Wasp sting-induced acute kidney injury

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Abstract

Background: Wasp stings are a common form of envenomation in tropical countries, especially in farmers. The aim of this study was to document the clinical presentation, treatment and outcomes of patients with acute kidney injury (AKI) due to multiple wasp stings in a tertiary care hospital.

Methods: We conducted a retrospective observational study of patients with multiple wasp stings and AKI at the Department of Nephrology between July 2011 and August 2015. The clinical features, laboratory data, treatment details and outcomes were noted.

Results: A total of 11 patients were included. All were from rural areas. All of them were males with age ranging from 21 to 70 years, mean age 45 ± 23 years. Six had oliguria and two had hypotension. All 11 patients had evidence of rhabdomyolysis and three also had hemolysis. Ten patients required hemodialysis with a mean number of hemodialysis sessions of 8.7 ± 2.8. Renal biopsy carried out on four patients, showed acute interstitial nephritis (AIN) in one patient, acute tubular necrosis (ATN) in two patients, and one patient had both AIN and ATN. The two patients with AIN were given steroids, while all other patients were managed with supportive measures. One patient died within 48 h of presentation due to shock. At a mean follow-up of 24 months, one had progressed to chronic kidney disease and the remaining nine had normal renal function.

Conclusions: Wasp sting is an occupational hazard. AKI was most commonly due to rhabdomyolysis. Early renal biopsy is indicated in those patients who do not respond to supportive measures. Timely dialysis and steroid in the case of AIN improves renal survival.

Key words: acute kidney injury, hemodialysis, rhabdomyolysis, steroids, wasp stings

Introduction

Animal toxin envenomation is an important health problem in tropical countries. As a highly vascularized organ, the kidney is more vulnerable to toxins [1]. Vespid wasps (wasps and bees) stings cause mortality by anaphylaxis and multiorgan involvement ranging from acute kidney injury (AKI), hepatic/cardiac dysfunction to coagulopathy [2]. AKI is due to acute tubular necrosis (ATN) as a result of intravascular hemolysis, rhabdomyolysis or shock [3]. Rarely it can be due to acute interstitial nephritis (AIN), which responds to steroids. Here we present a case series of 11 patients with multiple wasp stings and AKI.
**Materials and methods**

A retrospective study was performed of patients admitted to our department between July 2011 and August 2015 who presented with multiple wasp stings and AKI. The diagnosis of wasp stings was based on clinical history and findings on physical examination. Demographic details including age, sex, clinical history and clinical findings were collected. Laboratory investigation details including complete hemogram, renal function tests, liver function test, creatine phosphokinase (CPK), serum lactate dehydrogenase (LDH) and coagulation profile tests were noted.

All the patients received supportive care, and forced alkaline diuresis was given when patients presented early without volume overload or oliguria. Indications for hemodialysis were oliguria (urine output <400 mL/day), hyperkalemia (>5.5 mEq/L), metabolic acidosis and acute pulmonary edema. Mean duration of dialysis dependency and mean number of dialysis sessions were noted. Renal biopsy was done in patients who had persistent oliguria for >7 days and renal failure for >14 days despite supportive treatment after obtaining written consent. Complete recovery of kidney function was defined as a decrease in the serum creatinine level to within a normal range. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate <60 mL/min/1.73 m² at 3 months after the onset of AKI. For statistical analysis, data are expressed as mean (± standard deviation), percentage and range wherever appropriate.

**Results**

A total of 11 patients were included. All patients were males and farmers by occupation. All had multiple sting marks varying in number from 12 to 72. The time lag between sting and hospitalization ranged from 2 to 11 days. The clinical profiles, laboratory data, treatment and outcomes are described in Table 1. Oliguria was noted in six patients, hypertension in two and hypotension in two. All patients had evidence of rhabdomyolysis with elevated serum CPK (>390 IU/L) and urine myoglobin was detected in two patients. Three showed evidence of hemolysis with elevated LDH (>400 IU/L), anemia and elevated bilirubin. One patient had elevated transaminases. Mild thrombocytopenia was seen in two patient and altered coagulation parameters in one. Microhematuria was seen in four and proteinuria in two, with a mean urine protein creatinine ratio of 1.2 ± 0.5. Hyperkalemia was seen in three. No cardiac or neurological manifestations were seen in any patient.

