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Local Dermonecrosis with Generalized Urticaria Probably Due to *Loxosceles rufescens* Bite

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ABSTRACT

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Keywords: Spider bites; Animal venoms; Skin lesions; Microbiologic examination; *Loxosceles rufescens*; Brown recluse spider

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BACKGROUND: The spiders of the *Loxosceles* genus, commonly denoted as “brown spiders” or “Mediterranean recluse” or “brown recluse,” belong to the spider family Sicariidae, suborder Labidognatha, order Araneida, class Arachnida, and phylum Arthropoda. This spider is widespread in Africa and South/Central America, but it is also distributed in North America, in the West Indies, in the Mediterranean Europe, and in China.

CASE REPORT: Here, we report the case of a severe dermonecrotic loxoscelism identified in Southern Italy, probably due to the bite of *Loxosceles rufescens*. The patient was a woman admitted at hospital ER because of a little skin erythema that evolved toward a severe necrosis and ulceration within 20 days. After clinical and laboratory data excluded other local and systemic diseases, she was treated with a systemic and local therapy using corticosteroids and antibiotics with the diagnosis of loxoscelism. The healing from the local skin lesion occurred within 2 months, but the local pain, weakness, and discomfort lasted for a long time.

CONCLUSION: It is the first time that a possible case of systemic loxoscelism with skin generalized urticaria is reported in Italy.

Introduction

Nearly 45,000 species of spiders have been described worldwide; approximately 200 species are actually considered dangerous to humans [1]. The spiders of the *Loxosceles* genus, commonly denoted as “brown spiders” or “Mediterranean recluse” or “brown recluse,” belong to the spider family Sicariidae, suborder Labidognatha, order Araneida, class Arachnida, and phylum Arthropoda. This spider is widespread in Africa and South/Central America, but it is also distributed in North America, in the West Indies, in the Mediterranean Europe, and in China [2]. All spiders in *Loxosceles* genus have a violin or fiddle marking on their back surface (Figure 1). *Loxosceles rufescens* is considered a highly venomous spider and the most dangerous to humans: when it pierces its prey with the fang, it squeezes out the venom, injecting the skin with it as tool for defense when it is accidentally trampled or victim of predation [3], [4]. Although most Mediterranean recluse spider bites do not cause dangerous and systemic symptoms, just dermonecrotic skin lesions, severe reactions can occur, known as “loxoscelism.”

Diagnosis of *Loxosceles* spider's bite is often difficult for several reasons: Mainly because it is not

possible to identify the spider when the bite happens silently; in fact, humans are bitten usually occur when the spider is inadvertently pressed against the skin by getting trapped in bed lines or clothing; in addition, the bite is frequently painless, hence, the patient is often unaware of it [5]; this delay between the silent bite and the time of a medical examination makes the diagnosis difficult and the treatment less effective; furthermore, the necrotic skin lesion is not always the typical one and it can be confused with an unapparent traumatic skin lesion. Moreover, at a first moment, the bite site is not painful; a mild to severe pain often begins 2–8 hours after the bite. On the skin, a small puncture wound may appear, associated with transient erythema, itching and swelling, and mild to severe tenderness. Blebs or blisters usually appear in 12–24 hours, sometimes becoming hemorrhagic and surrounded by a halo of ischemic tissue [5], [6], [7], [8], [9]. The spider's venom contains lots of proteolytic toxins to degrade the extracellular matrix components, such as fibrinogen, fibronectin, entactin, and heparin sulfate proteoglycan and to disrupt basement membrane structures, thereby causing local dermonecrosis, inflammation, hemorrhage, gravitational spreading, disseminated intravascular coagulation (DIC), and renal failure. The activity of hydrolytic enzymes “sphingomyelinase D,”

one of the enzymes identified in its the venom, is the responsible agent for hemorrhagic and necrotic lesions. Fortunately, this species injects its venom only in 40% of its bites [10], [11] (Figure 2).



Characteristic violin marking on the Cephalothorax

Figure 1: *Loxosceles rufescens* (photo by authors)

Systemic effects are less common (about 10% of cases), but may be severe or even fatal in some patients; they include nausea, vomiting, chills, fever, myalgia, generalized urticaria or purpuric rash, morbilliform rash, hemolytic anemia, disseminated intravascular coagulation, acute renal failure, shock, coma, and death [7]. There is no diagnostic test available to quickly help the physician make a diagnostic or therapeutic decision, but a rapid diagnosis is crucial for satisfactory treatment [7], [12]. In the present paper, a case, which we presumed to be due to the bite of *Loxosceles rufescens*, is evaluated in the light of literature [13], [14], [15], [16], [17], [18], [19], [20], [21].

