

## Uncommon differential diagnosis of a breast ulcer: a case study

**Introduction:** Spider bites are common worldwide. Frequently symptoms resolve without any adverse outcome, but in rare cases the bite can cause severe morbidity. The most typical presentation of Mediterranean recluse spider (*Loxosceles Rufescens*) bite is a dermatonecrotic lesion of the skin (skin loxoscelism). When the only manifestation of a spider bite is an ulcerated skin lesion, clinical suspicion and differential diagnosis strongly depend on its site. We present the case of an ulcerated wound of the breast, diagnosed as a Mediterranean recluse spider bite.

**Case presentation:** A 79-year-old woman presented a 10cm-wide soft tissue ulceration of her left breast. At first, the diagnostic hypothesis of an ulcerated cancer was ruled out. Two family members revealed a recent history of Mediterranean recluse spider bite and the same clinical diagnosis was made for our patient. A wide excision was

performed, with complete resolution of symptoms.

**Discussion:** No specific diagnostic criteria for spider bites are available. Diagnosis is usually clinical. Skin loxoscelism could be easily mistaken for cellulitis, various types of skin infections, cutaneous anthrax, vasculitis, scorpion sting, pyoderma gangrenosum, erythema migrans of Lyme disease or prurigo nodularis. A thorough anamnestic interview is fundamental to raise the diagnostic hypothesis. When possible, a biopsy is recommended and it is extremely important when the ulcer can mimic a cancer, as is the case in breast tissue.

**Conclusion:** We recommend a wide excision of the wound after failure of conservative treatment, in order to obtain local control and to perform histological examination on a more representative specimen.

**Declaration of interest:** The authors have no conflicts of interest to declare.

**breast • cancer • cellulitis • differential diagnosis • excision • spider • ulcer • wound • wound healing**

Spider bites are common worldwide. In some cases targets do not even realise they have been bitten. Frequently symptoms resolve quickly without any adverse outcome, but in extremely rare situations, spider bites can trigger severe morbidity and lead to death.<sup>1</sup>

The Mediterranean recluse spider (*Loxosceles Rufescens*), also known as the brown recluse or fiddleback (violin) spider, is a poisonous spider of the *Loxosceles* genus, which is widespread in the Mediterranean area.<sup>2</sup> It belongs to the Sicariidae family and it is a medium-small-sized, six-eyed brown-coloured spider, with a violin-shaped mark on the dorsum of the cephalothorax.<sup>3</sup> It is a nocturnal, non-aggressive spider that prefers older, dark and isolated buildings like garages and attic spaces, but it can nestle into closets, boxes and clothing.<sup>4,5</sup> Its bite is mostly painless and occurs while sleeping. The venom of the Mediterranean recluse spider is composed of proteolytic enzymes, low molecular weight proteins and non-enzymatic polypeptides able to cause dermatonecrotic lesions of the skin. This is actually

the most typical clinical presentation of its bite (skin loxoscelism). Frequently the skin manifestation is a painful circular wound surrounded by a whitish ring and a blush pink area; in other cases the onset is characterised by vesicles or bullae with surrounding erythema in the first hours, which then usually lead to a cutaneous necrosis. In extremely rare cases, skin necrosis spreads into subcutaneous tissues, possibly leading to systemic toxicity. Often, the patient develops fever, rash, myalgia and arthralgia, and rarely, in severe forms, shock, renal failure and disseminated intravascular coagulation.<sup>5</sup>

**Francesca Combi,<sup>1,2</sup> MD\***; **Simona Papi,<sup>2</sup> MD**; **Denise Marchesini,<sup>2,3</sup> MD**; **Alessia Andreotti,<sup>2</sup> MD**; **Anna Gambini,<sup>2</sup> MD**; **Enza Palma,<sup>2</sup> MD**; **Giovanni Tazzioli,<sup>2</sup> MD**

\*Corresponding email: francesca.combi@unimore.it; francescacombi@msn.com

**1** PhD Clinical and Experimental Medicine, University of Modena and Reggio Emilia, Italy.

**2** Division of Breast Surgical Oncology, Department of Medical and Surgical, Maternal-Infantile and Adult Sciences, University Hospital of Modena, Italy.

