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Brown recluse spider bites in patients with neutropenia: a single-institution experience

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Abstract

Brown recluse spider bites can cause local and systemic signs, including rash, dermonecrosis, edema, hemolysis, and acute kidney failure. These are mostly attributed to sphingomyelinase D, the main toxin. To evaluate the severity of the disease in pediatric patients with and without neutropenia, we retrospectively reviewed records of patients treated at St. Jude Children's Research Hospital between 1970 and 2015 and identified 19 patients who met the inclusion criteria. Variables of interest included the type of underlying illness, presence of neutropenia, number of days of hospitalization, disease signs and outcome of the bite, and treatments administered. We used descriptive statistics to summarize the manifestations and severity of spider bites in patients with and without neutropenia. Six patients experienced pain from the bite, 11 had erythema, 7 developed edema, and 5 had fever. The response to spider bites in neutropenic patients was no milder than that in non-neutropenic individuals. Six patients developed systemic complications. Compared to non-neutropenic patients, neutropenic patients had antibiotics prescribed more often and experienced longer hospital stays. Spider bites do not appear to have a different clinical course in neutropenic patients. Therefore, a conservative approach may be best for these patients, with close monitoring and local wound care.

Keywords

Loxoscelism, leukemia; solid tumors; HIV/AIDS; dermonecrosis; sphingomyelinase D

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1 INTRODUCTION

The venomous brown recluse spider (*Loxosceles reclusa*) poses a health risk to people living in the southeastern and south-central portions of the United States, with more than 1,300 bites being reported in 2013.^{1,2} Bites by this spider can result in cutaneous or systemic forms of loxoscelism. Cutaneous loxoscelism is mild and more common than the systemic condition, and its signs include rash, edema, dermonecrosis, and/or erythema around the bite site.¹ Systemic loxoscelism is much more severe and can cause hemolysis, thrombocytopenia, rhabdomyolysis, and acute kidney failure.^{3–7} In the general population, approximately 1% of people bitten by *L. reclusa* develop systemic loxoscelism requiring hospitalization;² however, in the pediatric population, this percentage is close to 15%.⁸ Cutaneous loxoscelism and its association with neutrophils have been studied previously.^{9,10} *Loxosceles reclusa* venom activates endothelial cells, resulting in the sequestration and on-site degranulation of neutrophils and the release of lytic enzymes from those cells, which could explain why necrosis occurs at the site of an *L. reclusa* bite.¹⁰

Neutropenia, defined as an absolute neutrophil count of less than 1,500 cells/ μ L, is a risk factor for infections.¹¹ Neutropenia occurs frequently in patients receiving cancer care and is caused by cytotoxic therapy or malignant neoplasms affecting the bone marrow.^{11,12} Because the presence of neutrophils was found to be important for the skin manifestation of a brown recluse spider bite,^{9,10} we reviewed the symptomatology of such bites among patients, including those with neutropenia, who were cared for at St. Jude Children's Research Hospital (St. Jude). Here, we describe the characteristics and severity of local and systemic signs of loxoscelism and evaluate the severity of the disease in patients with and without neutropenia. We also describe the approaches used to treat neutropenic patients who have been bitten by brown recluse spiders.

2 PATIENTS AND METHODS

2.1 Study design

This study retrospectively reviewed the medical records of all patients seen at St. Jude Children's Research Hospital between January 1, 1970, and June 15, 2015, in whom a brown recluse spider bite was diagnosed. The study was reviewed and approved by the St. Jude Institutional Review Board.

2.2 Patients

St. Jude is a tertiary referral center for pediatric patients who have hematologic malignant neoplasms or solid tumors or who require a bone marrow transplant. St. Jude also cares for children and young adults with HIV/AIDS or sickle cell disease. Patients who had been bitten by spiders and seen at St. Jude were identified by the Health Information Management team of the Information Services department. Once the medical records of these patients had been obtained, we determined the eligibility of the patients for inclusion in the study based on the presence, before they were bitten, of an underlying disease such as cancer, HIV infection, and/or a hematologic disorder.

