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Exceptional Case

Clinicopathological course of acute kidney injury following brown recluse (*Loxoscles reclusa*) envenomation

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Abstract

We report a case of severe systemic loxoscelism in a previously healthy young man. This was associated with a Coombs-positive hemolytic anemia, striking leukomid reaction, renal failure, respiratory failure and cardiovascular collapse. This is the first documented case of a renal biopsy in a patient with renal failure after envenomation by the brown recluse spider. Associated systemic toxicity usually resolves but requires prompt recognition and supportive care in an intensive care setting. We also discuss the potential mechanism by which the venom of this small spider can lead to multiorgan failure and possibly death.

Keywords: acute kidney injury; brown recluse envenomation; Coombs-positive hemolytic anemia; loxoscelism; renal biopsy

Case report

J.C., a 20-year-old African American male, presented to an outside hospital after several days of nausea with vomiting, dark-red-colored urine, fatigue, and a tender, swollen, red area in his upper medial right thigh. His fatigue progressed to weakness causing him to collapse without loss of consciousness. After witnessing her son collapse for a third straight day and noticing yellowing of his eyes, his mother called 911 and the patient was sent to a local emergency department. The patient admitted to having chills for the past 2 days and a headache for the previous week. Initial physical examination revealed a fever of 38.6°C, tachycardia (140 beats/min), blood pressure (BP) of 103/25 mmHg, scleral icterus and tenderness to palpation of his right upper quadrant and right inner thigh. The area of the 'bite' was described as a grapefruit-sized red patch localized to the right medial thigh with induration.

Initial laboratory data showed a white blood count (WBC) count of $33.4 \times 10^3/\mu L$ ($33.4 \times 10^9/L$) with 89.9% neutrophils, proteinuria, hematuria, pyuria, and hyperbilirubinemia. Computed tomography of the abdomen and pelvis demonstrated a heterogeneous enhancement pattern in both kidneys. The patient received antibiotics and fluid resuscitation. The following day the patient's clinical course deteriorated with worsening chills, his blood pressure dropped to 92/45 mmHg, WBC increased to $54.2 \times 10^3/\mu L$ ($54.2 \times 10^9/L$) and his hemoglobin decreased from 12.4 to 6.5 g/dL (124–65 g/L). His lactate and haptoglobin levels were 67.3 mg/dL (7.4 mmol/L) and <10 mg/dL (0.1 g/L), respectively. He was transferred to Barnes-Jewish Hospital

(BJH) and admitted. At BJH, the patient's condition worsened, his temperature increased to 39.2°C and he became somnolent with worsening oxygenation. The laboratory values became more concerning, especially a hemoglobin drop to 3.2 g/dL (32 g/L) with a hematocrit of 10%. His creatinine increased to 1.42 mg/dL (125.5 μmol/L), BUN to 42 mg/dL (15 mmol/L), HCO_3^- of 16 mEq/L (16 mmol/L), anion gap of 24 mEq/L (24 mmol/L), blood gas with a pH of 7.27, pCO_2 of 37 mmHg, pO_2 of 92 mm Hg with a WBC count of $62.7 \times 10^3/\mu L$ ($62.7 \times 10^9/L$) and platelet count of $264 \times 10^3/\mu L$ ($264 \times 10^9/L$).

He was intubated for hypoxic respiratory failure and continued on antibiotics. The following day he became oliguric and was started on renal replacement therapy. The laboratory peak or nadir values during the patient's hospital stay were HCO_3^- 9 mEq/L (9 mmol/L), BUN 140 mg/dL (50 mmol/L), Cr. 9.05 mg/dL (800 μmol/L), anion gap 30 mEq/L (30 mmol/L), WBC count of $71.3 \times 10^3/\mu L$ ($71.3 \times 10^9/L$), lactic acid 195.5 mg/dL (21.7 mmol/L), creatine kinase 845 U/L, LDH 13 080 U/L, AST 6399 U/L, ALT 3404 U/L, bilirubin 8.7 mg/dL (148.77 μmol/L), INR of 1.55 and mild elevations in lipase and amylase. These parameters indicated multisystem involvement, including hemolytic anemia, leukemoid reaction, transaminitis, pancreatitis, acidosis, renal failure and respiratory failure. The hemolytic anemia was Coombs direct positive for IgG and complement (C3) and a transthoracic echocardiogram demonstrated a new cardiomyopathy with ejection fraction of 35%.