We report the history of a Caucasian 48 years old woman which was at work when started to develop a severe itch on the inner side of her right thigh, but she did not consider it important. She had no idea how she got this injury, she was completely unaware that she had been bitten. Before she left for work, she slept in her house with open windows and just with light bed sheets. Two hours later, she noticed an erythematous area on her right thigh. She was not suffering from any disease and she was not taking any prescribed medications. Next day, she decided to ask the physician how to treat the skin lesion, but also because she developed a strong sense of heaviness and tension in the leg which quickly became a real excruciating pain before the onset of claudication. Her physician prescribed Bentelan tablets (Betamethasone

21-sodium phosphate) and Clavulin tablets (amoxicillin and clavulanic acid) to treat it. She went to the drugstore in order to buy an antihistaminic and a topical unguent: The pharmacist gave to her “*Allerin*,” an homeopathic medicinal remedy for allergies (ingredients: *Nux vomica*, *apis mell*, *pollen*, *histaminum*, *Lufah operculata*, *sabadilla*, *ammonium carb*, *allium cepa*, *euphrasia*, and *neutral globules*) and “*Gentalyn beta*” which is a topical unguent containing betamethasone 0,1% and gentamicin 0,1%. After few hours, the pain in the leg increased a lot, *becoming* insufferable and continuous. The day after (after 48 h from the alleged bite of the spider), a gray plaque appeared in the area previously erythematous (Figure 2a). She felt extreme pain with allodynia, which is pain from non-painful stimuli, such as the bed sheets contact with the skin. The skin plaque progressed to an eschar, turning black, and then it dropped off leaving a wide ulcer within 20 days, surrounded by a halo of hemorrhagic and ischemic tissue (Figure 3b-f). She felt a sense of extreme tiredness and discomfort. She continued the oral and topical therapies for 3 weeks without benefits; moreover, pruritus and generalized urticarial appeared on her face, especially on her ears (Figure 2c), so she decided to call the poison center of the “Azienda Ospedaliero-Universitaria, Ospedali Riuniti di Foggia” to ask medical aid. After an accurate evaluation of the reported symptoms, the physician recommended to go to the same hospital emergency room for an assessment of a probable spider bite and envenomation. Unfortunately, there is no single clinical laboratory test that can be used to diagnose a *Loxosceles*’ bite. On October 10th, she was admitted in the infectious disease ward for 5 days, where she underwent to several medical tests to investigate on the cause of her skin ulceration, particularly if it could be associated to the spider’s venom, or with another infectious or an autoimmune disease. Meanwhile, she developed an acute skin rash on her neck, on the trunk and the abdomen, and on the upper limbs. She was treated with prednisone tablets (25 mg/day) for 5 days, lansoprazole tablets (30 mg/day), and Minocin (100 mg twice daily) for 10 days. The dermatologist also prescribed Bionect Start cream and “Connettivina” gauzes to medicate the