**3** General Surgery Residency Program, University of Modena and Reggio Emilia, Italy.

When the only manifestation of a spider bite is an ulcerated skin lesion, the clinical suspicion and differential diagnosis strongly depend on the site of the bite.

We present the case of an ulcerated wound of the breast for which a Mediterranean recluse spider bite could have been a plausible cause.

### Case presentation

A 79-year-old woman with no significant familial history, was referred to the Division of Breast Surgical Oncology of the University Hospital of Modena (Italy) because of the appearance of a wide soft tissue ulceration of her left breast, in the lower-inner quadrant. Her past medical history was significant for diabetes, hypertension and pacemaker implantation for symptomatic atrioventricular (AV)-block. No allergies were reported. The patient gave written informed consent for publication of her details, including photographs.

The physical examination showed a 10cm ulcerated wound, extending to the breast tissue of the left lower-inner quadrant, surrounded by a blush pink area (shown in Fig 1).

We first considered the diagnostic hypothesis of an ulcerated breast cancer. The patient underwent a radiologic assessment with bilateral mammography and ultrasound that did not reveal any pathological finding. The diagnostic procedure was completed by performing a 6mm punch-biopsy, which only revealed the presence of fibrous-inflammatory tissue, without any evidence of carcinoma. A microbiological examination on multiple swabs was positive for a *Staphylococcus Aureus* infection, for which the patient underwent target antibiotic therapy with amoxicillin and clavulanic acid (3g per day for six days). The local clinical situation did not improve after the therapy and the wound kept expanding. After having a negative control swab, we applied a negative-pressure wound therapy (PICO system, Smith+Nephew, UK), that did not substantially modify the lesion after two weeks.

After anamnestic questioning, the patient reported that two weeks before the onset of the ulcer she suffered from an itching sensation of the site, with no simultaneous pain, redness or swelling. One month before, her daughter and cohabitant showed the typical circular superficial lesion on the lower limbs and the hypothesis of a Mediterranean recluse spider bite was raised.

The surgical team finally decided to treat the patient

Fig 1. Left breast skin loxoscelism



with a wide lumpectomy, designed to excise all the necrotic area (shown in Fig 2). A tubular drain was placed. The specimen was sent for histology, which confirmed the diagnosis of dermatonecrotic ulceration with clear margins. The patient was referred to our outpatient service for local dressing once a week and drain removal seven days after surgery. The scars healed regularly as shown in Fig 3.

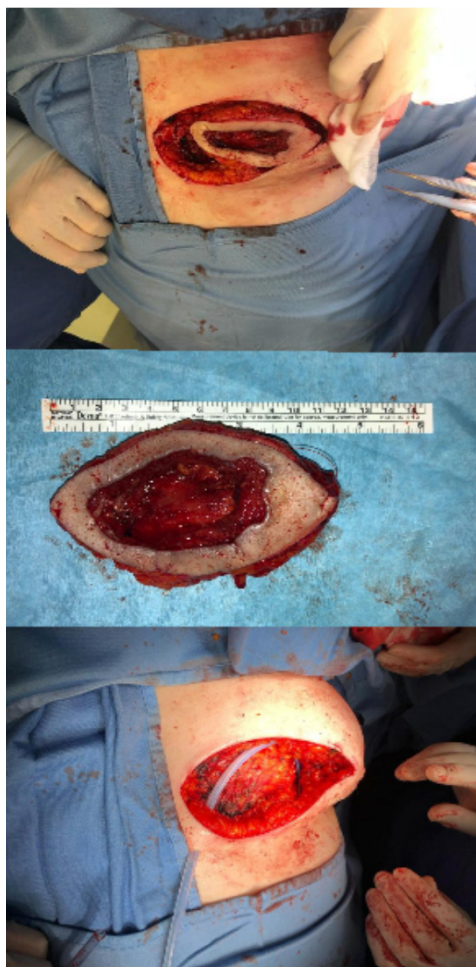
### Discussion

As things stand, no specific diagnostic criteria for spider bites are available. In previous literature, several studies have approached this question<sup>6</sup> and four points have been identified, that allow turning a suspected diagnosis into a more specific diagnosis:

- The spider must have been observed while biting
- The spider must have been captured while biting or immediately afterward
- An expert has identified the spider
- Symptoms and clinical course must agree with the species.

