics were stopped by

Table 1. Clinical and biochemical characteristics of patients with snakebite-induced AIN

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (y)	40	22	29	50	32
Sex	Male	Male	Male	Female	Male
Occupation	Farmer	Student	Farmer	Housewife	Farmer
Snake species	<i>D russelii</i>	<i>D russelii</i>	Unidentified	<i>D russelii</i>	Unidentified
Creatinine (mg/dL) at presentation	4.0	6.8	12.0	3.2	2.0
Nadir platelet count	50,000	15,000	18,000	58,000	27,000
PT INR	2.5	3.0	2.5	2.0	1.7
Resolution of DIC	5 days	16 days	7 days	10 days	10 days
Total dose of SAV received*	21 vials	35 vials	Treated elsewhere, details not available	10 vials	50 vials
Antibiotics received	Vancomycin ceftriaxone	Piperacillin-Tazobactam	Vancomycin, piperacillin-tazobactam, meropenam	Ceftriaxone cloxacillin	Piperacillin-Tazobactam
Other drugs received†	Metoclopramide frusemide	Famotidine metoclopramide	Pantoprazole metoclopramide lorazepam	Famotidine amlodipine ondansetron	Pantoprazole metoclopramide
Bite to biopsy time (days)	33	30	46	32	30
Renal function at the time of biopsy	On dialysis	On dialysis	On dialysis	3.4 mg/dL	On dialysis
Response to steroids	Yes	Yes	No	Yes	Partial
Duration of follow-up	> 1 year	> 1 year	Lost after 3 months	9 months	5 months
Creatinine on last follow-up (mg/dL)	1.2	0.9	10	1.3	1.6

AIN, acute interstitial nephritis; PT-INR, prothrombin time and international normalized ratio; DIC, disseminated intravascular coagulation; SAV, snake antivenom.

* All 4 patients received 70 to 100 mL (7–10 vials) of polyvalent ASV diluted in 100 mL saline over 6 hours followed by 30–50 mL every 6 hours until whole blood clotting time <20 minutes.

† Prescribed according to patient requirements as per the discretion of treating physician.

Table 2. Histological characteristics of patients with snakebite-induced AIN

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Cell types in interstitial infiltrates	Lymphocytes, occasional eosinophils	Lymphocytes, eosinophils (30%), neutrophils (10%)	Lymphocytes, neutrophils (40%) + neutrophil cast	Lymphocytes, eosinophils, plasma cells (20%)	Lymphocytes
Tubular atrophy (%)	30%	10%	0%	0%	15%
Interstitial fibrosis (%)	20%	0%	0%	0%	0%
Tubular necrosis	0%	10 %	10 %	10%	15%
Glomerular morphology	Normal weak 1+ C1q deposits on IF	Normal	Normal	Diffuse mesangial proliferation; No immune deposits	Normal

AIN, acute interstitial nephritis; IF, immunofluorescence microscopy.

the end of first week in patients 1, 2, and 5 because the cultures were negative and cellulitis resolved. Antibiotics were continued for 1 more week in patients 3 and 4. Patient 3 had catheter-related blood stream infection with *Klebsiella*, and patient 5 had cellulitis with *Staphylococci*. Four patients remained oliguric and dialysis-dependent even 4 weeks post-envenomation. One patient became nonoliguric in the third week, but serum creatinine remained abnormal. Renal biopsy was performed in view of persistent renal failure (Tables 1 and 2; Figure).

All patients received 1 mg/kilogram body weight prednisolone for 4 weeks, followed by a taper over the next 4 weeks. Patients 1, 2, and 4 started to have diuresis within 48 hours of receiving steroids. Serum creatinine found a progressively declining trend and dropped to less than 2 mg/dL by the end of 2 weeks. Patient 5 experienced a delayed response. Clinical response was noticed after 2 weeks of corticosteroid therapy; the fall in serum creatinine was more gradual and reached 1.6 mg/dL at the end of the second month. One patient did not respond to treatment and remained dialysis dependent at the end of 3 months. All patients except patient 3 are under regular follow-up, and the serum creatinine levels are remaining stable.