2.3 Identification and case definitions

Cases of spider bite were identified by reviewing the medical records coding system for eligible patients, searching for the keyword “venomous spiders.” We used the classification system of Rader et al.¹³ to classify the bites as putative, presumptive, or probable brown recluse spider bites. Under this system, a bite is deemed putative if a patient received a subjective diagnosis after being bitten while in a geographic location outside the known habitat of the brown recluse spider and the lesion lacks features typical of brown recluse spider bites. A bite is presumptive if it occurred in a geographic location within the known habitat of the spider and the lesion exhibits one or more positive examination features. A bite is probable if it occurred in a geographic location within the known habitat of the spider, the lesion exhibits one or more positive examination features, and there are no features indicative of an alternative diagnosis.¹³

The medical records of the identified patients were reviewed for demographic information, underlying medical conditions, receipt of immunosuppressive therapy, the extent and duration of neutropenia, microbiology culture results, diagnostic procedures (biopsies, autopsies, and imaging), the extent of disease, therapy received, and outcome.

Patients who had an absolute neutrophil count of 1,500 cells/ μ L or less within 7 days of being bitten (or at the measurement time closest to 7 days after the bite) were considered to have neutropenia. Neutropenia was further classified as mild (1,000–1,500 cells/ μ L), moderate (500–999 cells/ μ L), or severe (<500 cells/ μ L).¹¹ Patients without previously diagnosed underlying medical conditions and those whose records lacked information on the variables of interest were excluded.

2.4 Statistical analyses

An exact Wilcoxon rank-sum test was used to compare continuous variables, and Fisher’s exact test was performed for categorical variables. All statistical analyses were performed in SAS, Windows version 9.3 (SAS Institute, Cary, NC). A *P*-value of 0.05 or less was considered to indicate significance, and no multiple testing correction was made. All tests were 2-sided unless otherwise specified.

3 RESULTS

We identified 29 St. Jude patients with spider bites. However, 10 of these patients were excluded from the study: 5 because they had no underlying disease at the time they were bitten; 1 because they were bitten before the initial consult for suspected cancer; 2 because their records contained insufficient information for reliable review; and 2 because their records did not include absolute neutrophil counts. Therefore, a total of 19 patients were included in the review. Thirteen of these patients were classified as having a probable brown recluse spider bite (Figure 1); 5 were classified as having a presumptive bite; and 1 was classified as having a putative bite (Table 1).

The 19 patients included in the study were demographically similar, regardless of whether neutropenia was present (Table 2), but had diverse underlying medical conditions typical of the patient population seen at St. Jude. Within our sample, significantly more neutropenic

patients than non-neutropenic patients had recently undergone chemotherapy ($P=0.004$) (Table 1).

Patients with neutropenia reported less bite pain, erythema, and edema than did non-neutropenic patients; however, the differences were not statistically significant. Furthermore, 3 of the patients with neutropenia had fever associated with the bite, whereas 2 patients without neutropenia had fever. There was no significant difference between the 2 groups in the extent of the lesion, erythema, or edema.

Eight of the 19 patients (42%) were admitted to the hospital. Four (50%) of these 8 were neutropenic: 3 were severely neutropenic and 1 was moderately neutropenic. The median length of stay in the hospital was 3 days longer for patients with neutropenia than for those without neutropenia (4.5 days [range, 3–7 days] vs. 1.5 days [range, 1–5 days]), although the difference was not statistically significant ($P=0.14$). Six patients (3 without neutropenia and 3 with neutropenia) developed systemic complications associated with the spider bite (1 had hemolysis and 5 had fever) (Table 1).

Before being bitten, 7 patients (3 with neutropenia, 4 without neutropenia) were already receiving antimicrobial drugs as part of their prophylaxis regimen for neutropenia, *Pneumocystis jirovecii*, and/or *Streptococcus pneumoniae*. After being bitten, a total of 17 patients were receiving antimicrobials (all 5 patients with neutropenia and 12 of those without neutropenia). These antibiotics were given for fever and neutropenia and/or the presence of skin lesions. The antibiotics received by the patients after being bitten were of broad spectrum, as required by immunocompromised patients. The most frequently used antibiotics were vancomycin and clindamycin, which were received by 5 patients each. Eight patients were prescribed 1 antibiotic; 3 patients were taking 2 antibiotics; 3 patients were taking 3 antibiotics; and 3 patients were taking 4 antibiotics. Compared to patients without neutropenia, those with neutropenia were prescribed more antibiotics after being bitten ($P=0.02$).

