Coombs-Positive Hemolytic Anemia Secondary to Brown Recluse Spider Bite: A Review of the Literature and Discussion of Treatment

David R. Lane, MD; Jeremy S. Youse, BS

GOAL

To understand the potential reactions to a brown recluse spider bite

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the cutaneous reactions encountered with brown recluse spider bites.
2. Explain the cutaneous reactions encountered with brown recluse spider bites.
3. Explore the treatment options for brown recluse spider bites.

CME Test on page 348.

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The bite of the brown recluse spider (Loxosceles reclusa) *typically results in local, dermonecrotic skin lesions. Rarely, these bites may precipitate systemic disturbances of varying severity collectively known as systemic loxoscelism. The more severe systemic alterations attributed to the venom of this arachnid include hemolytic anemia, multiorgan failure, disseminated intravascular coagulation, or even death. Coombs-positive hemolysis associated with brown recluse spider bites has rarely been documented in the literature. We report 2 cases of systemic loxoscelism*

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From the University of Missouri-Columbia, University Health Care. Dr. Lane is Chief Resident in the Department of Dermatology. Mr. Youse is a medical student.

Reprints: David R. Lane, MD, 1 Hospital Dr, MA111, Columbia, MO 65212 (e-mail: lanedr@health.missouri.edu).

in young women associated with severe Coombs-positive hemolytic anemia and systemic symptoms requiring hospitalization. Both patients were treated with aggressive wound care, hematologic monitoring with blood transfusion, and intravenous fluid replacement. Recovery was excellent in both cases. We review the literature and discuss the controversies surrounding the treatment of more severe brown recluse bite reactions.

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The bite of the brown recluse spider, also known as *Loxosceles reclusa*, usually causes a local hemorrhagic lesion characterized by areas of red, white, and blue discoloration.[1] Rarely, the venom from this spider may cause a systemic response characterized by fever, malaise, myalgia, hemolysis, acute renal failure, disseminated intravascular coagulation, or even death. The condition is called systemic loxoscelism and can be particularly dangerous in childhood, when most deaths from loxoscelism occur. The hemolysis in patients with systemic loxoscelism is not completely understood, despite extensive research into the components of this deadly spider's venom.[2-4] Why this venom results in systemic symptoms in some patients and local reactions in others also is not completely understood. This variation in symptomatology likely has to do with the location of the initial spider bite and a possible predisposition of some individuals to environmental red blood cell toxins.

The treatment of necrotic arachnidism is as controversial as the pathophysiology of the hemolysis. No standard of care exists for the more severe or anatomically vital spider bites. Several systemic medications have been tried with extensive anecdotal support, but no large controlled trials have been performed in humans to prove these agents are more effective than aggressive and meticulous wound care. Previous studies have shown that patients treated with early surgery resulted in prolonged healing times and increased negative outcomes compared with patients treated with supportive wound care.[5,6] Patients generally do very well with only supportive measures, which should remain the treatment of choice until larger studies elucidate the role of systemic medications. We report 2 cases of systemic loxoscelism causing a Coombs-positive intravascular hemolysis requiring blood transfusion and review the treatment options of this condition.

Case Reports

Patient 1—A 19-year-old African American woman with a medical history significant only for asthma presented to her primary care physician 2 days after a painless bite from a "brown spider" in her bed. At this initial evaluation, she had a diffuse maculopapular rash with mild systemic symptoms including malaise and arthralgia. No laboratory workups were done, and she was started on a 5-day steroid dose pack.

The patient was seen in our urgent care department 2 days later with documentation of a 2×2-cm ecchymotic area on her right posterior thigh with surrounding erythema and a diffuse maculopapular rash. Her laboratory workup at this time showed a mildly elevated total bilirubin level, mild leukocytosis, anemia with a hemoglobin level of 11.7 mg/dL, elevated reticulocyte count, and normal coagulation profile. She was given intramuscular methylprednisolone 125 mg, acetaminophen for pain, and hydroxyzine for pruritus, with plans for follow-up in urgent care the next day.