The patient was extubated 2 days later and subsequently transitioned to intermittent hemodialysis. Retroperitoneal ultrasonography demonstrated ascites and renal parenchymal disease without hydronephrosis.

Evaluation by hematology/oncology with a bone marrow biopsy and peripheral blood flow cytometry did not reveal any clonal oncologic irregularities. Other pertinent negative results included absence of schistocytes, negative workup of serum autoantibodies, normal glucose-6-phosphate dehydrogenase and negative Lyme and Rickettsial serology.

After 6 days in the ICU, he was transferred to the floor but remained somnolent for several days; he was otherwise stable. Skin examination revealed a generalized exanthematous pustulosis and eschar formation measuring ~2.5 × 5 inches located in his medial, proximal right thigh, with marked reduction of swelling compared with prior examination.

Urine output which remained <100 mL/day for 1 week improved to 600 mL/day by the second week, with further improvement over subsequent days. Ten days after his initial admission to BJH, a kidney biopsy was performed. The biopsy demonstrated two glomeruli out of 14 that appeared to be degenerating with inflammatory cells in Bowman's space of one of the degenerating glomeruli, Figure 2A. There was mild interstitial inflammation, and the tubules showed acute tubular injury with WBC casts and red blood cells (RBCs) in the tubular lumens. Special stains confirmed acute tubular injury. There was no evidence of thrombotic microangiopathy. Immunofluorescence revealed the presence of diffuse and strong granular mesangial or capillary loop C3 deposition, Figure 2B, in the glomeruli, and mild IgG deposition. Electron microscopy showed minor foot process effacement with reactive changes in the podocytes, and an intact glomerular basement membrane (GBM). There were no electron dense deposits seen and subendothelial edema with out fibrin deposits was appreciated, Figure 2C. During the patient's third week at BJH, urine output increased to 2.5 L per day, dialysis was stopped, and he was discharged home. At discharge, the patient's laboratory values either normalized or were approaching normalization. After his mental status cleared, we elicited a history of him being bitten on his thigh while sleeping which awakened him. This occurred 1 day prior to the onset of his symptomatology. He did not however admit to seeing a spider. He mentioned that there were renovations taking place at home and the floor boards had been removed.

During the patient's hospitalization various treatments were initiated due to initially not recognizing the etiology combined with the dramatic clinical presentation. The treatments included intravenous immunoglobulin for 1 day, vancomycin, piperacillin/tazobactam and doxycycline for several days, corticosteroids and clindamycin for the entirety of the admission, six units of packed red blood cell transfusions and debridement of his bite site. The Coombs test became negative by the time of discharge.

Discussion

Loxosceles reclusa belongs to genus Loxosceles which in turn is part of the Sicariidae family. More than 100 described species of Loxosceles have been described all over the world but the majority are in the Americas, West Indies and Africa [1]. Owing to human transportation, certain species have been described in the Mediterranean, Middle East, Australia and China [1]. Loxosceles are notorious for the ability of their venoms to cause dermonecrotic lesions and systemic manifestations including intravascular hemolysis, disseminated intravascular coagulation and acute renal failure, an effect termed Loxoscelism, this has been documented across the geographic distribution of the genus [2, 3].

The brown recluse spider, *L. reclusa* (See Figure 1A), is responsible for most episodes of envenomation in its endemic regions in central and southern USA [4] (see Figure 1B). The common name refers to its color and as it prefers seclusion.