Ten patients required hemodialysis support and two patients received alkaline diuresis. Time taken for normalization of serum CPK and LDH ranged from 5 to 11 days. Renal biopsy carried out in four patients showed AIN (Figure 1) in one patient, ATN with pigment cast (Figure 2) in two, of which one patient had positivity for histochemical stain for myoglobin, and one patient had both AIN and ATN. The two patients who showed AIN in the biopsy were treated with oral steroids 1 mg/kg, tapered off over the following 4 weeks. One patient died within 48 h of presentation due to shock. At a mean follow-up of 24 ± 8 months, nine patients had

| Variables                          | Pt1   | Pt2   | Pt3   | Pt4   | Pt5   | Pt6   | Pt7   | Pt8   | Pt9   | Pt10  | Pt11  |
|-----------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Age (years)                       | 21    | 70    | 40    | 38    | 85    | 35    | 51    | 45    | 35    | 42    | 33    |
| No. of stings                     | 24    | 30    | 72    | 42    | 48    | 22    | 27    | 12    | 33    | 14    | 30    |
| Blood urea (mg/dL)                | 172   | 98    | 120   | 86    | 107   | 106   | 100   | 65    | 102   | 99    | 55    |
| Serum creatinine (mg/dL)          | 14    | 7.5   | 8.5   | 9.1   | 7.1   | 6.5   | 5.2   | 4.5   | 7.5   | 7.0   | 4.0   |
| Serum potassium (mEq/L)           | 3.7   | 3.2   | 5.8   | 4.0   | 5.6   | 34.5  | 4.2   | 4.1   | 6.2   | 4.8   | 3.8   |
| Serum CPK (IU/L)                  | 549   | 412   | 3328  | 650   | 983   | 1040  | 1120  | 620   | 1500  | 890   | 560   |
| Serum LDH (IU/L)                  | 123   | 128   | 728   | 108   | 340   | 480   | 367   | 300   | 750   | 306   | 379   |
| Total no. of hemodialysis sessions| 5     | 5     | 11    | 7     | 8     | 11    | 12    | Not done | 12    | 12    | 2     |
| Duration of HD (days)             | 10    | 8     | 20    | 12    | 10    | 17    | 18    | –     | 14    | 18    | 2     |
| Improvement of oliguria (days)    | 4     | 8     | 12    | 7     | 5     | 8     | 9     | 2     | 13    | 8     | Died  |
| Creatinine at discharge (mg/dL)   | 0.9   | 1     | 0.9   | 0.8   | 0.9   | 1.1   | 1.1   | 0.9   | 1.9   | 1.2   | –     |
| Creatinine at mean follow-up (mg/dL)| 0.9  | 1.1   | 1     | 0.9   | 1     | 1.2   | 1.2   | 0.9   | 3.5   | 1     | –     |

Fig. 1. Renal biopsy showing interstitial infiltrates rich in eosinophils (H&E stain).

Fig. 2. Renal biopsy showing acute tubular injury with pigment casts (H&E stain).
complete recovery, and one patient had progressed to CKD with serum creatinine of 3.5 mg/dL.

Discussion

The important families of the order Hymenoptera [4] are Apoidea (bees), Vespoidea (wasps, hornets and yellow jackets) and Formicidae (ants). Toxins in wasp venom include enzymes such as phospholipase A2 and hyaluronidase, peptides such as melittin and chemotactic peptides, amines such as histamine, serotonin and catecholamines, and others such as mastoparan, kinins, apamine, acetylcholine, antigen S and neurotoxic cynines. Phospholipase A2 initiates inflammation, hyaluronidase causes spread of venom, melittin has hemolytic, vasoactive, cellular antimembrane properties, histamine increases vascular permeability and apamine is a neurotoxin [5].

