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Systemic Loxoscelism Confirmation by Bite-Site Skin Surface ELISA:

This case illustrates the most common symptomatic effect in systemic loxoscelism-hemolytic anemia

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Abstract

We report here a case of systemic loxoscelism, confirmed by bite-site skin surface swab. Features of systemic loxoscelism present in this case included debilitating symptoms, a classic local bite-site reaction, hemolysis causing loss of approximately 15% of the blood volume within 72 hours, and a symptomatic exanthem. A skin surface ELISA test was used to confirm the presence of venom. This test enables confirmation of cases of loxoscelism for which no spider is found.

Systemic Loxoscelism: Case Presentation

A 16-year-old male presented with a 3-day history of a suspected spider bite. While cleaning a garage, he felt a painless sensation in the subaxillary area. Shortly thereafter, he brushed a "large brown spider" off his head. The spider was never retrieved. Within hours, he noticed a papule in the subaxillary area. About 7 hours later, he had malaise, lightheadedness, headache, felt "hot all over," "shaky," and "nearly passed out." He was admitted to his local hospital with a diagnosis of a suspected spider bite and "urinary tract infection." On admission to the regional pediatric referral hospital three days later, he had moderate distress, scleral icterus, abdominal pain and a generalized, pruritic exanthem described as scarlatinaform. In the left T5 subaxillary area, he had a grayish 2×2 cm area of pallor, with an adjacent area of ecchymosis, 3 cm by 1.5 cm displaying gravitational spread, and a painful area of erythema extending over most of the lateral chest. The erythema, pallor and ecchymosis together comprise the "red, white and blue" sign.[1] A 1 cm central intact bulla was present. A smaller (3 mm) vesicle was present just anterior to this area. Lymphadenopathy was absent. This case presentation, using the "putative, presumptive, probable, documented" systems of Sams et al[1], was consistent with a probable brown recluse spider bite.

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Disclosure
None reported.

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Abnormal laboratory values, at the first and second admissions, on the first and fourth day of illness, respectively, showed a fall in hemoglobin/hematocrit and platelets as well as a rise in bilirubin and transaminases, summarized in table 1. The urine on the second admission had only 3–10 RBCs per high-powered field but 4+ urobilinogen, indicative of extravascular hemolysis. The urine and blood cultures were all negative. Hematologic coagulant indices were normal except for the D-dimers, which were 1.0–2.0 μg/mL (normal < 0.5 μg/mL).

The lesion was swabbed for 30 seconds using a cotton swab dipped in saline. An ELISA was performed as noted in Stoecker et al, using venom-affinity-purified polyclonal antibodies.[2] A horseradish peroxidase assay determined that 0.1898 ± 0.015 picogram (189.8 ± 15 femtograms) of venom was present in the sample well, significantly above assay background. Swab samples taken from a number of other types of skin lesions were negative.

The patient received intravenous high-dose corticosteroid therapy- a loading dose of methylprednisolone 1 mg/kg, then 0.5mg/kg IV q6h for 3 days. On day 4 after envenomation, this was reduced to 0.25mg/kg IV q6h for one day, and on day 5 reduced again to 0.25mg/kg IV twice daily for one day, and then stopped on day 6 after envenomation, the day of discharge. The patient recovered without sequelae.

Discussion

According to Anderson, the current medical literature on loxoscelism is deficient, as most clinical cases are published without indisputable evidence of an actual brown recluse spider bite.[3] A proven case was defined by Anderson[3] as a case with a “spider found in immediate proximity to bite”, and by Sams *et al*[1] as “spider found after bite, identified by qualified person, typical lesion, typical clinical course.” As the spider is identified in only 7–14% of putative spider bite cases[4, 5], the remaining 86–93% of cases cannot meet either the Anderson or Sams benchmarks for proof. In all 8 fatal cases of loxoscelism reported in the medical literature, no spider was found.[1] In one Brazilian series of 13 cases of systemic loxoscelism, no spider was found in any of the cases.[5] In a fatal St. Louis, Missouri case of systemic loxoscelism in 2008, it was reported that no spider was found.[6] An emergency room physician, commenting on cases without an identified spider, said “there is no way to confirm a diagnosis of a recluse spider bite.” [6] The confirmation of *Loxosceles* venom by ELISA presented in this case provides an alternate method of confirmation for cases of systemic loxoscelism for which no spider is found.

This case illustrates the most common symptomatic effect in systemic loxoscelism- hemolytic anemia. In this case, extravascular hemolysis was confirmed, although intravascular hemolysis can occur as well.[7] Although the patient reported here had a drop in hemoglobin of about 15%, rarely, lysis of 70% of the red blood cell mass can occur.[3]

Hemolysis and associated findings may develop within hours or may develop insidiously and may not be appreciated until 48–96 hours post envenomation. Hemolysis almost always occurs within first 96 hours post-bite but may be difficult to detect. It rarely may occur or reoccur 7–10 days post-envenomation. Hemolysis usually persists for 4–7 days, rarely longer. Hemolysis may be “intravascular, “extravascular,” or, often, a combination of both. Intravascular hemolysis is easy to diagnose once free hemoglobin is seen in the serum/ plasma or urine. However extravascular hemolysis can not be readily detected in either the blood or urine but rather occurs in the endothelial reticulum system in locations such as the spleen & lymphatic system. LDH elevation and sometimes urine urobilinogen and/or bilirubinuria help determine pure extravascular hemolysis. Otherwise, extravascular

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hemolysis can only be determined when Hb/Hct are continually decreasing without an obvious source of blood loss.

