J. Med. Toxicol.
DOI 10.1007/s13181-015-0485-9

TOXICOLOGY OBSERVATION

Therapeutic Plasma Exchange for Refractory Hemolysis After Brown Recluse Spider (*Loxosceles reclusa*) Envenomation

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Abstract
Introduction The brown recluse spider (BRS) (*Loxosceles reclusa*) envenomation can lead to multiple complications, including hemolysis. We present a case of refractory hemolysis after a BRS bite treated with therapeutic plasma exchange (TPE).
Case Report A 17-year-old female presented with fever, fatigue, and dyspnea. She was diagnosed with sepsis and received intravenous (IV) fluids, inotropic support, and antibiotics. On hospital day 1 she was noted to have skin lesion consistent with a BRS bite and developed hemolysis. Systemic loxoscelism with hemolysis was then suspected and methylprednisolone IV was initiated. She was discharged with a stable HGB on hospital day 3 on oral prednisolone. She was re-admitted 24 h later, with signs of worsening hemolysis. Methylprednisolone was restarted and she was transfused 4 units of packed red blood cells. TPE was initiated due to the refractory hemolysis. Shortly after the TPE session, her clinical and laboratory status improved. She required no further transfusions and was discharged on a steroid taper.
Discussion TPE is an extra-corporeal method to remove substances from the blood by separating plasma from cellular blood components and replacing it with physiologic fluids. TPE has been used for snake envenomation but there are no reports detailing its use for BRS envenomations. Improvement was associated with TPE initiation and may have been due to removal of complement components activated by the spider venom. This report suggests that TPE could be a possible treatment modality for systemic loxoscelism with refractory hemolysis due to BRS envenomation. Further investigation is warranted.

Keywords Total plasma exchange · Brown recluse · Loxoceles reclusa · Spider bite · Hemolysis

This paper has not previously been presented and was not funded.

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Introduction

The brown recluse spider (*Loxosceles reclusa*) is a small hunting spider commonly found in the central and southeastern parts of the USA [1]. Most envenomations are thought to be self-limiting although necrotic arachnidism and systemic loxoscelism can occur [2, 3]. Systemic loxoscelism can result in life-threatening hemolysis and death. Management of brown recluse spider (BRS) bites is primarily supportive. Therapeutic plasma exchange (TPE) is a process by which plasma is separated from cellular blood components and then replaced with crystalloid or donor plasma. It has previously been described for treatment of snake envenomation [4]. There are no prior reports of its use for BRS or other spider envenomations. We report the use of TPE in a case of refractory hemolysis secondary to systemic loxoscelism.

Published online: 23 May 2015

Case Report

A previously healthy 17-year-old female weighing 53 kg presented to the emergency department complaining of fever, fatigue, and shortness of breath for 1 day. Her initial vital signs were as follows: blood pressure 86/45 mmHg, heart rate 110 beats/min, respiratory rate 22 breaths/min and an oxygen saturation of 97 % on room air. Laboratory evaluation was notable for a white blood cell count of 8.6 k/μL (normal 4.5–11 k/μL), hemoglobin 13.9 g/dL (normal 12–15 g/dL), INR of 1.8, a serum lactate of 4.1 mmol/L (normal 0.5 to 2.0 mmol/L), a serum creatinine of 1.15 mg/dL (normal 0.3 to 1.0 mg/dL), and a C-reactive protein of 13.19 mg/dL (normal <1.0 mg/dL). A clean-catch urine analysis demonstrated too numerous to count white blood cells and bacteria in clumps but also showed too numerous to count red blood cells and squamous epithelial cells. A repeat urine specimen was normal the next day. A chest radiograph was normal. She was diagnosed with severe urosepsis and started on ceftriaxone, vancomycin, and gentamicin. Epinephrine was given at 0.04 mcg/kg/min for ionotropic support and she was admitted to the pediatric intensive care unit (PICU). On hospital day 1, she was noted to have a 2×3 cm tender, erythematous, and edematous lesion on her right knee. Initially, this was thought to be cellulitis. Gentamicin and cefriaxone were discontinued and clindamycin 600 mg intravenous (IV) and cefipime 2 g every 8 h were started. All antibiotics were discontinued after an infectious disease consultant disagreed with the diagnosis of cellulitis and felt the wound more concerning for an envenomation. The diagnosis of a probable BRS bite complicated by systemic loxocelism was then made. Repeat labs were consistent with hemolysis with a 2.4 g/dL drop in hemoglobin and a total bilirubin of 2.3 mg/dL (range 0.3–1.2 mg/dL). Blood cultures and urine cultures were negative. Due to the hemolysis, methylprednisolone 1 mg/kg (50 mg) every 8 h was started. Her clinical course appeared to stabilize, and on hospital day 3, she was discharged with a stable hemoglobin of 10.9 g/dL and improved symptoms. She was continued on 20 mg of prednisone orally twice daily for 2 days.

