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Case Report

A rare concurrence: bee venom associated acute tubular necrosis and acute interstitial nephritis

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Abstract

Acute kidney injury (AKI) is generally associated with increased morbidity and mortality and is even more devastating in patients with comorbidities. Although AKI due to multiple bee stings is well established in the literature, it is still a rare entity with complex pathophysiologic mechanisms. The most commonly reported histological findings in AKI due to bee stings is acute tubular necrosis (ATN), with a few studies attributing it to acute interstitial nephritis (AIN), whereas the concurrence of both ATN and AIN is rarely reported. We hereby present a 50-year-old known Type 2 diabetes mellitus patient with a prior normal renal function, who developed AKI following multiple stings from >1000 bees. He had a kidney biopsy on account of non-recovery of his kidney function despite being on intermittent hemodialysis that showed combined features of ATN and AIN. He subsequently had a full recovery of his renal function following appropriate management.

INTRODUCTION

In line with the international society of Nephrology initiative '0 by 25' with the goal that no one should die of untreated AKI by the year 2025 [1], it is necessary to identify and highlight the importance of some of the under-reported causes of acute kidney injury (AKI). Although AKI due to multiple bee stings is well established in the literature, it is still a rare entity with complex pathophysiologic mechanisms. Mass envenomation from bee stings trigger a cascade of immunological reactions leading to hypotension, intravascular hemolysis and rhabdomyolysis, in addition to its direct cytotoxic effects on the renal tubules [2]. Though other organs may be affected, kidney being a highly vascularized and excretory organ is more susceptible to the detrimental effect of the toxin following bee stings [3].

CASE REPORT

A 50-year-old known Type 2 diabetes mellitus patient with a prior normal renal function (baseline serum creatinine of 79 μmol/l), presented to our emergency unit a few hours (4 h) following multiple stings from >1000 bees. He was drowsy, restless and had facial swelling with multiple erythematous lesions on the face and trunk. His baseline vitals signs were: blood pressure of 140/90 mmHg, tachycardic with a pulse rate of 104 beats/min, respiratory rate of 20 breaths per minute with an oxygen saturation of 92%. Twenty-four hours post admission, he was noticed to be anuric despite receiving 3 l of intravenous normal saline with elevated urea (21.9 mmol/l) and creatinine (602 μmol/l). Five days post admission, he developed generalized body swelling and angioneurotic edema with a drop in his oxygen saturation ranging between 80 and 88%.

Investigations

Baseline biochemical parameters revealed elevated urea (21.9 mmol/l) and creatinine (602 μmol/l), which were indicative of acute kidney injury. Subsequent serial levels of urea, creatinine and other laboratory results were as shown in Table 1.

Had a kidney biopsy on account of non-recovery of his kidney function despite on intermittent hemodialysis 2 weeks post admission. The biopsy Sections showed 16 glomeruli. The tubules demonstrated varying degrees of epithelial necrosis, regeneration and extensive tubular granular casts affecting predominantly proximal and fewer distal tubules. The interstitium was edematous and revealed foci of intense mixed lymphoplasmacytic, and fewer neutrophilic and eosinophilic infiltrates. Immunoglobulin (Ig) G, IgA, IgM and Complement component 3 were negative. See Figs 1–4.

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Table 1. Serial laboratory results

Parameters	0 h	48 h	Day 3	Day 5	Day 10	Day 11	Day 12	Day 15	Day 22	Day 23	Day 24	Day 25	Day 29	Day 31	Day 37	Day 40
Urea (mmol/l)	21.9	22.3	23.2	18.5	28	30.5	23.8	18.6	26.2	17.4	19	20.7	19.3	16.3	10.9	10.2
Creatinine (μmol/l)	602	601	843	861	1434	1643	1066	1207	903	481	671	744	408	354	227	254
Sodium (mmol/l)	142	142	138	136	137	140	140	140	140	136	136	143	138	139	139	137
Potassium (mmol/l)	4.0	4.6	4.2	4.4	4.2	4.4	4.8	4.8	4.2	4.8	4.0	4.8	5	4	3.8	3.8
Bicarbonate (mmol/l)	27	27	26	26	26	27	27	27	26	24	25	28	26	26	26	25
PCV %	32				33	29										
Hb (g/dl)	11.0				12	10.7										
Leukocyte ($\times 10^9$cells/ml)	4.3				6.3	4.1										
Neutrophils %	63.5				53.3	64.6										
Lymphocyte%	25.1				30.7	39.9										
Monocytes %	4.6				16											
Eosinophils %	1															
Basophils %	4.2															
Platelets ($\times 10^9$/ml)	107				525	498										
S.creatinine kinase (U/l)									229							
Total bilirubin (μmol/l)			7.0													
ALP (U/l)			33													
AST (U/l)			31													
ALT (U/l)			29													
Urinalysis																
Protein	++															
Blood	++															
Granular casts	numerous															

