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Nephrology Dialysis Transplantation

In-Depth Clinical Review

Scorpion sting nephropathy

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Abstract

Scorpion envenomations are ubiquitous, but nephropathy is a rare manifestation, reported mainly from the Middle East and North Africa. Rapid venom redistribution from blood, delayed excretion from the kidneys, direct toxicity of venom enzymes, cytokine release and afferent arteriolar constriction have been seen in experimental animals. Haemoglobinuria, acute tubular necrosis, interstitial nephritis and haemolytic–uraemic syndrome have been documented in human victims of scorpion envenomation. Epidemiology, venom components and toxins, effects on the laboratory mammals especially the kidneys and reports of renal failure in humans are reviewed in this article.

Keywords: kidney; renal failure; scorpion envenomation; scorpion sting; venom

Introduction

Nephropathy arising from animal origin includes toxins of snakes, scorpions, hymenoptera, jelly fish, spiders, centipedes, caterpillars and grass carp (raw bile) [1]. Acute renal failure is the commonest nephropathy, but subnephrotic proteinuria, vasculitis, haemolytic–uraemic syndrome (HUS), pigment nephropathy and interstitial nephritis have been reported [1]. We recently admitted a 64-year-old lady with oedema and reduced urine output of 3 days duration. She had been stung by a red scorpion on her left thumb 10 days previously and she had then applied lime to the site of the sting. At admission, she had a linear healing ulcer on her thumb, anasarca, pallor and hypertension of 160/90 mmHg. Her investigations were haemoglobin 95 g/L, total counts 5.7×10^9/L, platelets 150×10^9/L, erythrocyte sedimentation rate 35 mm/h, urea nitrogen 12.48 mmol/L, creatinine 97.24 μmol/L, total cholesterol 2.98 mmol/L, triglycerides 1.23 mmol/L, low-density lipoprotein 1.4 mmol/L, high-density lipoprotein 0.93 mmol/L, thyroid-stimulating hormone 2.2 mIU/L, C3 1.06 g/L (0.90–1.70), C4 0.21 g/L (0.15–0.45), negative anti-nuclear antibodies, ds-DNA, Antineutrophil cytoplasmic autoantibodies, cytoplasmic (c-ANCA) and hepatitis panel and normal liver function tests. Facilities for cryoglobulin testing were unavailable. Dipstick urine testing revealed albumin 3+ and 24 h urinary protein was 735 mg; urine microscopy showed 1–2 red blood cells (RBCs), 2–3 pus cells and 6–8 epithelial cells without RBC casts. Ultrasonogram revealed minimal bilateral pleural effusion and normal-sized kidneys. Renal biopsy was performed on the seventh day of admission and showed focal irregularity of the basement membrane, mild interstitial infiltrate of lymphocytes, plasma cells and neutrophils with fraying of some tubules and without granulomas or inclusion bodies. We had treated her with diuretics, calcium channel blockers and her renal functions and urinalysis were normal at a follow-up visit 6 weeks later. Therefore, we had reviewed the topic of renal failure following scorpion sting envenomation. In the following review, we will discuss the epidemiology of scorpionism, its venom and toxins, systemic effects of venom especially in relation to the kidney and describe the known reports of scorpion sting nephropathy. An online literature search was performed using the terms 'scorpion sting', 'scorpion envenomation', 'renal failure', 'venom' and 'kidney' in the following databases—PubMed, Science Direct, EBSCO, Wiley Online, Springerlink, Ovid and Google Scholar.