Other laboratory tests for hemolytic anemia may be used to screen for hemolysis. At Kansas City Children's Mercy Hospital, we sometimes use the plasma free hemoglobin (free hemoglobin, PFHb). This provides a direct and quantitative measure of intravascular free hemoglobin and is quite sensitive in detecting intravascular hemolysis. The problem with PFHb is that traumatic drawing technique of the blood specimen can lead to false positives. Serum haptoglobin is an alternative test used for intravascular hemolysis but is not a direct quantitative hemoglobin measure.[8] A reticulocyte count would not be useful early in the case when clinical decisions are needed, due to the delay in reticulocyte elevation. Systemic loxoscelism can uncommonly lead to coagulopathy and multiple organ system failure.[3, 7,9,10] Other secondary effects include sepsis, necrotizing fasciitis and shock.[3, 9, 10]

The high-dose corticosteroid therapy used in this case has been advocated for systemic loxoscelism [1, 3, 9–13], but this has not been subjected to a double blind controlled clinical study. The consensus of a number of reviews is that corticosteroids are not recommended for cutaneous loxoscelism but are indicated for systemic loxoscelism with hemolysis.[1, 3, 9–13] Corticosteroids should ameliorate hemolysis since it is auto-immune in origin, whether or not the Coombs antiglobulin antibody test is positive. The patient should be loaded with 1–2mg/kg IV methylprednisolone IV push (IVP) and maintain every 6 hrs with 0.5–1mg IVP (no maximum). After several days of systemic corticosteroid therapy, expect a significant elevation in WBC to as high as 30,000 per μL. Treat low hemoglobin with appropriate transfusion of packed red blood cells as necessary. Do *not* administer fresh frozen plasma or cryoprecipitate as complement in the liquid will further stimulate hemolysis. A reticulocyte response occurs about 3–4 days after onset of hemolysis, even following RBC transfusion(s).

Dapsone, a sulfone with leukocyte inhibition properties, has been advocated by both case reports and some animal studies of brown recluse bites.[1, 14–16] Although dapsone has been recommended [1] for cutaneous loxoscelism in which the area of necrosis exceeds 1 cm^2, some animal studies have shown no benefit from this treatment.[17, 18] Note that dapsone is not advocated for systemic loxoscelism and is only used in cutaneous loxoscelism after testing for G6PD deficiency is performed.[1] Dapsone can cause hemolytic anemia and methemoglobinemia of varying severity, complicating the hemolysis associated with brown recluse spider bite, with potentially fatal results.

Specific loxoscelism antivenom therapy has also been advocated for systemic loxoscelism in South America [9, 11], but this intervention also lacks a double blind controlled study in humans and it is not available in the US. Some observers have expressed doubts about its real capacity to neutralize local and systemic effects of the envenomation and the ideal period for its administration. [9, 14] The typical delay between envenomation and treatment may reduce effectiveness. De Almeida et al have reported that anti-sphingomyelinase neutralization therapy better neutralizes the effects of *L. laeta* and *L. intermedia* venom than the anti-whole venom therapy currently in use in South America.[19] For studies of these and other systemic loxoscelism interventions, a test for presence of venom could serve to identify candidates for studies, enabling better evaluation of effectiveness.

Conclusion

The case presented here illustrates the essential features of systemic loxoscelism—debilitating symptoms, a classic cutaneous bite-site reaction with a red, white and blue sign, a large, tender erythematous area, no lymphadenopathy, significant hemolysis, and a

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symptomatic exanthem. With adequate hydration and close attention to hematologic, electrolyte and renal status, this case and most similar cases have had a good outcome. [2, 3–6, 8,9,11]

The venom affinity-purified version of the ELISA used in our laboratory, improved over the previous non-affinity-purified version of the ELISA reported[2] in 2006, has been able to detect venom in many cases scored as "probable" on the scale of Sams.[1] For systemic loxoscelism, in cases such as this when no spider is found, the skin surface swab ELISA test may provide a useful confirmation of the presence of *Loxosceles reclusa* venom.

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Table 1

Brown recluse spider bite confirmed by ELISA testing. Laboratory tests on 1st and 4th day of illness.

Laboratory Test	1st day of illness	4th day of illness
Hemoglobin	16.2 gm/dL	13.8 gm/dL
Hematocrit	45 %	37.6%
Platelets	271,000/mm^3	166,000/mm^3
White blood cell count	13,900/μL	5,500/μL
Alanine transaminase (ALT/SGPT)	19 (5–50) U/L	50 (5–50) U/L
Aspartate aminotransferase (AST/SGOT)	24 (12–50) U/L	62 (12–50) U/L
Alkaline Phosphatase	73 (50–130) U/L	65 (50–130) U/L
Total bilirubin	1.7 (0–1.2 mg/dL)	6.9 (2.1 direct (0–0.4 mg/dL)
Urine RBCs	Not reported	3–10/HPF
Urine uroblilinogen	Not reported	4+