Approaching an extending ulceration of the breast, we first ruled out the oncological origin.

After that, the differential diagnosis was hard and only the fourth of the above-cited criteria was found in our case report.

**Fig 2.** Surgical excision of the ulcerated lesion**Fig 3.** Left breast two weeks after surgery

especially to sphingomyelinase D (SMaseD), a deleterious enzyme producing choline to generate ceramide-1-phosphate from sphingomyelin, or lysophosphatidic acid from lysophosphatidylcholine (substrate for enzymes found in cytoplasmic cell membranes), with the result of a profound alteration of the lateral structure and morphology of the target membranes, until their destruction.<sup>9-11</sup>

Diagnosis is usually clinical. Our immune system produces IgG antibodies that cross-react with the toxin of the venom, but they are completely nonspecific, since they appear also in the presence of the venom of other arachnids. Diagnostic immune assays are not totally reliable: an enzyme-linked immunosorbent assay (ELISA) for *Loxosceles Rufescens* exists, but it is not yet part of the diagnostic protocols.<sup>6</sup>

Treatment options are controversial and there are no guidelines. Several indications are found in the literature: cleaning and disinfecting the bite site and applying cold gauze to reduce the inflammation and risk of infection; symptomatic therapy (analgesic to reduce pain, antihistamines to relieve itching and systemic corticosteroids to decrease inflammation and prevent its spread). Antibiotic therapy can be useful to treat secondary or systemic infections. Topical tetracycline has been recommended in some previous reports.<sup>12,13</sup> Anti-venom administration is the exact treatment for loxoscelism but it is not available worldwide and the delay between bite and diagnosis makes the effectiveness questionable.<sup>14</sup> Surgical treatment and debridement are restricted to severe cases that can require a multiple-stage reconstruction and skin graft.<sup>15</sup>

Ongoing studies on monoclonal antibody fragments targeting venom toxins will potentially offer a safe and

In the literature four categories of loxosceles bites are described:

- Unremarkable (local damage and self-healing)
- Mild (erythema, itch and a slight lesion)
- Dermonecrotic (the typical necrotic skin lesion)
- Systemic or viscerocutaneous.<sup>7</sup>

In contrast to most spiders' venoms, which rely on neurotoxic compounds,<sup>8</sup> the venom of *Loxosceles* is different in molecular composition, often containing proteins, enzymes and nonenzymatic polypeptides. The most important is a family of toxins, the phospholipases-D (PLDs), that trigger most of the major clinical symptoms of loxoscelism, such as dermonecrosis, thrombocytopenia, haemolysis and acute renal failure. The main cause of human skin necrosis is linked

effective treatment.<sup>16</sup>

The clinical manifestations of loxoscelism could be easily mistaken for cellulitis, various types of skin infections, cutaneous anthrax, vasculitis, scorpion sting, pyoderma gangrenosum, erythema migrans of Lyme disease or prurigo nodularis.<sup>12,17,18</sup>

Even if skin loxoscelism is quite rare, we recommend considering its manifestation in the differential diagnosis of ulcerated skin lesions. In this case description, a thorough anamnestic interview has been

fundamental to raise the hypothesis of this diagnostic entity. When possible, obtaining a bioptic specimen is recommended<sup>6,19</sup> and it is extremely important when the ulcer can mimic the onset of a neoplastic disease, as is the case in breast tissue.

We recommend considering a wide excision of the wound after failure of conservative treatment, in order to obtain local control of the disease and to perform histological examination on a more representative specimen. **JWC**