The patient did not follow-up until 2 days later, at which time she reported worsening systemic symptoms including nausea, peripheral edema, lymphadenopathy, fever, and dysuria, along with worsening pain and erythema at the bite site. She was febrile, and her anemia progressed when her hemoglobin level fell to 8.3 mg/dL. She was admitted for hematologic monitoring and supportive measures. At the time of admission, her skin examination results were pertinent for a diffuse, faint maculopapular rash and a 3×3-cm necrotic eschar with surrounding erythema (Figure 1).

The day after admission, the patient continued to be febrile, and her hemoglobin level dropped to 6.9 mg/dL. She was transfused with 2 units of packed red blood cells, and the hematology department was consulted to assist with the progressing anemia. The dermatology department also was consulted to assist with wound care and treatment. The hematologist recommended performing an indirect and direct Coombs test. The indirect Coombs test results were negative, but the direct Coombs test results were positive for complement 3 and negative for immunoglobulin G (IgG). The patient's anemia and systemic symptoms continued to progress (hemoglobin nadir level, 5.7 mg/dL), requiring 2 more units of blood. The hematologist recommended starting intravenous steroids to improve the patient's "immunohemolytic anemia secondary to spider bite with positive Coombs test." The patient was started on methylprednisolone 125 mg/d intravenously. Per dermatology's recommendation, wound care was initiated along with elevation and ice to the affected extremity.

The patient's clinical status began to improve on hospital day 4, with absence of systemic symptoms and regression of her lesional erythema. She was

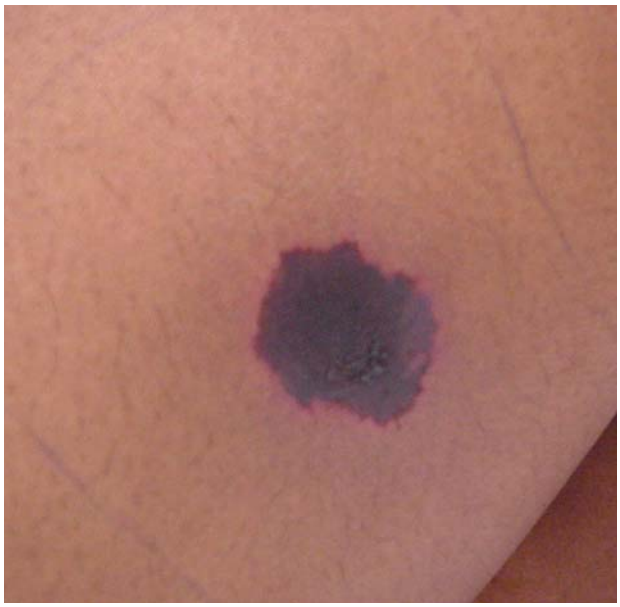

Figure 1. A diffuse, faint maculopapular rash and a 3×3-cm necrotic eschar with surrounding erythema in patient 1.

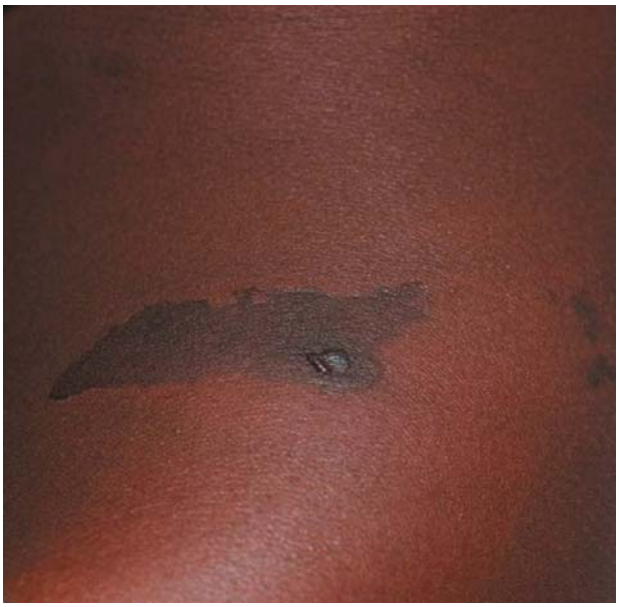

Figure 2. A 5×2-cm necrotic eschar on the left flank of patient 2 with a surrounding area of erythema.

discharged on a quick-taper oral steroid regimen, per the hematologist's recommendation, and was instructed to continue her wound care. At the patient's hospital follow-up visit, her bite site was healing well, and she had no further evidence of anemia.