4 DISCUSSION

We have presented a retrospective review of 19 patients with brown recluse spider bites, 5 of whom were neutropenic. This is the first report of the clinical manifestations and outcomes of spider bites in neutropenic patients. Our study showed that the response to the spider bite in these patients was no milder than that in patients without neutropenia, despite the role of neutrophils in the local reaction to the bite.^{14,15} Because of the neutropenia and the uncertainty regarding the etiology of the dermonecrosis and other skin lesions observed in our patients with spider bites, most of them received antimicrobials.

In our series of 19 patients with local reactions, 6 patients had signs of systemic symptoms (fever and hemolysis). After a brown recluse spider bite, local and systemic signs of illness can develop.^{8,13,16} Systemic or viscero-cutaneous manifestations are reported more frequently in children and possibly depend on a dose effect of the venom, the sex of the spider, the level of sphingomyelinase D (SMD) activity, or other patient-related factors.^{2,3,8,17,18} In our study, we observed hemolysis in 1 patient. Hemolysis is a complication

attributed to the hydrolysis by SMD of the phospholipid sphingomyelin in the membranes of red blood cells,¹⁹ which leads to complement-mediated immune destruction.³ In a series of 6 adolescents who developed acute hemolytic anemia after being bitten by brown recluse spiders, 3 required intensive care but all recovered with no recurrence of hemolysis.³ Other hematologic effects include thrombocytopenia, possibly due to both the direct effect of the venom and the immune system, for which administration of corticosteroids was beneficial.⁴

The components of brown recluse spider venom include alkaline phosphatases, 5'-ribonucleotide phosphohydrolase, hyaluronidase, and sphingomyelinase;^{19,20} however, the key enzyme in producing the necrotic lesion is SMD,¹⁹ which is unique to the *Loxosceles* genus.¹⁹ Patel et al. demonstrated that neutrophils are recruited to the site of a spider bite.⁹ Neutrophils can cause local inflammation, activate platelets, and initiate dermonecrosis.^{6,18} Once a neutrophil has been recruited to the site of inflammation or infection, it can phagocytize and release its lytic granules.¹⁰ Neutrophil participation and the inflammatory response appear to be dependent on an endothelial-cell agonist effect triggered by the venom, leading to an indirect and dysregulated neutrophil activation that is involved in dermonecrosis.¹⁹ The occurrence of this activity was proved by histopathologic findings in animal models²⁰ and biopsies of human patients.²¹ In our study, we found that, despite the role of neutrophils in the pathogenesis of cutaneous loxoscelism, patients with neutropenia had signs and symptoms that were no less severe than those in non-neutropenic patients, indicating that the presence of SMD *per se* might contribute to the characteristic dermonecrosis.

Most of our patients had skin manifestations characterized by erythema and edema, some with a necrotic appearance and fewer with local pain. Brown recluse spider bites are generally painless and only discovered after the fact.²¹ After a bite, cutaneous loxoscelism is manifested by pain starting in the first 8 h, the intensity of which can increase from mild to severe, and a small bite mark may be visible at the site of the bite, with surrounding erythema and pruritus. A vesicular lesion develops 12 to 24 h after the bite, and the "red, white, and blue sign" appears, due to erythema, ischemia, and thrombosis.²⁰ A hemorrhagic vesicle can develop, followed over the next few days by a necrotic lesion with a bluish coloration.¹⁶ An eschar becomes indurated and may detach, revealing a deep ulcer of variable dimensions. The lesion may heal spontaneously after 6 to 8 weeks, or skin grafting may be required.¹⁶ Treatment is supportive, and debridement of necrotic tissue may be required to facilitate healing. None of the patients in our study required a surgical intervention, but because of their underlying diagnosis and the uncertainty regarding the cause of their lesions, 17 of the 19 patients received antibiotics. These were broad-spectrum antibiotics, most of them effective for skin and soft tissue infections and anaerobes. Antibiotic administration might be necessary in any case, because *Clostridium perfringens* has been found in the fangs of spiders, and this pathogen could exacerbate the venom action.²² Therefore, careful study, including cultures for anaerobic pathogens, might be necessary in some situations, especially if the wound is worsening and healing is delayed.