These are usually 5–20 mm but may grow larger. Males are slightly smaller than females, but both sexes are venomous. The cephalothorax and abdomen may not necessarily be the same color—while typically brown, the color can range between cream-colored to blackish grey. In adults the dark violin marking is well defined, with the neck of the violin pointing toward the bulbous abdomen but this is not diagnostic of this species. These spiders have six eyes which are characteristic to this species and arranged in pairs (dyads), with one anterior and two lateral dyads. They have large leg-to-body ratio with flat bodies, especially in males allowing them to hide in crevices. The female lays the eggs from May to July and it usually takes 1 year for them to reach adult stage. Their life span is usually 1–2 years. They are found in dark, warm, dry basements in both rural and urban homes in endemic areas. They are nocturnal and bites usually occur at night when they feel threatened or trapped [5]. The spider that causes the envenomation is often not identified but can be inferred by observing another in the environment where the bite occurred.
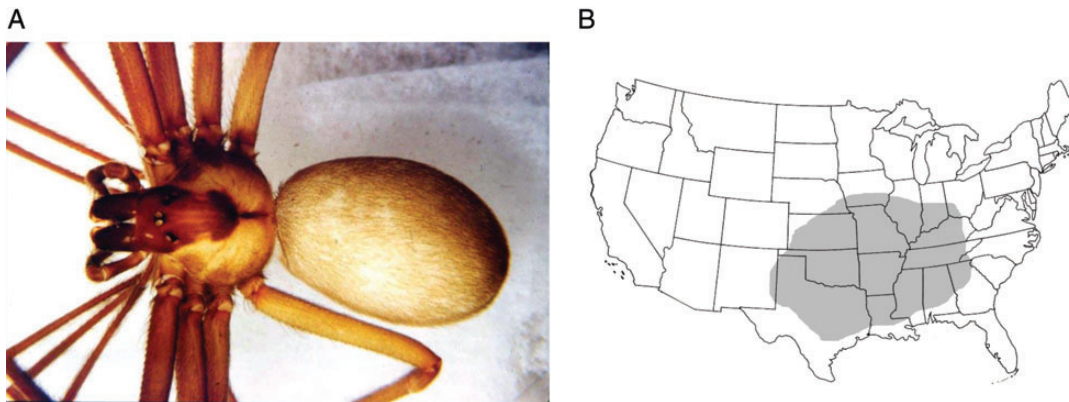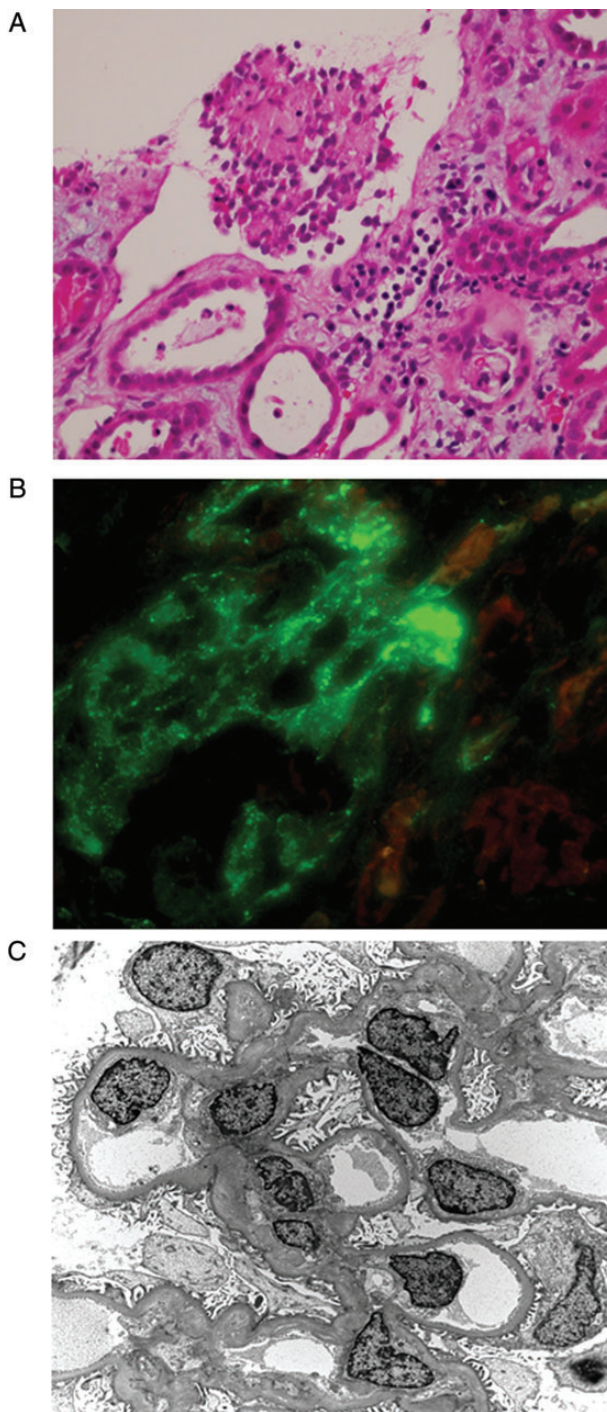