AST = aspartate aminotransferase, ALT = alanine transferase, Hb = hemoglobin, PCV = packed cell volume, Hb = hemoglobin, S = serum.

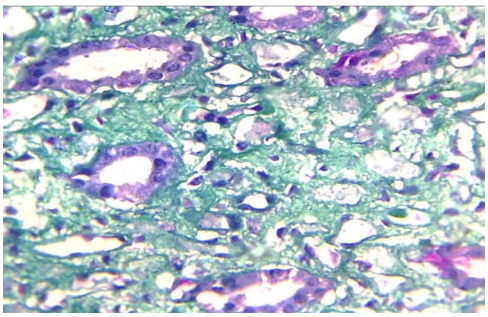

Figure 1. Shows interstitium expanded by edema and displacing the tubules. Masson Trichrome stain, ×40.

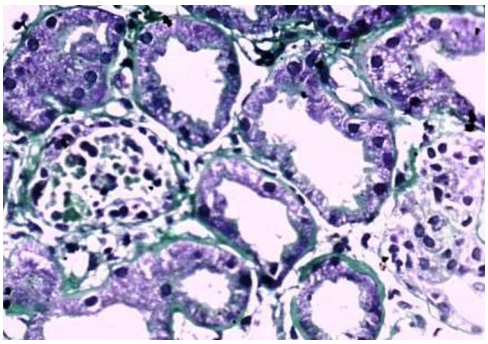

Figure 2. Shows necrotic tubules containing necrotic epithelial cells and granular debris. Masson Trichrome stain, ×40.

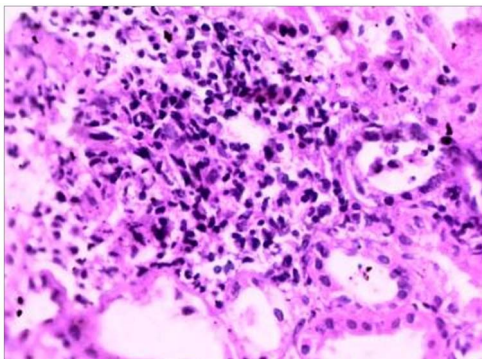

Figure 3. Shows intense mixed neutrophilic, lymphocytic and eosinophilic infiltrates. PAS stain, ×20.

Treatment

At presentation he was given 0.5 mg of intramuscular epinephrine, received 3 l of 0.9% saline over a period of 12 h, intravenous hydrocortisone for 5 days in addition to antihistamines. He was immediately commenced on intermittent hemodialysis. Subcutaneous soluble insulin was given to achieve good glycemic control. Five days post admission, he was noticed to have developed generalized body swelling associated with shortness of breath with spo2 ranging between 80 and 88%. Therefore, he was commenced on intermittent oxygen via nasal prongs and the ultra-filtration during dialysis was increased.

Outcome and follow up

After the seventh session of hemodialysis, his urine output gradually increased to 2500 ml/24 h on Day 23 and

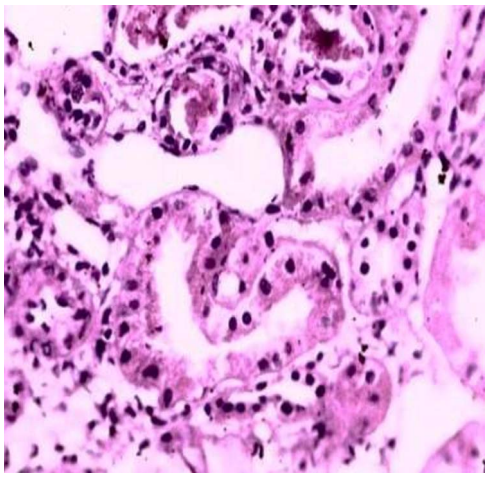

Figure 4. Shows necrotic tubules with focal red cell casts. PAS stain, ×20.

subsequently went into polyuric phase with urine output ranging between 5 and 8 l/24 h. Duration of hospital stay was 31 days. His serum creatinine level was 118 μmol/l seventh week post initial event.