Epidemiology

Scorpion stings are the second most common cause of human envenomation after snake bites [2]. Scorpions are ancient creatures that have not seen much evolutionary changes over millions of years [3]. They are nocturnal beings and are exclusively carnivorous, sensing their prey through their pedipalps and also through hearing [3]. The order Scorpionidae (Class—Arachnida) constitutes of 18 families and ~1500 species [2]. The Buthidae family is the largest and has the most number of species that are toxic to humans [4]. Except Antartica, scorpions survive on every other continent and in almost every type of habitat [5]. The genera of the Old World include *Androctonus* (North Africa, Saudi Arabia and Turkey), *Hottenta* (Morocco and India), *Buthus* (East Mediterranean), *Leiurus* (Africa and Middle East), *Parabuthus* (South Africa), *Hemiscorpius* (Iran and Iraq) and *Mesobuthus* (Turkey and Iran) [6]. The New World genera comprises of *Centruroides* (Southern United States and Mexico) and *Tityus* (Brazil, Argentina and Venezuela)

[6]. Asia and Africa have the most dangerous scorpions [7]. Health hazards are the greatest in the Indian subcontinent, Mexico and the North African countries [3].

Thirty odd scorpion species among the 1500 are dangerous to man. There are 134 species in Mexico and only the *Centruroides* species (8 in numbers) are poisonous [7]. About 250 000 scorpion events are registered in Mexico every year, with the highest mortality rate in the world [2, 8]. *Centruroides exilicauda* (formerly *Centruroides sculpturatus*) found in Arizona is the only poisonous species in the USA [7, 9]. *Tityus serrulatus* is the most prevalent species in South America and accounts for most of the fatal stings on that continent, especially in Brazil [10, 11]. About 40 000 scorpion stings are reported in Tunisia every year [12]. Intensive care admission following scorpion stings in Tunisia generally arises from either *Androctonus australis* or *Buthus occitanus* species envenomation [13]. About 130 species, falling into four families—Buthidae, Scorpionidae, Bothriuridae and Ischnuridae, are seen in Southern Africa [14]. *Hemiscorpius lepturus* accounts for 90% of scorpion-related deaths in Iran [15]. In Saudi Arabia, the commonest species include *Leirurus quinquestriatus and Androctonus crassicauda* [16], while in Turkey, *Euscorpius carpaticus* and *Euscorpius germanus* are the most frequent [17]. *Mesobuthus tamulus* and *Palmoneus gravimanus* are the commonest species in India, with the former being among the most toxic of scorpions [18].

Venom components

The stinger contains a pair of venomous glands. Venom is either species or genus specific. Volume of venom per sting, protein content and toxicity vary with the individual scorpion [3]. Peptide compositions of toxins vary within the same scorpion species depending on the region they inhabit [19]. Signs of envenomation depend upon the species, venom components and the physiological response of the person stung [5]. Anaphylaxis is rare when compared to hymenoptera stings. Venom is toxic due to its proteolytic content and phospolipase A_2 [18]. Proteins constitute ~30–75% of dry venom weight [19]. Each venom contains 50–100 different polypeptides [20]. Only ~0.4% of the 100 000 odd venom peptides have been isolated [21]. Venom is an aqueous mixture of low-molecular-weight (LMW) peptides, antimicrobial peptides [14], mucopolysaccharides, protease inhibitors and high-molecular weight proteins (HMW) [20]. LMW (<1500 Da) proteins form the largest subgroups (1/3rd) of these proteins [19]. Scorpion neurotoxins mainly weigh between 3000 and 9000 Da [21]. Bradykinin-potentiating peptides (BPP)] account for more than half of the LMW proteins that have been identified. The major constituents of the kinin system are the kininogens, kallikreins and kininases [22]. The kininases act on metabolites of LMW kininogens to form bradykinin (BK). BPPs have been found in venoms of *Heterometrus bengalensis* and *Leiurus quinquestriatus* [22]. The 3001–4500 and 6100–7500 Da groups that contain the predominant mass of known scorpion toxins comprise 20% each [19]. The HMW proteins (>9000 Da) mainly include phospholipase, hyaluronidase and lyzozymes [19]. Most venom

is stored as pre-pro-peptides. Scorpion venom lacks enzyme activity or have very low levels of enzyme activity compared to that of snake and hymenoptera venom [19, 23]. Exceptions are the *Heterometerus scaber* and *fulvipes*, *M. tamulus* and *C. exilicauda* species [23].