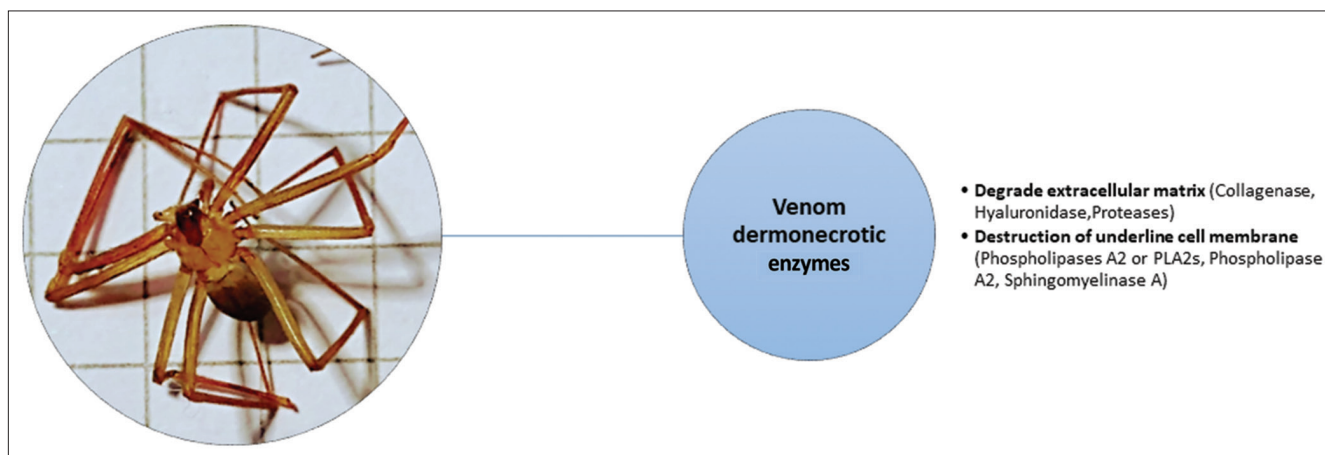


Figure 2: The “Mediterranean Recluse Spider” and its venom’s enzymatic functions (spider not alive, photo by authors)

lesion once daily for 10 days. During hospitalization, all the blood chemistry tests, bacteriological and virological laboratory tests resulted in the normal range. All tests for autoimmune diseases were negative.



Figure 3: Clinical evolution of the spider bite on the right thigh and of the skin rash of the trunk

She was discharged after 5 days and she continued the home therapy with prednisone tablets (25 mg/day) for 5 days and then 12,5 mg for others 5 days, lansoprazole tablets (30 mg/day) for 10 days, Minocin (100 mg twice daily) per 10 days, and Advantan cream + Bionect Start + Connettivina to medicate the lesion (she continued with the local therapy until December 2018 because the ulcer was not healed yet). She felt completely healed just in February 2019, when the sense of thickness and the pain on the leg finally disappeared. All the systemic and local treatments of this case are resumed in Figure 4.

Home treatment <ul style="list-style-type: none"> • Antibiotics (oral and local) • Corticosteroid • Antihistamine • Local disinfection 	↓
EMERGENCY ROOM <ul style="list-style-type: none"> • Normal vital sign ranges / body temperature 37.1 C° • Main Blood laboratory exams they are negative • Team Consultation: Toxicologist, dermatologist, infectivologist • Therapy: cortisteroids 	
Hospitalization in Department of infectious diseases: <ul style="list-style-type: none"> • Main Blood and viral tests they are negative • Laboratory tests performed to diagnose autoimmune disorders they were negative • Therapy: Oral Antibiotics (clavulin ed minociclina), cortisteroids, locally disinfection, hyaluronic acid sodium salt 0.2% ointments, collagenase with silicone patches) • Follow up: Toxicologist, Dermatologist • After 8 days dismissed 	
Home therapy <ul style="list-style-type: none"> • Oral: Antibiotics, Corticosteroids • Local: collagenase with silicone patches Follow up team: Toxicologist, dermatologist and infectivologist	

Figure 4: Resume of medical treatments of the reported case of presumed *Loxosceles rufescens* bite

Discussion

The case we report about this woman is probably due to a *Loxosceles rufescens* bite. To confirm

a brown recluse spider bite, it is very important to collect the spider for exact identification, but only 10% of patients can do it because, as mentioned above, the bite is usually unnoticed. In these cases, diagnosis can be based on the patient's story, on skin's lesion appearance and other local and systemic manifestations, so, the diagnosis is often as presumptive of brown recluse spider bite. Despite loxoscelism can be associated with changes in laboratory values, including hemolysis, thrombocytopenia, coagulopathy, altered chemistry, and urinalysis results, she did not manifested these signs during the hospital stay; however, we cannot exclude the possibility that she developed them before consulting a specialist. The severity of clinical condition also depends on individual immune response and the amount of the injected venom: 90% of bites heal without complications and, in other 10%, not every symptom or sign which characterized loxoscelism must be necessary be present. The presence of the skin lesion without other systemic parameters such as fever and negative blood tests do not exclude the hypothesis of brown recluse spider bite, but on the other hand, she might have developed them but without any laboratory test to demonstrate it [5], [16], [17].

The diagnosis, in the absence of spider identification, is based on epidemiology data (presence of the *Loxosceles* spider on the territory), medical history and clinical signs (skin manifestations, progressive painful solitary plaque with an ischemic necrotic central part surrounded by intense erythema), and unspecific manifestations such as fever, headache, and a generalized, itchy rash of measles or scarlet-like type that appears in the first 24–48 h after the bite. In addition, diagnosis is supported by the exclusion of other possible causes of the same clinical picture (differential diagnosis in Table 1) [4], [7], [16].