DISCUSSION

The bee venom is largely made up of melittin (40–60%) and phospholipase A (12%) and other less lethal components, which are in minor quantity (serotonin, hyaluronidase, histamine, catecholamines and kinin; [4]). These constituents have vasoactive, neurologic, hemolytic and cytotoxic effects that are capable of inducing rhabdomyolysis, intravascular hemolysis, cardiac dysfunction, hepatic injury, paralysis of respiratory muscles, thrombocytopenia and acute kidney injury [2]. The observed mild thrombocytopenia in our patient may be attributed to the inhibitory effect of phospholipase A2 on platelet aggregation through a plasma cofactor [5]. Melittin and phospholipase A2 are known to cause non traumatic rhabdomyolysis. This seems to be a common occurrence following multiple bee stings as previous studies have reported rhabdomyolysis in more than half of their patients [6, 7]. Although we could not tentatively exclude rhabdomyolysis in our patient, the elevated serum creatinine kinase, which is a more specific marker of muscle injury seen in our patient during the recovery stage indicates that the patient might have had rhabdomyolysis.

Although acute tubular necrosis (ATN) is usually the most commonly reported histological findings in AKI due to bee stings, a few studies have reported acute interstitial nephritis (AIN) [8, 9]. While concurrence of both ATN and AIN as seen in this index patient is rarely reported. The first case with combined ATN and AIN findings was reported in 2004 by Chao *et al.* [9]. The frequently observed ATN has been attributed to hypotension or pigment nephropathy as a result of intravascular hemolysis or rhabdomyolysis. However, some studies have reported AKI with no evidence of shock or intravascular hemolysis

and thus proposed other mechanisms of AKI other than toxic/ischemic ATN [8]. The venom as allergens can initiate other forms of renal injuries such as immune mediated (antibody -antigen) glomerulonephritis, vasculitis and tubulointerstitial nephritis [8]. In this index patient, after excluding the use of medications that can cause AIN, the observed AIN may be due to hypersensitivity to the venom. The duration for the recovery of kidney function have been shown to be shorter in ATN than AIN. This may partly explain the delayed recovery of kidney function in this patient despite repeated intermittent HD. This further supports the importance of renal biopsy in this setting as commencement of steroids may enhance recovery of kidney function and prevent progression to interstitial fibrosis.

The mainstay of management for bee stings entails prevention or abating of anaphylactic reaction with intramuscular adrenaline, corticosteroids and antihistamines, prompt volume replacement with the use of crystalloids and airway support [2]. Our patient received a dose of intramuscular epinephrine, intravenous crystalloid and Intravenous hydrocortisone along with histamines for 5 days.

For patients that developed AKI, basic measures for management of AKI as in other causes should be instituted in conjunction with prompt initiation of dialysis for patients with indications. Although there is no available anti bee venom, hemodialysis alone or in combination with plasmapheresis may play a vital role in the removal of the venom from the circulation [6, 10].

Conflicting reports exist regarding effectiveness of removal of stings as a treatment modality for multiple bee stings. For example, some authors reported that a significant proportion of the venom remain on the stingers and thus encouraged removal to avoid further inoculation of the venom into the circulation [11, 12]. While another study showed that ~90% of the venom will be inoculated within 20 s of a sting and full delivery will occur within one minute [13].

In our patient, an attempt was made by the caregivers to remove the majority of the stings from his body, while the deposited stingers in the eyes were removed by an ophthalmologist.

In conclusion, aggressive attack from bees should be treated as a medical emergency and prompt management should be instituted to prevent AKI. However, when AKI ensues dialysis can be instituted when indicated, in addition to performing early renal biopsy for those with non- recovery of kidney function.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

ETHICAL APPROVAL

Ethical approval was not required.

CONSENT

Patient read through the manuscript and gave a written informed consent to publish the images and the article.

GUARANTOR

Bala Waziri.

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