Venom toxins

Venoms are classified based on their mode of action and binding site. Based on their molecular size, they are either long-chain or short-chain peptides. Toxins can be mammalian, crustacean or insect specific. They can be also neurotoxic or cytotoxic [21]. Chlorotoxin from *L. quinquestriatus* has binding ability to matrix metalloproteinase II of glioma cell lines and shows anti-cancer activity [20]. Scorpion venom toxins are divided into four classes [23, 24]—sodium channel toxins (NaTx), potassium channel toxins (KTx), chloride channel toxins (ClTx) and calcium channel toxins (CaTx). All these toxins have disulphide bridges. Targets for scorpion venom are usually the voltage-gated Na^+ and K^+ channels. NaTx are neurotoxins [23, 25]. NaTx are mainly anti-mammal and anti-insect toxins (e.g. Butal T from *Buthus tumulus*) [20, 21]. The α-NaTx inactivates sodium channels by binding to Site 3 of the receptor and prolongs nerve action potential [22]. The α-group has α, α-like and insect α toxins. The β-toxin produces a more negative membrane potential by binding to Site 4 of the receptor. The β-toxins group either act exclusively on mammalian systems or on both insects and mammals [14, 23]. The β-toxins include CssIV from *Centruroide*s *suffussus* and Ts1 from *T. serrulatus* [5, 26].

The KTx affect voltage-gated K^+ channels, outward delayed rectifier K^+ channels and the maxi-Ca^+-activated K^+ channels [23]. The K^+ channels are physically occluded; blockage of these channels prolongs action potential durations. KTx comprise of α-KTx, β-KTx, γ-KTx and κ- KTx [21]. KTx are involved in immune responsiveness: blockage of these channels causes decrease in T-cell activation and subsequent delayed-type hypersensitivity. The amino acid and its alignment (especially cysteine) on the external surface of the toxin decide the specificity and affinity of the K^+ toxin [14]. The Indian red scorpion (*M. tamulus*) venom contains KTx like iberiotoxin, tamulustoxin and tamapin [27]. Iberiotoxin is specific to maxi-K^+ channels [23]. Butantoxin blocks K^+ channels and inhibits IL-2 production [5]. The K^+ channel blockers have short-chain peptides and belong to the 3000–4500 Da group, whereas the Na^+ channel modulators are long chained with molecular weights of 6001–7500 Da [19]. Short-chain peptides (30–40 amino acids) mainly recognize K^+ channels, while long-chain peptides (58–64 amino acids) recognize Na^+ channels [2, 28].

Venom effects and clinical manifestations

Venom acts via cholinergic and adrenergic stimulation. The cholinergic activity is either due to reduced destruction of acetylcholine (Ach) or excessive Ach release, acting on postganglionic nerve endings [26, 29]. Serotonin and noradrenaline are also released by scorpion venom [25]. Catecholamine release causes rennin secretion by beta adrenergic stimulation

and increases blood pressure [24]. Studies in rats (*A. australis hector* scorpions), mice (*Centruroides noxius* scorpions) and rabbits (*L. quinquestriatus* scorpions) have shown that venom also induces release of both pro- and anti-inflammatory cytokines [5]. Venom also causes an inflammatory reaction in the lungs, kidneys, heart and intestine of experimental rats. Vasodilation due to inflammatory cytokines probably causes renal hypovolaemia. Imbalances between pro- and anti-inflammatory mediators lead to organ damage [5].

An initial phase of hyperadrenergism (inotropic phase) followed by a phase of hypotension and depressed myocardial contractility is seen in experimental rabbits [30]. The late phase has been hypothesized to be due to cholinergic effects, fluid loss or vasodilatory substance release by venom or its peptides [30]. Inflammatory cytokines like interleukin (IL)-1β, IL-6, IL-8, IL-10, TNF-α and nitric oxide (NO) have been observed in children with scorpion envenomation. Possibly, the NO synthase activity is enhanced resulting in vasodilation and hypotension. TNF-α, IL-1β or IL-6 have all been postulated to play a role in leucocyte activation and leucocytosis [30]. Leucocyte activation may lead to production of reactive oxygen species and subsequent multi-organ failure. Liver and renal dysfunction generally occur during the late hypotensive stages of envenomation [30].