Fig. 1. (**A**) A close-up of a brown recluse spider. (**B**) Geographic distribution of brown recluse spider.

Fig. 2. Features of the renal biopsy. (**A**) H&E staining showing one of the disintegrating glomeruli and the damage to the tubules. (**B**) Deposition of C3 in the mesangium and capillary loops. (**C**) Intact GBM, mild podocyte effacement and mild endothelial edema.

A brown recluse spider bite (BRSB) causes a dermonecrotic lesion which in most cases is restricted to local erythema, pruritus and eschar formation. However, in about 15% of cases, the clinical outcome is more severe and systemic complications can ultimately lead to death [6]. Differences in the clinical outcome have been ascribed to spider gender and age, amount of venom injected and the

victim's age [7]. Female spiders have more concentrated venom estimated to be as much as twice that of the male [8]. The venom of the *Loxosceles* species is a mixture of proteins with electrophoretic mobility in the range of 20–40 kDa. One of the components, sphingomyelinase D, a 32 kDa protein, has biological properties, many of which are seen in systemic loxoscelism such as dermatonecrosis, platelet aggregation and complement-dependent hemolytic activites [9, 10]. Other investigators have identified additional enzymatic activites, including hyaluronidase [11], alkaline phosphatase, esterases, ATPases and a number of small molecules including citric acid, glutamic acid, octopamine, sulfated nucleotides and other nucleotides [12]. In addition, the venom of *Loxosceles* is a potent endothelial agonist and induces E-selectin expression [13]. Furthermore, it stimulates the release of IL-8 and large amounts of GM-CSF. In our case, it is likely that the leukemoid reaction seen with WBC counts peaking at $71.3 \times 10^3/$μL $(71.3 \times 10^9/L)$ were stimulated by the granulocyte-monocyte colony-stimulating factor (GM-CSF). While the mechanism of the direct Coombs-positive hemolytic anemia is not completely understood, it is clear that it was both complement and IgG mediated. This observation has been noted before following *L. reclusa* envenomation [14]. We found no record in the literature of a renal biopsy performed in a patient with AKI following BRSB, so our observations may represent the first documentation of the renal changes. The finding of both 3+ complement and 1+ IgG deposited in the renal glomerulus is intriguing and may represent an 'innocent' deposition since the glomerulus also demonstrated 3+ albumin.

The major renal lesion was felt to be acute tubular necrosis probably from the venom, and the clinical course and resolution was consistent with that view. The damage to the glomerulus also suggested that the venom may have played a role in the observed histological derangements and alterations in the glomerular permselectivity and proteinuria.

Conflict of interest statement. None declared.

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