Local reactions after wasp sting include pain and swelling, while systemic allergic reactions may be mild, moderate (anigeo- dema/asthma) or severe (laryngeal edema/shock) [6]. Systemic complications include the renal, cardiac (myocarditis/myocardial infarction), hepatic (centrilobular necrosis), neurological (acute encephalopathy/stroke) and hematological (hemolysis/disseminated intravascular coagulation/thrombocytopenia). Mostly, anaphylaxis results from single or a few wasp stings, whereas multiple wasp stings result in systemic complication [7].

The average number of sting marks, which were seen predominantly on the face, trunk and upper extremities, in our study was 36 as compared with 96.4 ± 70.1 (range 35–300) in one study [8]. Xie et al. [9] showed that elevation of all laboratory parameters was higher in patients with >10 stings than in patients with ≤10 stings. The in-hospital mortality was five times higher in the >10 stings group than that in the ≤10 stings group. Renal failure or death may occur in the range of 20–200 wasp stings. The mean length of time between wasp sting and hospitalization was 10.7 h in one study [8], whereas it ranges from 2 to 11 days in our study.

The main clinical features at presentation included oliguria (55%), microhematuria (36%), hypertension (18%) and hypotension (18%), while oliguria, red urine and jaundice were the main symptoms in a study of 18 patients with wasp stings [8]. None of the patients had eosinophilia or eosinophiluria. One patient had history suggestive of anaphylaxis. There was evidence of rhabdomyolysis in all and hemolysis in three patients. Altered liver function tests were seen in 36%, mild thrombocytopenia in 18% and altered coagulation parameters in 18%. Coagulopathy in wasp sting has been related to increased levels of antithrombin and decreased levels of fibrinogen, high molecular weight kininogen, factors V and VIII [10]. Vikrant et al. [11] reported three cases of acute renal failure following wasp sting but only two had evidence of intravascular hemolysis.

Ten patients required hemodialysis support with a mean number of 8.7 ± 2.8 sessions over a time period of 16.2 ± 6.3 days. Improvement of oliguria occurred over a mean duration of 8.2 ± 1.7 days. Sigdel et al. [8] studied 18 patients in which all developed AKI requiring dialysis with the mean number of hemodialysis sessions being 7.4 ± 5.3 (range 1–20). Mean time to resolution of oliguria was 15.9 ± 9.5 days (range 2–35). Mean length of hospital stay was 18.7 ± 13.4 days (range 1–46), with those having a higher number of stings having a longer stay. Xie et al. [9] showed presence of AKI in 21.0% of patients. Rhabdomyolysis was seen in 24.1% of patients, hemolysis in 19.2%, liver injury in 30.1% and coagulopathy in 22.5%. Regression analysis revealed that high creatinine level, shock, oliguria and anemia were risk factors for death. One patient in our study died due to shock.

The mechanisms of AKI include pigment-induced ATN, AIN, and, rarely, acute cortical necrosis [12] and thrombotic microangio- pathy. Mellitin and phospholipase in wasp venom cause rhabdomyolysis and hemolysis. Myoglobin is freely filtered in glomeruli; when it is present in high concentration, along with dehydration and acidic urine, it is first transformed to ferrihematin precipitates in the proximal tubule to form obstructive pigment casts [13]. It is also a potent inhibitor of nitric oxide and triggers intrarenal vasoconstriction and ischemia. A summary of venomous animals, their toxins and the mechanism of AKI is given in Table 2.

Initial management of rhabdomyolysis consists of rapid expansion of intravascular volume by using normal saline to maintain urine output at more than 200–300 mL/h followed by alkalization of urine, which may prevent development of AKI [14, 15]. Alkaline diuresis was done in two patients; one did not require hemodialysis. The treatment of AKI with hemodialysis, hemofiltration or peritoneal dialysis has been described [16]. Exchange transfusion or plasmapheresis should be reserved for the treatment of life-threatening multisystem organ failure.