Immediate pain and, in children, screaming and irritability, are observed after a scorpion sting. Local reactions are generally uncommon in stings of the Indian red scorpion (*M. tamulus*). Pain and sweating with faintness constitute Stage I of envenomation [6]. Local pain and parasthesias apart, signs and symptoms of envenomation arising from exaggerated autonomic activity (parasympathetic and sympathetic) include cool extremities, vomiting, diarrhoea, hyperthermia, abdominal colic, priapism, hypotension or hypertension, sinus tachycardia, congestive heart failure, myocarditis, dysrhythmias, heart blocks and pulmonary oedema [31]. These features occur within 30 min to 4 h and can last for up to 72 h (especially tachycardia) [32]. Pulmonary oedema is either cardiogenic, neurogenic or due to direct lung damage [26]. Studies have shown that venom injection in anaesthetized Sprague–Dawley rats caused down-regulation of Na$^+$–K$^+$-ATPase in the basolateral membrane of alveolar epithelial cells and reduces alveolar oedema clearance [33]. Toxin of *T. serrulatus* causes abnormal breathing patterns like Cheyne–Stokes and Biot breathing in mice [26]. Stage II envenomation is comprised mainly of muscarinic signs and symptoms, while Stage III is associated with pulmonary oedema, arrhythmias and cardiovascular collapse. Sequential progress through all stages may not occur in children. The nervous system manifestations are infrequent and they include encephalopathy, seizures, restlessness, areflexia, psychosis, strokes and muscle cramps [31]. The first two neurological complications are invariably fatal in children [32]. Strokes can occur due to a hypercoagulable state and fibrin deposition in the arterioles. Pancreatitis (systemic inflammatory response related) in Israel and Trinidad, acute renal failure from the Middle East and North Africa, and abortions, are the other unusual manifestations that have been described [26, 32].

Necropsy studies have revealed haemorrhages in the lung and kidney and thrombi occluding capillaries in the kidney, liver, spleen, intestines, lung and the heart [34]. Vasculitis,

arteritis and fibrin deposition have also been reported [35]. Scorpion venom mobilizes inflammatory cells and leucocytes [36]. Haematological findings include thrombocytopenia and deficiency in coagulation factors V, VII, VIII and XIII [8]. Scorpion envenoming in dogs revealed prolonged prothrombin time and hypofibrinogenaemia [34]. In ventilated rats, scorpion venom infusion has been shown to produce metabolic acidosis, hyperglycaemia, hypermagnesaemia and hyperkalaemia. Blood flow was reduced in the renal, cutaneous and mesenteric circulation. Acidosis was mainly metabolic (lactic) and due to tissue hypoperfusion. Hyperkalaemia was possibly due to hypoinsulinaemia and inhibition of Na$^+$–K$^+$-ATPase [36].

Venom and the kidney

The kidneys and liver are the main routes of excretion from the human body [24]. The kidneys have the largest concentration of venom (and the brain, the lowest), mainly because of the rapid redistribution of the venom from the blood to the tissues coupled with slow removal from the kidney. The liver, lungs and the heart have successively lower venom concentrations when compared to the kidney [37]. Even though the scorpion injects venom into the interstitial spaces, 70% blood concentration is achieved within 15 min. Radiolabelling of *M. tamulus* venom in Wistar rats revealed a rapid high concentration that reduced to 1/3rd of concentrations within 30 min indicating rapid elimination from blood. Renal uptake at 30 min (32%) reduced to only 22% at 3 h indicating slow elimination from the kidneys [24]. During redistribution from blood, toxins disappear faster compared to other venom components and hence local tissue concentration of toxins, especially in the kidney, can cause direct toxicity [6].

