Editorial

Systemic Manifestations and Treatment of Brown Recluse Spider Bites

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On page 341 of this issue, Lane and Youse[1] describe 2 patients who developed Coombs-positive hemolytic anemia secondary to brown recluse spider bites. Their report raises several issues worthy of comment. Although the outcome of *Loxosceles reclusa* envenomation is generally good, bites may result in local dermonecrotic reactions. Systemic loxoscelism also may occur. Constitutional symptoms often include myalgia, fever, and malaise. Hemolysis, renal failure, and disseminated intravascular coagulation may occur, and the hemolysis may be dramatic and life threatening.[2,3] *L reclusa* is the brown spider most closely lined to these reactions, but shock also has been reported after a bite from *Loxosceles arizonica*, a related species indigenous to Arizona, southern California, and northwestern Mexico.[4]

The pathogenesis of local and systemic reactions has been only partially elucidated. Neutrophils are the predominant cell type in dermonecrotic lesions, yet the venom does not activate neutrophils directly. It does, however, stimulate release of interleukin 8 and granulocyte-macrophage colony-stimulating factor, which may result in the influx of neutrophils.[5] Sphingomyelinase D is involved in the pathogenesis of local necrotic reactions and may cause hemolysis through a direct effect on red cell membranes.[6] Little venom is present in a bite, and endogenous metalloproteinases may augment the hemolytic response and be responsible for much of the hemolysis.[7] Bite reactions with little necrosis may pose a greater risk of systemic toxicity, as venom may be absorbed more thoroughly when it is not sequestered within the necrotic eschar. It is of interest that the 2 patients described by Lane and Youse[1] developed sizable eschars (3×3 cm and 5×2 cm, respectively). This clearly demonstrates the need for vigilance for systemic reactions in all patients with brown recluse bites.

In the report in this issue, Lane and Youse[1] confirmed earlier findings that both immunoglobulin G and complement are associated with the Coombs-positive hemolytic anemia following brown recluse bites. Both of their patients were treated with local wound care, hematologic support, and intravenous fluid replacement. One also was treated with systemic corticosteroids, and both patients recovered well. When evaluating patients with systemic reactions following brown recluse bites, it is important to note that brisk intravascular hemolysis may be associated with a positive direct Coombs test. Spherocytosis, erythrophagocytosis, and leukoerythroblastosis have been noted in Coombs-positive hemolytic anemia following spider bites.[8] Jaundice also may be associated with sudden massive hemolysis, and a high index of suspicion is required in patients with and without local necrotic reactions.[9]

The treatment of brown recluse bites is controversial. Dapsone has been used, but conclusive evidence of any clinical benefit is lacking. Although the combination of dapsone and antivenin has shown efficacy in an animal model of brown recluse spider envenomation of the eyelid,[10] the delay inherent in starting therapy in clinical practice may negate any benefit from the agents. Well-established risks of dapsone include hemolysis and methemoglobinemia. Dapsone hypersensitivity syndrome (consisting of fever, headache, nausea, vomiting, lymphadenopathy, hepatitis, hemolysis, leukopenia, and mononucleosis) also has been described during treatment of a brown recluse bite.[11] The drug is contraindicated in those with glucose-6-phosphate dehydrogenase deficiency, and testing for the enzyme results in further delays in the initiation of therapy, adding to the complexities of treatment in

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many ethnic groups. In one series, both systemic corticosteroids and dapsone were associated with slower healing, and dapsone was associated with an increased probability of scarring.[12] Of course, selection bias may have had some influence on the outcome, but nonetheless, the results cast further doubt on the usefulness of dapsone.

There is no role for early excision of the site, because this has been associated with prolonged healing times.[13,14] Conservative debridement may be performed after the eschar is clearly defined, and some patients do require skin grafts.

Fortunately, most patients do well[15] and supportive measures are generally all that is required. In a study of 111 patients with suspected brown recluse spider bites, most bites (59%) involved the leg, with 81% of these manifesting central discoloration and 37% demonstrating necrosis.[16] Systemic reactions were noted in 16 patients (14%), and 6 (5%) were admitted to the hospital. Only 3 patients (3%) required skin grafting. Two patients developed signs of hemolysis, one with mild hemolytic anemia and another with mild hemolysis and a mild coagulopathy. One weakness of this review was that only 13 patients (12%) brought the spider to the hospital for identification. Twenty-two (20%) saw a spider at the time of the bite, but a definitive identification was not made. An exclusively clinical diagnosis was made in the remaining 76 patients (68%).[16]

There is evidence that brown recluse bites are overdiagnosed in clinical practice. The reports of bites often outnumber the spiders actually present in a given geographic area. In one study, medical personnel diagnosed 124 brown recluse spider bites in Florida during a 6-year period. In contrast, only 70 *Loxosceles* spiders have been found in Florida over the past 100 years.[17] As the name implies, brown recluse spiders are shy and reclusive. Few bites occur even when spiders are present in significant numbers. In one report, 2055 brown recluse spiders were collected from a currently occupied home during a 6-month period, and at least 400 of these spiders were large enough to have caused envenomation, yet no bites occurred.[18]

The optimal treatment for local reactions remains undetermined, but the preponderance of evidence supports supportive care and monitoring for systemic toxicity. Treatment of systemic reactions is another area of controversy. Systemic corticosteroids are commonly used, but controlled trails are lacking. Corticosteroids are commonly used in immune-mediated hemolytic anemia, and the finding of Coombs-positive hemolytic anemia related in immunoglobulin G and complement in some patients suggests that corticosteroids may be of benefit in at least a subset of patients with systemic reactions following brown recluse bites. It should be noted that 1 of the 2 patients reported by Lane and Youse[1] did well with only supportive care. For the present, the role of corticosteroids in patients with immune-mediated hemolytic anemia remains unclear. The role of corticosteroids in hemolytic anemia that is not mediated by antibody and complement is even less clearly established.

Animal models are important for evaluating possible treatments for envenomation, but clinical trials are the ultimate tests of safety and efficacy. Clinical trials for brown recluse bites are difficult, as bites are uncommon, the spider is often not definitively identified, and there is often a significant delay before therapy is instituted. For the present, clinicians will have to weigh the existing data. For most patients, supportive therapy and observation is all that is indicated.

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