Discussion

Renal failure is a common complication of some severe envenomation inflicted by *D russelii*, the species that presumably inflicted these bites. The reported prevalence of AKI after envenomation in India varies from 13% to 32%.³ The clinical manifestations of hemotoxic snakebites are similar, characterized by local reaction, bleeding tendencies, haemolysis, disseminated intravascular coagulation, and renal failure. Oliguria develops in a few hours but can be delayed up to 96

hours. The classic renal lesions described in hemotoxic snakebite are acute tubular necrosis and cortical necrosis. Three-fourths of patients with snakebite-induced AKI are reported to have ATN, with diffuse or patchy cortical necrosis in the rest.^{3,4} Milder degrees of interstitial inflammation, edema, and hemorrhage have been reported in conjunction with ATN.

There is only limited information on AIN after *D russelii* envenomation. Varying degrees of interstitial edema and infiltration by mononuclear cells are described in patients who develop ATN after envenomation,^{3,6-8} but diffuse interstitial inflammation out of proportion to tubular damage is uncommon. AIN after snake envenomation was first reported by Sant and Purandare⁹ in postmortem biopsy samples. This was followed by single case reports by Sitprija et al,¹⁰ Indraprasit et al,¹¹ and Gundappa et al.¹² Golay et al¹³ reported the clinicohistological characteristics and outcomes of 5 patients with snake envenomation and AIN. We had reported 1 case of AIN following presumed *D russelii* envenomation.⁵ Golay et al¹³ also reported tubular injury in 4 of 5 patients in addition to diffuse interstitial infiltrates.

The clinical presentation of our series is similar to that reported previously. All patients had severe envenomation and prolonged renal failure that could not be accounted by ATN. There is significant heterogeneity in the nature of interstitial infiltrates described in snakebite-related AIN. Lymphocytic infiltrates were described in the initial case reports. Golay et al¹³ described a mixed infiltrate comprising of lymphocytes, eosinophils, and neutrophils. In the current series, histopathology found a lymphocyte-predominant infiltrate in all patients. In addition, 4 patients had admixture of other cell types including eosinophils, neutrophils, and plasma cells. In addition to diffuse interstitial inflammation, patients 2 through 5 showed minimal

Figure. A, Marked interstitial inflammatory cell infiltrate composed of mainly lymphocytes (hematoxylin and eosin $\times 400$). B, Interstitial inflammatory cells and neutrophilic casts in tubules (black arrows) (hematoxylin and eosin $\times 400$). C, Severe tubular epithelial damage and interstitial inflammatory cells composed of lymphocytes and few eosinophils (hematoxylin and eosin $\times 40$).

ATN, which might represent secondary tubular damage due to infiltrating cells.

We came across neutrophil cast in 1 patient, a finding that has not been described previously in snakebite-related AIN. The patient had no evidence of pyelonephritis. All except 2 patients had normal glomerular morphology. One patient had diffuse mesangial proliferation without any immune complex deposition. One patient had normal glomeruli by light microscopy, with weak C1q deposits on immunofluorescence microscopy.

The intermediate and long-term outcomes of snakebite-related AIN is poorly defined due to the paucity of literature. Golay et al¹³ reported a response rate of 20%, with remaining patients progressing to various stages of chronic kidney disease/end-stage renal disease. In contrast, we observed a favorable response to corticosteroids. The response rate to corticosteroids observed in our series was 80%, but the sample size is only 5, which limits generalization. It is noteworthy that a favorable response to steroids could be elicited even after a lapse of 4 to 6 weeks from the inciting event.

The mechanism of AIN in snakebite is not clear; it is believed to be secondary to the immunogenic effects of snake venom.⁴ Another proposed mechanism is the tubular injury leading to neoantigen release resulting in interstitial inflammation.⁷ There may be a possible contributory role for drugs as well, as all the patients received antibiotics and proton pump inhibitors/H⁺ receptor blockers.

AIN after hemotoxic snakebites seems to be more common than it was previously believed. It is possible that there is underreporting of this entity due to the heterogeneity in renal biopsy practices among physicians managing patients with snakebites. It seems prudent to perform kidney biopsy in patients with AKI after snake envenomation when there is a delayed or incomplete recovery after AKI. Identifying AIN is imperative due to its potentially reversible nature.

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