Venom administration to rats has shown increased vascular resistance, increased perfusion pressure, decreased renal blood flow, decreased glomerular filtration rate (GFR) and decreased urinary flow [37]. Afferent arteriolar vasoconstriction was probably caused by renal α-adrenoreceptor activation or was due to K$^+$ channel blockade that causes vascular smooth muscle depolarization and contraction [37]. Proteinaceous deposits found in the renal tubules was possibly due to high perfusion pressures or action of a yet unrecognized substance similar to the pore-forming peptides of some scorpion venoms (*Buthus martensii*) that damage the glomerular basement membrane (GBM). The vasoconstrictor actions were temporary phenomena lasting for ~10 min akin to that of an adrenergic vascular escape phenomenon seen in the enteric circulation. In another study, effects of *Buthus occitanus tunetanus* venom was compared in pregnant and non-pregnant rats—plasma creatinine was higher in pregnant rats 30 min after venom exposure when compared to their non-pregnant counterparts; the plasma creatinine dropped significantly at 4 h only in the non-pregnant rats [38]. Haemoconcentration was noted in non-pregnant rats that were partly offset by anaemia in pregnant animals. There was a significant negative correlation of blood urea nitrogen in pregnant rats and a positive correlation of blood urea nitrogen/creatinine ratio in their non-pregnant counterparts. Polyuria (contributing to haemoconcentration), metrorrhagia (possibly due to coagulation

defects), significant reduction in platelet size (in non-pregnant animals contributing to coagulation defects) and haemolysis may predispose to renal insufficiency [38].

In a review from Iran, envenomation by *H. lepturus* in rats led to focal necrosis and haemorrhage in the kidney and other lipid-containing organs like the liver and heart [15]. Kidney findings were seen in 70% of envenomed animals [15]. Morphological changes in the glomerular apparatus and the proximal tubular cell-like interstitial oedema, dose-dependent collapse of the proximal and distal tubules, lymphocytic infiltration of the medulla and glomerular destruction were observed [15]. Haemolysis and renal failure are associated with *H. lepturus* envenomation [39]. Its venom has gelatinase, caseinase and hyaluronidase (>40 kDa) activity. The hyaluronidase affects vessel wall stability and may cause the spread of venom in tissues [39]. *Loxosceles deserta*, the brown recluse spider, also has similar molecular weight enzymes, especially in the 30–35 kDa band of antigenic components, and the spider venom is known to promote the complement cascade [39]. Sphingomyelinase D, an enzyme, is seen in the venom of both *H. lepturus* and *L. deserta* and predisposes to skin necrosis, local ischaemia, thrombosis and haemolysis.

In a study of 12 dogs with *T. serrulatus* envenomation by injecting 250 µg/kg of venom, no significant electrolyte imbalances, dehydration, nausea or vomiting were observed. Cytokines (IL-1, IL-6 and TNF-α) and kinins increased in these dogs [10]. Renal functions were preserved in all envenomed dogs. One dog had glucosuria and hyperglycaemia. Urinalysis remained normal in these dogs except for mildly lower urinary pH in envenomed dogs. IL-12 is a determinant in glomerulonephritis (GN) and absence of IL-12 prevented the formation of anti-GBM GN. IL-12 is also produced by renal cells [40]. Focal proliferative glomerulonephritis in rats, mice and rabbits is caused when Habu snake venom is injected intravenously. In experimental lupus nephritis, cresentic GN and IgA nephropathy, IL-12 absence reduces glomerular injury. Reduced glomerular macrophages and T cells were noted especially in IL-12-deficient mice with lupus nephritis [40]. Reduced IL-12 decreased activity of mesangial cell proliferation without affecting the course of mesangial glomerulonephritis. Surprisingly, butantoxin from *T. serrulatus* inhibits T-cell proliferation and IL-12 synthesis; hence other factors in scorpion envenomation may mediate glomerular injury [5].