Table 2. Animal toxins and mechanisms of AKI

| Animal            | Principal toxin                   | Incidence of AKI | Mechanism of envenomation | Characteristics of renal damage                  |
|-------------------|-----------------------------------|------------------|---------------------------|--------------------------------------------------|
| Snakes            | Zinc metalloproteases, phospholipase A2, serine protease, hyaluronidase | 5–50%            | Neurotoxic, myotoxic, hemotoxic, nephrotic          | ATN, AIN, myoglobinuria, renal cortical necrosis, thrombotic microangiopathy |
| Scorpion          | Histamine, serotonin, phospholipase A2 | 2–10%            | Hemotoxic, cardiotoxic, myotoxic                       | ATN, AIN |
| Spiders           | Phospholipase D, collagenase, astacin like metalloproteinase | 4–10%            | Proteolytic, demeronecrotic, hemolytic, nephrotic     | ATN, myoglobinuria |
| Bees              | Melittin, phospholipase A2, acid phosphatase | 10–30%           | Hemotoxic, cardiotoxic, nephrotic                      | AIN, ATN, myoglobinuria, hemoglobinuria |
| Wasps             | Phospholipase A1, hyaluronidase    | 20–50%           | Hemotoxic, proteolytic, fibrogenolytic                 | ATN, myoglobinuria, hemoglobinuria |
| Caterpillars      | Lipocalin, cysteine protease       | 2–18%            | Direct nephrotxicity, Myotoxic, hemotoxic             | ATN, ATN |
| Raw bile carp     | Cyprinol                           | 50–60%           | Direct nephrotxicity                                   | ATN |
| Jellyfish         | Catecholamines, serotonin, kinins  | 1–5%             | Direct nephrotxicity                                   | ATN |
| Beetles consumption | Cantharidine                      | 2–10%            | Direct nephrotxicity                                   | ATN | 
Ain was seen in one patient, ATN with pigment cast in two, and one had both Ain and ATN. The two patients with Ain, who were treated with steroids, responded well to treatment. Three of the five patients with hornet sting and AKI reported by Sakhju et al. [17] had histopathological evidence of pigment-induced ATN. Thiruventhiran et al. [18] analyzed 24 cases of AKI due to hymenopteran bites. Hemolysis (14 cases), rhabdomyolysis (11), hypotension (6) and altered liver function tests (9) were seen. Hemodialysis was done in 17 patients and 6 patients died. Renal biopsy was done in nine patients and all showed ATN. The first case of Ain due to wasp sting was reported by Zhang et al. [19]. It was postulated that polypeptides in venom can mediate immune complex-mediated glomerulonephritis, interstitial nephritis, renal microangiitis or vasculitis. Chao et al. [20] and Sharma et al. [21] each reported a case with combined Ain and ATN after wasp stings. These patients showed good response to steroids, which help in reducing interstitial fibrosis and early renal recovery. The long-term renal morbidity of wasp stings is not known precisely, so early recognition and treatment is essential to prevent renal damage. Early renal biopsy is justified in selected cases to diagnose Ain and to initiate steroid therapy [22].

At a mean follow-up of 24 ± 8 months, one patient had progressed to CKD and the other nine maintained normal renal function. In a study of 75 patients from China, 9.5% of patients died, and 10.7% developed CKD. The average time of renal replacement therapy was 18.2 days, and the average kidney function recovery time was 36 days. Subgroup analysis showed no difference in the mortality rates between continuous venovenous hemofiltration (CVVH), intermittent hemodialysis (IHD) and CVVH plus plasma exchange (PE). The kidney function recovery time was significantly shorter in CVVH and CVVH + PE groups than in the IHD group. PE is advantageous in clearing the venom components, secondary toxic agents and inflammation mediators [23].

In conclusion, AKI in wasp stings is commonly due to pigment nephropathy as a result of rhabdomyolysis and hemolysis. Early recognition of this syndrome is crucial to the successful management of these patients. Early biopsy is indicated in patients who do not respond to supportive measures. Steroid treatment is found to be beneficial in patients with Ain.

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Conflict of interest statement

None declared.

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