#### References

- 1 Isbister GK, Gray MR. A prospective study of 750 definite spider bites, with expert spider identification. *QJM* 2002; 95(11):723–731. <https://doi.org/10.1093/qjmed/95.11.723>
- 2 Swanson DL, Vetter RS. Loxoscelism. *Clin Dermatol* 2006; 24(3):213–221. <https://doi.org/10.1016/j.clindermatol.2005.11.006>
- 3 Anwar S, Torosyan R, Ginsberg C et al. Clinicopathological course of acute kidney injury following brown recluse (*Loxosceles reclusa*) envenomation. *Clin Kidney J* 2013; 6(6):609–612. <https://doi.org/10.1093/ckj/sft111>
- 4 Isbister GK, Fan HW. Spider bite. *Lancet* 2011; 378(9808):2039–2047. [https://doi.org/10.1016/S0140-6736\(10\)62230-1](https://doi.org/10.1016/S0140-6736(10)62230-1)
- 5 Borkan J, Gross E, Lubin Y, Oryan I. An outbreak of venomous spider bites in a citrus grove. *Am J Trop Med Hyg* 1995; 52(3):228–230. <https://doi.org/10.4269/ajtmh.1995.52.228>
- 6 Nentwig W, Pantini P, Vetter RS. Distribution and medical aspects of *Loxosceles rufescens*, one of the most invasive spiders of the world (Araneae: Sicariidae). *Toxicon* 2017; 132:19–28. <https://doi.org/10.1016/j.toxicon.2017.04.007>
- 7 Vetter RS. Spiders of the genus *Loxosceles* (Araneae, Sicariidae): a review of biological, medical and psychological aspects regarding envenomations. *J Arachnol* 2008; 36:150–163. <https://doi.org/10.1636/RSt08-06.1>
- 8 Nentwig W. Spider ecophysiology. Springer Science & Business Media; 2013.
- 9 Rivera I-G, Ordoñez M, Presa N et al. Sphingomyelinase D/ceramide 1-phosphate in cell survival and inflammation. *Toxins* 2015; 7(5):1457–1466. <https://doi.org/10.3390/toxins7051457>
- 10 Gremski LH, da Justa HC, da Silva TP et al. Forty years of the description of brown spider venom phospholipases-D. *Toxins* 2020; 12(3):164. <https://doi.org/10.3390/toxins12030164>
- 11 Dias-Lopes C, Neshich IAP, Neshich G et al. Identification of new sphingomyelinases D in pathogenic fungi and other pathogenic organisms. *PLoS ONE* 2013; 8(11):e79240. <https://doi.org/10.1371/journal.pone.0079240>
- 12 Shahi M, Shahi A, Khademi Z et al. Loxoscelism: a case report from Bandar Abbas in south of Iran. *Hormozgan Med J* 2014; 18:7
- 13 King LE. Common ground?: Tetracyclines, matrix metalloproteinases, pustular dermatoses, and loxoscelism. *J Invest Dermatol* 2007; 127(6):1284–1286
- 14 Pauli I, Puka J, Gubert IC, Minozzo JC. The efficacy of antivenom in loxoscelism treatment. *Toxicon* 2006; 48(2):123–137. <https://doi.org/10.1016/j.toxicon.2006.05.005>
- 15 Mikkelsen J, Schmidt G, Holmgaard R. Reconstructive considerations following a necrotic spider bite on the face: a case report. *Int J Surg Case Rep* 2017; 32:76–79. <https://doi.org/10.1016/j.ijscr.2017.02.023>
- 16 Karim-Silva S, Becker-Finco A, Jiacomini IG et al. Loxoscelism: advances and challenges in the design of antibody fragments with therapeutic potential. *Toxins* 2020; 12(4):256. <https://doi.org/10.3390/toxins12040256>
- 17 Schwartz RA, Steen CJ. Chapter 210. Arthropod bites and stings. In: Goldsmith LA, Katz SI, Gilchrist BA et al. (Eds). *Fitzpatrick's dermatology in general medicine* [Internet]. 8th ed. New York, NY: The McGraw-Hill Companies; 2012. <https://tinyurl.com/pae32j7> (accessed 27 May 2020)
- 18 Paolino G, Vaira F, Mercuri SR, Di Nicola MR. Fast recognition of *Loxosceles rufescens* in Italian spider bites to avoid misdiagnosis, alarmism and start a prompt treatment. *J Eur Acad Dermatol Venereol* 2020; 34(9):e482–e484. <https://doi.org/10.1111/jdv.16395>
- 19 Pezzi M, Giglio AM, Scozzafava A et al. Spider bite: a rare case of acute necrotic arachnidism with rapid and fatal evolution. *Case Rep Emerg Med* 2016; 2016:7640789. <https://doi.org/10.1155/2016/7640789>