Rat kidney glomeruli secretes prostaglandins (PG) PGE_2, $PGEI_2$, PGD_2 and thromboxane B_2 (TxB_2) [41]. Increase in vasodilatory PGs mediates increases in GFR, while PGE_2 inhibition reduces creatinine clearance. Modulatory activity of PGs depends on their interactions with angiotensin II (AII) and arginine vasopressin (AVP). AII and AVP stimulate PGE_2 in kidney mesangial cells due to the tight linking of AII and AVP receptors to the phopholipase (PL), COX and PGE_2 isomerase [41]. Scorpion and snake venom have BPP or fractions (BPP/BPF). BK releases PGEs in isolated rat kidney and rabbit kidneys. BKs activate PL and increases arachidonic acid conversion. Increases in blood flow and dilatation of renal capillaries have been seen with BPP [41]. The peptide fraction of the Egyptian scorpion *B. occitanus* has BPP that may increase urea and creatinine clearance.

Thus, it is seen that scorpion venom administration in experimental animals predisposes towards renal failure by way of concentration of venom in the kidneys, large molecular weight enzymes, high perfusion pressures, hypotension, reduced renal blood flow, polyuria, haemoconcentration, haemolysis, coagulation defects and systemic inflammatory response also involving complements, vasculitis, fibrin deposition and haemorrhages. This is to be partly sobered by the fact that some venom components like BPP can increase blood flow and creatinine clearance and some toxins can inhibit T-cell proliferation and IL-12 production. There are no studies correlating nephropathy with the innumerous ion channel toxins, on a scale of the literature available on the toxin effects on the nervous, musculoskeletal and cardiorespiratory system. K^+ channel toxins may mediate vascular contraction by causing smooth muscle depolarization and hence contribute to reduced renal blood flow. On the other hand, K^+ channel toxins like butantoxin mediate delayed hypersensitivity and reduce IL-12 as previously mentioned and hence may play a protective role in kidney injury. In spite of the vulnerability of the kidney due to its ability to concentrate toxins, direct toxin-mediated kidney injury (except pigmenturia-related tubular damage) has not been conclusively demonstrated. Since anaphylaxis is also rare, it could be partly explained that most of the known scorpion toxins are <9000 Da and may not induce an antigenic response of sufficient magnitude. The known toxins mostly mediate neuromuscular and autonomic effects. The HMW (>9000 Da) peptides that include enzymes like hyaluronidase and sphingomyelinase which mediate tissue injury and complement activation comprise a very small portion of scorpion venom. Direct venom toxicity in general is due to these HMW proteolytic enzymes. Also, venom components vary from habitat to habitat. This might also contribute to renal failure being reported from very few countries in the world—viz., the Middle East and North Africa compared to their vast habitat. Hence, a combination of other non-toxin-related factors causes renal injury.

Nephropathy

Causes of venom-induced acute kidney injury in Asia includes snakes, hymenoptera, spiders, jellyfish and scorpions [37, 42]. About 100 odd cases of Hymenoptera sting-related renal failure have been reported [43]. These stings cause renal involvement by pigment nephropathy, interstitial nephritis, rhabdomyolysis or intravascular haemolysis, vasculitis or direct toxin effect, which is similarly seen in scorpion stings. A review of nephrotoxic insect venom in 2008 did not mention kidney injury due to scorpion venom [44]. About 62 odd cases of renal failure resulting from scorpion envenomation have been reported (Table 1). In a multivariate analysis of cases of scorpion stings from Tunisia, mild urea and creatinine elevations were seen up to 132 mmol/L [13]. Urea elevations were associated with mortality and were generally observed in patient subsets with cardiac failure or hypovolaemia. All cases of scorpion sting-related nephropathy have been reported from one of these five countries—Iran, Tunisia, Turkey, Pakistan and Israel (Table 1).