Patient 2—A 9-year-old African American girl in otherwise excellent health was transferred from an outside emergency department one week after being bitten by "a brown spider" while lying in bed. Initially, the bite was painless, but she later developed swelling and warmth in the area. Due to increased pain, swelling, and blister formation, her primary physician saw her several days later and prescribed an oral cephalosporin for presumed cellulitis. Fever, fatigue, and malaise continued throughout the week. Two days prior to presentation at our hospital, she developed scleral icterus and vomiting.

During the patient's evaluation at the transferring emergency department, her laboratory workup revealed a profound anemia with a hemoglobin level of 5.2 mg/dL, elevated white blood cell count, indirect hyperbilirubinemia, and mildly prolonged international normalized ratio value. Her examination was significant for a tachycardia, holosystolic murmur, scleral icterus, and 5×2-cm necrotic eschar on her left flank with a surrounding area of erythema that was exquisitely tender to palpation (Figure 2). She was immediately admitted for close observation and treatment of her anemia. She was transfused with 2 units of packed red blood cells.

The patient's hemoglobin level rebounded to 8.2 mg/dL on hospital day 2, at which time the dermatology department was consulted for assistance with wound care management. Elevation of the extremity and continuing wound care was recommended, and debridement or systemic therapy was advised against. Results of the patient's direct Coombs test were positive for IgG and negative for complement 3. No specific treatment changes were made based on the Coombs test result.

The patient continued to improve with wound care and hemodynamic support and displayed improved erythema with less tenderness at the bite site after several days of hospitalization. She was sent home on hospital day 4 in improved condition. She was seen by a dermatologist at her follow-up visit, and her eschar was treated with hydrocolloid dressing changes and eventual debridement of the eschar with follow-up occlusive dressings until the lesion was completely healed.

Comment

Brown Recluse-Induced Hemolysis—Brown recluse spider bites are common in the Midwest, Southeast, and south central United States.[7] Although there are more than 70 species of *Loxosceles* found throughout the world, only approximately 15 species inhabit North America, with *L reclusa* being the most common encountered by humans.[8] Patients affected by this malady are often seen by physicians in various specialties, including primary care

providers, emergency physicians, dermatologists, general surgeons, and surgical subspecialists. It is important that physicians in these specialties recognize and treat this condition appropriately.

Although these bites usually cause a local necrotic lesion, sometimes a more serious systemic syndrome, known as systemic loxoscelism, occurs. This can result in high fever, significant intravascular hemolysis, renal failure, disseminated intravascular coagulation, and even death. Although most fatalities have been reported in children, 2 cases of adult deaths have been reported.[9,10]

The hemolytic anemia that accompanies systemic loxoscelism has been only partially described, and the full mechanism by which the venom of the brown recluse causes this syndrome is still a mystery. The prevailing theory for the cause of hemolysis has incriminated the phospholipase sphingomyelin D, an enzyme isolated from brown recluse venom, because of its effect on cell walls in vivo to cause lysis.[11] It was thought that sphingomyelinase disrupted cell membranes either directly or indirectly and resulted in the release of phospholipid-derived substances that bound complement and resulted in tissue hypoxia and necrosis.[12-14] Because such a small amount of venom and toxin actually enter the body after a bite, another mechanism is likely taking place to produce the symptoms involved in systemic loxoscelism. Activation and propagation of the immune system by a toxin in the venom could explain such a reaction.

A study on another member of the *Loxosceles* family, *Loxosceles intermedia*, may help elucidate the factors involved in the overwhelming reaction to the *Loxosceles* venom in some people.[15] In this study, it was found that the sphingomyelinase in the spider toxin did not directly affect glycophorins on red blood cell membranes but instead activated an endogenous metalloproteinase that then cleaved these glycophorins. The authors proposed that the altered glycophorins destabilized the red blood cell membrane, rendering the glycophorins vulnerable for complement-mediated lysis. The authors also observed that the hemolysis-inducing and glycophorin-cleaving activity of this activated metalloproteinase could be transferred from one erythrocyte to another, thereby propagating the hemolyzing response.[15] This type of transfer of sphingomyelinase and metalloproteinase activity between cells has been described before and could explain the overwhelming systemic response of the *Loxosceles* toxin in some individuals.[16]