Systemic involvement is much less common than cutaneous involvement and occurs in only a minority of spider-bite cases.²³ The exact frequency and range of clinical manifestations is difficult to establish because most reports of systemic loxoscelism result from presumed

rather than confirmed bites. Systemic involvement is characterized by intravascular hemolysis and renal failure on occasion.¹³ Only 6 of our patients had systemic complications, and these were mild by comparison with the cases of systemic symptoms described in the literature.^{5,7} Given the small number of cases in the present study, we cannot draw any conclusions about systemic manifestations of loxoscelism in our patient population.

All of our patients received symptomatic care and careful daily monitoring of wound evolution. Most of them also received antimicrobials, but none received other treatments, such as dapsone or corticosteroids. Dapsone, corticosteroids, and antibiotics have been used to prevent neutrophil migration to the affected site, decrease the inflammation, and prevent secondary infections;²² however, the use of these therapies has been controversial. For example, in some studies, dapsone made no difference²³ or resulted in an adverse event.²⁴ The use of anti-*Loxosceles* antivenom has also been reported, but this is usually reserved for severe cases of systemic or viscero-cutaneous loxoscelism.²⁵ Systemic envenomation studies in animals and humans have demonstrated that the antivenom neutralizes the deleterious effects of the venom.²⁶ The beneficial effects were seen if the antivenom was applied quickly (within 4 h) after envenomation.²⁷ Most clinical studies have demonstrated a significant delay between the patient being bitten and the presentation of the bite for treatment, and this delay is thought to result in the administration of a specific antivenom being ineffective.²⁸ Experiments in animal models have shown antivenom treatment to be beneficial in terms of reducing the size of the necrotic area when administered up to 24 h after envenomation.²⁶ In some regions of the world, e.g., Brazil and Chile, where loxoscelism is frequent, antivenom therapy has been indicated, but its efficacy is unclear.^{26,29} In a study conducted in Brazil, 237 of 359 patients with spider bites who received intravenous specific polyvalent antivenom 72 h after the bite exhibited less necrosis and ulcer formation when compared to patients who did not receive antivenom.³⁰ Other treatments used are hyperbaric therapy, early excision, and antihistamines.^{6, 8, 31, 32} None of our patients received specific therapy for spider bites, but they did receive a combination of close monitoring, local wound care, and, in some cases, antibiotics. Importantly, given that patients with neutropenia are more closely monitored because of their higher risk of severe infections, it is reasonable that this patient group had longer hospital stays after spider bites when compared to patients without neutropenia. For this same reason, it is also unsurprising that more neutropenic patients than non-neutropenic patients received antibiotics for spider bites.

This study had several limitations: It was retrospective in nature, which limited the quality and quantity of data that we could collect, and our sample size was also small, which limited the power of the study to establish differences between groups. A larger sample size is needed to determine whether the patterns of symptomology (less pain, erythema, and edema) found in this study are significant. The enzymes in the spider venom may play a larger role, locally, than the immune system of the host in determining the severity of the bite. But, the SMD dermal necrosis, the interaction of the SMD with red blood cells,^{8, 19} platelets,⁴ and endothelium;¹⁰ and the stimulation of the immune response explains the systemic effects.⁴ Despite the added role of the immune response in spider venom dermonecrosis,²⁹ we can assume that in our population extra processes intervened including

decrease inflammatory response, delayed wound healing and possibly skin dermonecrosis superinfection.^{22, 33}

5 CONCLUSION

Our findings show that patients with neutropenia who were bitten by brown recluse spiders experienced signs and symptoms that did not vary greatly from those in patients without neutropenia. Although the average length of hospital stay was longer and the number of antibiotics prescribed was higher for patients with neutropenia, these outcomes were probably due to the neutropenia itself and are not attributable to a more severe presentation related to the spider bites. Therefore, the best approach to treatment, even in the neutropenic population, may be the conservative use of close monitoring and local wound care. If skin lesions require the administration of an antibiotic, those covering pathogens that infect skin and soft tissue and/or anaerobes might be indicated.

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Abbreviation Key:

SMD sphingomyelinase D

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FIGURE 1:

A probable brown recluse bite on the distal right leg of a 20-year-old male with rhabdomyosarcoma (Patient 1).