Table 1. Reports of scorpion sting nephropathy[a]

Year	Reference	Cases	Diagnosis
1978	[43]	15	Nine patients <12 years; haematuria, haemoglobinuria oligoanuria, anaemia, anasarca, jaundice were the presentation; five were dialysed; four biopsies were performed—showed mesangial hypercellularity and interstitial infiltrates
1979	[45]	1	Twenty-eight-year-old female with haemolyis, haemoglobinuria, local dermonecrosis and renal failure treated with RBC transfusion, frusemide and peritoneal dialysis; diuresis from 11th day onwards; required extended hospital stay for dermonecrosis
1998	[46]	1	Sixty-year-old male with limb swelling, haematuria (first 2 days), oliguria (at 48 h), drowsiness. Two sessions haemodialysis given; diuresis from fourth day onwards; died due to DIC and ATN
1998	[17]	1	Twenty-eight-year-old male with vomiting, diarrhoea, altered sensorium, oliguria within 48 h of sting; deranged LFT and pancreatic enzymes, ARDS; haemodialysed; methylprednisolone and fresh frozen plasma administered; improved by 10th day
2000	[47]	1	Fifty-year-old female; referred for evaluation of renal failure with haemolysis, anaemia; negative autoimmune workup; biopsy showed interstitial nephritis; scorpion sting history obtained only after biopsy
2004	[48]	2	Two infants; both with severe haemolysis, anaemia, derange LFT, elevated CK, thrombocytopenia, altered sensorium and ended fatally—one at 5 days and the other at 24 h; the second had cerebral herniation
2004	[49]	6	Children; ATN; other details not available
2007	[50]	1	Fifty-four-year-old male; ATN and hepatitis within 24 h; haemodialysed on multiple occasions; improved by 25th day
2008	[51]	1	Seven-year female; haematuria, restlessness; anaemia and thrombocytopenia developed during second week; hydrocortisone, platelet and plasma transfusions and haemodialysis instituted; discharged at end of month with maintenance dialysis programme (?duration)
2010	[15]	33	All were children <10 years; haemoglobinuria and renal failure; 3 deaths due to renal failure; 73 children had haemoglobinuria without renal failure

[a]Y, years; DIC, disseminated intravascular coagulation; LFT, liver function tests; ARDS, acute respiratory distress syndrome; CK, creatine kinase; h, hours.

Both children and adults (young and middle-aged) can develop renal failure, with children having been more commonly reported (52/67) in literature. Patients develop renal insufficiency in the setting of hypovolaemia and cardiac failure-related acute tubular necrosis (ATN), pigmenturia, haemoglobin-related tubular damage, HUS or interstitial nephritis. Haemolysis, haemoglobinuria and HUS are more common in children. Delay in seeking hospital care and/or administration of anti-venom increases the risk of renal failure. Onset of illness is generally within a few days, although one report described development within 24 h and that particular patient also had hepatitis [50]. Haemoglobinuria and haematuria occur between a few hours to 24 h—haematuria clears within 1–5 days. Patients present with anaemia, urinary discolouration, ulcer or dermonecrosis, jaundice, oedema or anasarca, oliguria or anuria, breathlessness, hypo- or hypertension and altered sensorium. Investigations reveal anaemia, leukocytosis, thrombocytopenia, schistocytes, elevated urea, creatinine, transaminases, creatinine kinase and lactate dehydrogenase, bland or active urinary sediments, urinary haeme and proteinuria, and interstitial nephritis on biopsy. Biopsy changes are maximal during the early part of the illness. Most of these patients require renal replacement therapy along with RBC transfusions, inotropes, antivenom, respiratory support, diuretics, anti-hypertensives and occasional steroids (in HUS and interstitial nephritis). Diuresis begins by the end of the first week and most improve by 4 weeks if they do not die of disseminated intravascular coagulation or neurological or cardiovascular complications.