Historically, most cases of massive hemolysis due to brown recluse bites documented in the literature have been Coombs negative.[17] This also has been the case at our institution until recently.[11] We report 2 cases of life-threatening hemolytic anemia with positive direct Coombs testing in a span of 9 months. These results are a rarity but may help us understand the pathophysiology of systemic loxoscelism. To our knowledge, these are the fifth and sixth reported cases of a Coombs-positive hemolytic anemia from a brown recluse spider bite. The first case was documented by Nance[18] in 1961, but there was no mention of whether complement or immunoglobulin was involved. Eichner[17] reported the second and third cases of Coombs-positive anemia in loxoscelism, with both cases involving complement-mediated hemolysis. The fourth case of Coombs-positive anemia was reported by William et al[9] in 1995, and the Coombs test was positive for both IgG and complement. Our cases affirm that both IgG and complement can be involved in Coombs-positive hemolytic anemia. It is likely that the venom of the brown recluse is able to activate both IgG and complement in predisposed individuals by activation of an unknown endogenous mediator (eg, metalloproteinase) to cause massive intravascular hemolysis. Investigations into which patients may be predisposed to develop this complication are warranted.

Treatment—The treatment of local and systemic brown recluse spider bites also has been a source of controversy over the years. Several treatment regimens, including early and late surgical excision and debridement, systemic steroids, hyperbaric oxygen therapy, cryproheptadine, electric shock therapy, and dapsone, have been anecdotally described in the literature; however, none of these treatments have prospective human trials to back up this anecdotal evidence. With conservative wound management, ice, elevation, and analgesics, almost all patients exhibit a full recovery with minimal scarring that rarely needs surgical revision.[19]

Dapsone has been the most controversial of the treatments for brown recluse bites. Dapsone makes theoretical sense in the treatment of these lesions because of its ability to inhibit polymorphonuclear leukocytes from entering the wound area and causing local destruction. There are many anecdotal reports supporting the use of dapsone for more severe bites, the most famous being the King and Rees[20] case report of a patient with a brown recluse bite of the leg that was seen 24 hours after the bite had occurred. They reported that 2 days after prescribing dapsone 100 mg twice daily along with ice and local wound care, the bite site was pain free with marked reduction in induration and erythema. Their argument was based on an assumption that the lesion "probably would have

developed an indolent ulcer." They supported their use of dapsone with an animal model of guinea pigs that were pretreated with dapsone before being injected with *Loxosceles* venom. The authors reported that pretreated guinea pigs showed a reduction in lesion size at 24 hours compared with those without treatment.[20] The methods of this study have come into question primarily due to the rarity of patients with brown recluse bites pretreated with dapsone. Also, follow-up animal studies have conflicted with the benefit of dapsone for this indication.[21,22]

Although the benefit of dapsone is controversial, the side effects of this medicine are protean and well known. The development of hemolytic anemia has long been attributed to this medication and will occur to some degree in all patients.[23] This predictable hemolysis can sometimes become confused with the direct effects of the brown recluse venom, which can delay definitive diagnosis of the etiology of the hemolysis and expose patients to an unproven drug with multiple toxicities. Severe hemolysis can be expected in patients with glucose-6-phosphate dehydrogenase deficiency; therefore, dapsone is absolutely contraindicated in this patient population.

Methemoglobinemia is another feared side effect of dapsone. Although mostly asymptomatic and usually undetectable, sometimes elevated levels of methemoglobin can cause severe systemic symptoms requiring hospitalization.[24] Unfortunately, it is impossible to predict who will experience this complication because of a lack of simple blood testing such as that available for patients with subclinical glucose-6-phosphate dehydrogenase deficiency. Because of these serious and sometimes common adverse events attributed to dapsone, and the lack of solid evidence to support its effectiveness, there is no place for dapsone in the treatment of loxoscelism at this time.