In fact, this skin plaque and ulceration can be also associated to different medical conditions, including bacterial diseases (for example, *Staphylococcus aureus*, *Staphylococcus epidermidis*, anthrax, syphilis, and tularemia), viral infectious diseases (*Herpes simplex* and *Herpes zoster*), parasitosis (Lyme's disease, sporotrichosis, aspergillosis, and mucormycosis), skin cancer, vascular or diabetic ulceration, adverse drug skin reactions, traumatic skin injury, and autoimmunity diseases such as the "*pyoderma gangrenosum*" [18], [19], [22], [23], [24], [25], [26].

The hematological, bacteriological, and virological laboratory results allow to exclude bacterial and fungal infections of the skin. The clinical evolution of the skin lesion, the development of the generalized symptomatology and the exclusion of other systemic diseases must differentiate diagnosis of a systemic envenomation. In these cases, is very helpful the consultation of other specialists such as a toxicologist, dermatologist and infectivologist. Some features of the skin lesion may be related to an insect bite, particularly a spider one [18], [27] (Figure 5).

Table 1: The main differential diagnosis

Main diseases for differential diagnosis								
Bacteria	Virus	Fungi	Lymphoproliferative disorders	Systemic diseases, vasculitis	Drug adverse reactions	Contact dermatitis	Diseases transmitted by arthropods	Miscellany
<ul style="list-style-type: none"> • <i>Methicillin-resistant staphylococcus aureus</i> • <i>Streptococcus</i> • Gonococcal arthritis • Anthrax • <i>Mycobacterium ulcerans</i> • Syphilis • Tularemia 	<ul style="list-style-type: none"> • Herpes simplex • Herpes zoster 	<ul style="list-style-type: none"> • Sporotrichosis • Aspergillosis • Mucormycosis 	<ul style="list-style-type: none"> • Cutaneous T-cell lymphoma 	<ul style="list-style-type: none"> • Vascular or diabetic ulcer • Flesh-eating disease in patients with liver disease • Focal vasculitis • Purpura fulminans • Thromboembolism • Polyarteritis nodosa • Skin cancer 	<ul style="list-style-type: none"> • Warfarin 	<ul style="list-style-type: none"> • Canadian Ivy plant • Poison oak • Chemical burns 	<ul style="list-style-type: none"> • Lyme disease • Rocky Mountain spotted fever • Ornithodoros coriaceus bite • Insect bite 	<ul style="list-style-type: none"> • Pyoderma gangrenosum • Decubitus ulcer • Stevens-Johnson syndrome • Erythema nodosum • Toxic epidermal necrolysis • Lyell Syndrome

It is important asking help to an infectiologist because lots of skin lesions can be caused by the bites of non-venomous spiders, scorpions, bees, wasps, hornets, mosquitoes, and sand flies and they are quite indistinguishable from those of the brown spider. Finally, it is important the differential diagnosis between different species of insect that could cause this kind of skin lesions. Particularly, we must think about the most diffuse species of spiders which are present on the territory [22].

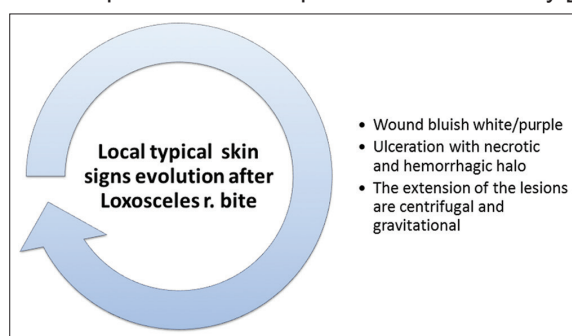


Figure 5: Typical skin lesion of *Loxosceles rufescens* bite

In Italy, in addition to the *Loxosceles rufescens* bite, other three types of spiders could give this kind of local and systemic reaction. The first one is the *Segestria florentina*, a spider which produces a neurotoxic venom; the *Cheiracanthium punctorium* which is a spider whose bite can be very painful, with a local reaction characterized by erythema, edema, and itchiness, while systemic symptoms are scarce; and *Latrodectus tredecimguttatus* (Mediterranean or European black widow) is mainly found in southern and central Italy along the Tyrrhenian coast, but also in Sardinia; patients bitten by this spider develop a mild to severe pain in the site of the bite, but also other systemic symptoms such as abdominal pain, chest pain, muscular contractures, and temporary psychomotor disabilities [27], [28], [29], [30], [31], [32], [33], [34].

Finally, we must mention that it is the first time that a possible case of systemic loxoscelism with skin generalized urticaria is reported in Italy.

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