Table 1

Characteristics of patients with brown recluse spider bites

Patient N°	Age (years)	Bite classification*	Sex	Underlying disease	Chemotherapy in preceding 30 days	Location of bite	ANC after bite (cells/ μ L)	Lesion description	Systemic signs
1	20	Probable	M	Rhabdomyosarcoma	Yes	Distal leg	100	Size: 1 cm Vesicle formation, necrosis, pain, erythema White center with surrounding bruising	Fever
2	7	Probable	F	ALL	Yes	Head/neck	6,000	Size: 1 cm Erythema	
3	14	Presumptive	M	ALL	Yes	Knee	1,800	Erythema Dark center	
4	17	Probable	F	APL	Yes	Proximal leg	1,100	Erythema, vesicle formation Red in color	
5	21	Presumptive	F	HIV/AIDS	N/A	Distal leg	2,100	Edema, pain, swelling	
6	7	Probable	M	AML	Yes	Proximal arm	700	Erythema Red in color	
7	7	Presumptive	M	Neuroblastoma	No	Not specified	2,100	Pink in color	
8	3	Probable	F	ALL	Yes	Distal arm	100	Erythema, swelling, edema Red in color	Fever
9	4	Probable	F	Sickle cell disease	N/A	Distal arm	4,200	Size: 5 cm Pain	
10	18	Putative	M	HIV/AIDS	N/A	Distal leg	2,550	Swelling	
11	11	Probable	F	Sickle cell disease	N/A	Distal arm	10,700	Size: 3 cm Erythema, edema, pain, swelling Dark grey with surrounding red color	Hemolysis
12	7	Probable	M	Medulloblastoma	Yes	Distal arm	0	Pain, erythema, swelling	Fever
13	14	Presumptive	F	ALL	None	Distal leg	3,300	Erythema, pain	
14	14	Probable	F	Sickle cell disease	N/A	Proximal arm	9,500	Edema, swelling	
15	27	Probable	F	Non-Hodgkin lymphoma	None	Proximal leg	4,000	Erythema Yellow center	Fever
16	33	Probable	M	APL	None	Trunk	5,400	Size: 3 cm Necrosis	
17	22	Probable	M	Synovial sarcoma	None	Proximal leg	5,300	No description	
18	5	Probable	F	Retinoblastoma	None	Knee	2,660	Size: <1 cm Hyperpigmentation	
19	15	Presumptive	M	Aplastic anemia	None	Proximal leg	1,558	Size: 1 cm Erythema, edema, swelling, pus draining, necrosis	Fever

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Patient N°	Age (years)	Bite classification*	Sex	Underlying disease	Chemotherapy in preceding 30 days	Location of bite	ANC after bite (cells/ μ L)	Lesion description	Systemic signs
Black in color									

Abbreviations: ANC = absolute neutrophil count; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; APL = acute promyelocytic leukemia; N/A = not applicable

* Definition follows that of Rader et al.¹³

Table 2

General characteristics of St. Jude Children's Research Hospital patients with spider bites

	No neutropenia n = 14 (%)	Neutropenia n = 5 (%)	P-value
Sex			0.63
Female	8(57.1)	2(40.0)	
Male	6(42.9)	3(60.0)	
Age(years)			0.83
<5	1(7.1)	1(20.0)	
5 to <10	3(21.4)	2(40.0)	
10 to <15	4(28.6)	----	
15 to <20	2(14.3)	1(20.0)	
20 to <25	3(21.4)	1(20.0)	
25	1(7.14)	----	
Race			0.13
Black/African American	6(42.9)	----	
White	8(57.1)	5(100.0)	
Ethnicity			1.00
Hispanic/Latino	2(14.3)	----	
Non-Hispanic/non-Latino	12(85.7)	5(100.0)	
Underlying diagnosis			0.48
Hematologic disorder (n = 12)	9(64.3)	3(60.0)	
Malignant	6(66.7)	3(100)	
Non-malignant	3(33.3)		
Solid tumor (n = 4)	3(21.4)	1(20.0)	
Brain tumor (n = 1)	----	1(20.0)	
Infectious disease (n = 2)	2(14.3)	----	
HIV/AIDS	2(100)	----	
Cancer treatment in preceding 30 days			0.004
Chemotherapy	2(14.3)	5(100.0)	
None	7(50.0)	----	
Not applicable (non-malignant disease)	5(35.7)		