The role of early surgical excision has changed over the past few decades. Reports prior to 1975 often suggested early surgical excision of bites with grafting as the treatment of choice.[25,26] Since then, multiple reports have shown that early surgical excision often does more harm than good in the treatment of brown recluse bites.[5,6] Early surgical excision is contraindicated because of the rapid spread of the toxin through the wound in the first weeks following a bite. The toxin may continue to spread for at least 4 weeks, which makes demarcation between envenomed and healthy tissue difficult.[27] DeLozier et al[6] suggested that the added surgical trauma from early excision may potentiate the inflammatory response to the brown recluse venom, prolonging healing time.

Conservative debridement may be performed to prevent secondary infection, but surgery should generally be withheld for 4 to 6 weeks. Early local wound care during this time followed by late surgical excision and grafting are more successful than early surgical excision. However, most wounds, if treated with supportive therapy alone, will ultimately heal with minimal scarring.[28] A retrospective study of 149 patients with brown recluse bites showed that nearly half of all bites healed within 2 weeks and only 13% of bites left a visible scar. None of these patients were treated with surgery.[29]

Corticosteroids also have been used extensively for more serious reactions after envenomation from a brown recluse spider, but documentation in the literature is sparse. In a white rabbit model, Jansen et al[30] did not find any treatment value for either intramuscular or intralesional methylprednisolone in the prevention of dermonecrosis after a brown recluse spider bite. Berger et al[31] also concluded that large doses of steroids had no effect on the progression or development of necrotic arachnidism. Despite this evidence, there are many who still advocate the use of steroids for more serious bites and for those associated with systemic symptoms.[32] Given the extensive use of corticosteroids in patients with autoimmune hemolytic anemia, this treatment may be of use in patients with Coombs-positive hemolytic anemia secondary to brown recluse envenomation.[33,34] For this reason, direct Coombs testing in patients with hemolytic anemia due to brown recluse bites could provide useful information in the inpatient management of these patients.

Other treatments also have been reported, including colchicine, hyperbaric oxygen, cyproheptadine, electrical shock treatment, and brown recluse specific antivenin.[7,21,35] Despite early promise, all of these treatments have been met with mixed results in subsequent studies. In one study, the early use of intradermal injection of polyclonal antiloxosceles Fab fragments was shown to attenuate necrosis in an animal model up to 4 hours after envenomation.[36] Unfortunately, it is difficult to predict which patients would benefit from the antivenin. Additionally, the antivenin has to be administered in the first 24 hours after a bite, before most patients are seen by a physician.

In our cases, both patients were young and presented with a recent history of a bite by a brown spider consistent with a brown recluse. They were both systemically ill with a profound hemolytic anemia. They were both treated with aggressive wound management, hematologic monitoring with blood transfusion, and expectant care. Patient 1 was

given intravenous corticosteroids, and patient 2 was treated with aggressive wound management only. It is not known whether the corticosteroids given in our first patient affected her clinical course because both patients experienced a complete recovery. Like other case reports of treatment in brown recluse spider bites, it is difficult to tell what effect, if any, the treatment has on clinical outcome because most patients, even those with serious systemic symptoms, make a complete recovery. This routine excellent outcome with supportive care only suggests that the use of systemic treatment or surgery is unnecessary and exposes the patient to risks of treatments with unproven efficacies.

Conclusion

Brown recluse spider bites usually cause a local dermonecrotic reaction but can cause a serious systemic illness and rarely death. We report the fifth and sixth cases of Coombs-positive hemolytic anemia associated with presumed *L reclusa* envenomation. The first 4 reported cases of Coombs-positive hemolysis were positive for IgG and/or complement. This was confirmed in our cases.

The treatment of loxoscelism is controversial in the literature and in practice. We must keep in mind to "first, do no harm" when choosing treatments for patients with brown recluse bites. Many of the treatments previously described, including dapsone, have only anecdotal support for their use. Others, such as early surgery, have been shown to actually delay healing and worsen outcomes. Patients with brown recluse bites typically do well with conservative management alone and agents such as dapsone and systemic corticosteroids can have serious adverse reactions. It is our view that patients with local dermonecrotic skin lesions should be treated with aggressive wound care only. For patients who develop systemic loxoscelism, hemodynamic support and blood transfusion should remain the mainstay of therapy. Further study is needed to determine the benefits of systemic corticosteroid use in patients with Coombs-positive hemolytic anemia secondary to systemic loxoscelism.

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