A review from Iran on acute renal failure in 2004 reported six children with ATN arising from scorpion sting envenomation [49]. A series of 15 cases of scorpion sting-related acute renal failure was reported in 1978 with all of them having haemoglobinuria and renal failure [52]. Eleven of them had oliguria, while one had anuria and five required haemodialysis. Mesangial hypercellularity and mild to moderate interstitial inflammation were documented. *In vitro* studies of scorpion venom on human RBCs have shown haemolysis. Possible immune glomerulonephritis had been hypothesized since venom peptides can rarely induce an antigenic response [43]. Cytokine release and activation of complement cascade activation are known with some scorpion venoms but glomerulopathy *per se* has not been described in the literature. Our patient only had focal irregularity of the basement membrane and a good quality immunofluorescence staining could not be obtained to detect glomerular deposits. *H. lepturus* species accounts for 90% of scorpion-related deaths in Iran causing haemoglobinuria and renal failure especially in children. In one review, 50% of 141 children admitted had haemoglobinuria alone, 20% had both haemoglobinuria and renal failure and 2.2% died due to renal failure [15]. Proteinuria may be an early indication of renal failure. The *Hemiscorpius* species apart, the *Buthus* and *Cosmobuthus* scorpions (the three, collectively called the yellow scorpions) also cause haemolysis and renal failure [45]. Haemolysis associated with renal failure and local necrosis was reported once from Israel, and the patient had been treated with steroids and had recovered over a course of 4 weeks [45].

Reports of HUS have been described in three instances—two from Tunisia and one each from Iran and Turkey [17, 48, 51]. The first three cases were in children, while the Turkish patient was a 28-year-old man. *Androctonus* envenomation led to fatal HUS in both infants from Tunisia even after treatment with anti-scorpion venom, inotropes and mechanical ventilation [48]. Blood pressure was normal in both infants; both had elevated liver enzymes and creatine kinase levels. Whether rhabdomyolysis also played a role was not mentioned. The second infant in addition developed subarachnoid haemorrhage and cerebral herniation. Renal insufficiency may occur if antivenom is not given early [51]. The other two patients who survived had received intravenous steroids and renal replacement therapy. Steroids had also been helpful in one other case from Tunisia wherein a 50-year-old lady stung possibly by *A. australis* had elevated creatinine, bland sediments, proteinuria (similar to our patient) and interstitial nephritis on biopsy [47]. The 60-year-old patient from Pakistan had albuminuria, active sediments, haemoglobinuria and developed ATN (post-mortem biopsy), disseminated intravascular coagulation and died 15 days after the scorpion sting [46].

It has been hypothesized by some authors that early antivenom therapy may prevent renal failure. But with a large number of scorpion envenomations worldwide, few people, especially from rural areas, ever manage to receive antivenom even if they are reached in time, due to its unavailability. Antivenoms are available in Africa, India, Turkey, Brazil, Morocco and Saudi Arabia [2]. They have been available in India since 2002. But in India, therapy is mostly with prazosin, dobutamine, nitroglycerine and mechanical ventilation since pharmacies of even large tertiary care teaching hospitals do not stock scorpion anti-venom. Anti-venom has been shown only to expedite recovery and lessen duration of hospital stay [53]. There are no reports of renal failure in India occurring due to scorpion envenomation.

Conclusion

Renal failure following scorpion stings has been reported mainly in the Middle East, Eastern Mediterranean region and North Africa. Though the problem of scorpion envenomation is huge, renal failure is very rare. The kidney is theoretically vulnerable due to higher venom/toxin concentrations, HMW antigenic peptides and enzyme-related direct renal damage and possibly venom-related effects on GFR and perfusion pressure. Also, a systemic inflammatory response syndrome, complement cascade activation and other effects like pulmonary oedema, myocarditis and adrenergic excess-related vasoconstriction or parasympathetic stimulation-related hypotension cause reduction in renal blood flow and increase the risk of ATN. Haemoglobinuria-related pigment nephropathy, ATN, HUS and interstitial nephritis have all been documented as the aetiology of renal failure in scorpion envenomation. The multitude of known ion channel toxins probably does not play a major role in development of renal insufficiency. Effective treatment includes early prazosin therapy, anti-venom, steroids, inotropes, diuretics, treatment of hyper- and hypotension, RBC transfusions and renal replacement therapy. Our patient improved with diuretics and calcium channel blockers alone.

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