However, less than 24 h after discharge, she was readmitted to the PICU for tachypnea and evidence of hemolysis with a hemoglobin of 9.6 g/dL, a total bilirubin of 5.6 mg/dL (normal 0.3–1.2 mg/dL), a total plasma hemoglobin of 60 mg/dL (normal 0–40 mg/dL), and a lactate dehydrogenase of 462 U/L (normal 100–200 U/L). She had a normal serum creatinine. A chest CT was negative for pulmonary embolism. At that point, the skin lesion on her knee had become indurated with a central bulla and underlying purple discoloration (Fig. 1).

She was found to be direct antiglobulin (DAT) positive for both anti-IgG and complement. She was restarted on methylprednisolone 1 mg/kg (50 mg) every 6 h, but her hemolysis and symptoms continued to progress over the next 12 h. Her hemoglobin declined to 6.1 g/dL while her LDH and total bilirubin rose to 1199 U/L and 8.0 mg/dL. She received 2 units of packed red blood cell (PRBC) transfusions, and methylprednisolone was changed to 1 g daily. However, her hemolysis continued and her hemoglobin level failed to increase.

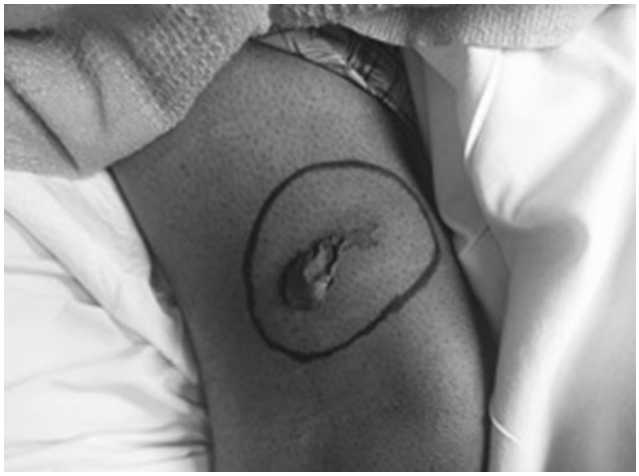

Fig. 1 Skin lesion on her knee with a central bulla and underlying purple discoloration

Six days after presentation and due to the refractory nature of her hemolysis, TPE was instituted along with the transfusion of 2 more unit PRBCs. One volume plasma exchange using 25 % saline/75 % albumin was performed. A total of 3 L of plasma was removed and replaced over 100 min. Shortly after completion of TPE, her clinical condition began to improve. The rate of hemolysis slowed as her hemoglobin stabilized and LDH, total bilirubin, and total plasma hemoglobin decreased.

She was continued on 1 g of methylprednisolone daily and required no further transfusions. She was discharged 4 days after TPE with a 2-week corticosteroid taper starting at 80 mg of prednisone three times a day. Quantitative glucose-6-phosphate dehydrogenase (G6PD) testing done during admission demonstrated low activity at 8.2 U/g hemoglobin (range 8.8–13.4 U/g hemoglobin). She developed a necrotic wound at the bite site and required surgical debridement and complex wound closure 2 months later but otherwise recovered uneventfully.

Discussion

The brown recluse spider (*L. reclusa*) is a 2–3-cm brown spider identifiable by the violin-like marking on its cephalothorax and three pairs of eyes. It is common in a geographical area encompassing much of the Missouri, Tennessee, and lower Mississippi river valleys extending into parts of Texas and Georgia [1].

BRS venom is a complex mixture including multiple enzymes. The main toxic components are thought to be hyalurodinase and sphingomyelinase D [5]. Hyalurodinase

prompts the spread of venom through subcutaneous tissue, and sphingomyelinase D is a cytotoxic enzyme thought to be responsible for complement-dependent hemolysis [6].

Most reported BRS bites result in local erythema, swelling, and pain [7]. In some cases, local dermatonecrosis or necrotic arachnidism can develop, though the true incidence of this complication is not known [2]. Systemic loxoscelism can also occur and is characterized by nausea, vomiting, headaches, fever, abdominal pain, a diffuse, reticular, erythematous rash, and in severe cases, hemolysis, coagulopathy, nephrotoxicity, and death [3]. This patient's clinical course was felt to be consistent with systemic loxoscelism.

Other potential causes of this patient's symptoms and hemolysis were considered. Sepsis was felt to be less likely as no infectious source was identified. Ceftriaxone induced hemolysis was considered but felt unlikely, as the lowest hemoglobin measured was almost 5 days after the first dose of ceftriaxone and it did not improve with cessation of the drug [8]. The other antibiotics this patient received are not typically associated with hemolysis [9].

Diagnosis of a BRS envenomation is difficult and there is no gold-standard test to confirm envenomation. Experts recommend that confirmed diagnosis should entail the collection and identification of the spider at the time of possible envenomation [10]. Otherwise, the envenomation must be considered probable or possible. In this case, the diagnosis of a probable BRS envenomation was made by taking into account the fact that the bite took place in an endemic area, had a wound typical for a BRS bite, and developed two complications (hemolysis and necrotic wound) described with BRS envenomation and there was no other more probable alternative diagnosis.

The appropriate treatment for systemic loxoscelism is unclear and poorly studied. While supportive care with red blood cell transfusions for symptomatic anemia forms the basis of treating these patients, high-dose corticosteroids are sometimes used in an attempt modify suspected complement-mediated hemolysis [11]. While corticosteroids are widely used in other hemolytic conditions, there is no medical literature regarding their efficacy in BRS envenomation. In this case, it is difficult to assess what effect the corticosteroids may have had on her outcome. The patient was initially treated with 1 mg/kg IV of methylprednisolone every 8 h and seemed to stabilize. She was then transitioned to a lower dose of oral corticosteroids which was temporally associated with a rapid worsening in her clinical status. However, even after resumption of high-dose methylprednisolone, she continued to deteriorate. Her mildly depressed G-6-PD activity may have contributed to the severity of her hemolysis.

Other treatment modalities have been attempted in cases of severe hemolysis attributed to BRS envenomation. Urinary alkalization was used in case of a 6 year old with massive hemolysis that survived [12]. Use of exchange transfusion has also been reported [13]. Nance described performing a 2000-mL exchange transfusion to successfully treat a 4 year old with severe systemic loxoscelism with hemolytic crisis.

TPE, also known as plasmapheresis, is an extra-corporeal method to remove substances from the blood. During TPE, plasma is separated from the cellular blood components and then replaced with physiologic fluids, such as albumin or fresh frozen plasma, to maintain oncotic pressure and blood volume. TPE effectively removes antibodies, immune complexes, complement components, and various cytokines [14]. It is widely used to treat conditions such as myasthenia gravis, Guillain-Barré syndrome, and certain autoimmune hemolytic anemias [14]. TPE has been described in the treatment of multiple drug intoxications, including anti-neoplastics, anti-epileptics, and cardiovascular agents [15]. Some report dramatic improvement such as in the case of an iatrogenic cisplatin overdose with severe acute toxicity who demonstrated complete recovery after two rounds of TPE [16]. There are previous reports of using TPE in snake envenomations [4]. Yildirim et al. describe using TPE to treat 16 cases of snake envenomation who did not receive antivenom. They noted statistically significant improvements in multiple laboratory abnormalities and no mortality. There are no prior reports of TPE use in BRS envenomation. While causation cannot be demonstrated from this case report, we did observe an association between initiation of TPE and improvement in this patient's clinical condition. Theoretically, TPE may have removed the BRS venom, resulting in clinical improvement. It is also possible that benefit was seen because the TPE removed complement components which had been activated by sphingomyelinase D as well as from the removal of immunoglobulin G. This hypothesis is further supported by this patient's positive DAT for both IgG and complement, which have previously been observed with BRS envenomation [17]. As there is currently no well-established treatment for severe hemolysis from BRS envenomation, further investigation into the appropriate role of TPE in these cases may be warranted.

Conclusion

This patient developed systemic loxoscelism with refractory hemolysis despite supportive care, corticosteroids, and red blood cell transfusions. Initiation of TPE was associated with an improvement in her clinical condition. Consideration and further investigation of TPE in cases of severe hemolysis from BRS envenomation may be warranted.

Conflict of Interest There are no conflicts to declare.

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