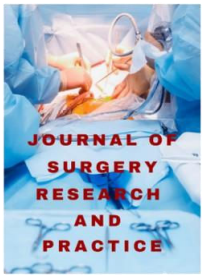

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Review Article

Spider Bite Dermonecrosis: A Review of Loxoscelism

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Abstract

Loxoscelism is the clinical condition caused by the bite of spiders belonging to the genus *Loxosceles* and is the only verified arachnological cause of dermonecrosis worldwide. More than 150 different species of this spider genus have been described, being *Loxosceles laeta* the only recognized cause of Loxoscelism in Chile.

It is of public health importance due to its potentially lethal bite, which results from venom containing catabolic enzymes, primarily sphingomyelinase-D and phospholipase-D. These enzymes participate in lipid hydrolysis within the cell membrane, triggering an inflammatory response and complement activation, leading to cutaneous dermonecrosis, also known as cutaneous Loxoscelism. In systemic cases, it can cause hemolysis, Disseminated Intravascular Coagulation (DIC), renal failure and thrombocytopenia, a condition known as cutaneous-visceral Loxoscelism.

Loxoscelism remains a diagnostic and clinical challenge due to both the difficulty, in identifying the spider species and the lack of consensus regarding treatment. Advances in bioengineering have facilitated research into new therapeutic strategies aimed at better understanding the venom's mechanism of action. This review discusses the nature of *Loxosceles laeta* in the context of diagnostic importance, as well as the clinical manifestations, medical and surgical management and new therapeutic strategies proposed based on the pathophysiology of Loxoscelism.

Keywords: Loxoscelism; Sphingomyelinase-D; Phospholipase-D; Dermo-necrosis; Novel Therapeutic Strategies

Introduction

Loxoscelism is the clinical syndrome produced by the bite of arachnids of the genus *Loxosceles*, commonly known as recluse spiders or brown spiders. It is the only confirmed cause of dermonecrosis due to spider bites [1,2]. The *Loxosceles genus* has a worldwide distribution, with more than 150 different species described, with Fig. 1,2 being the cause of loxoscelism in Chile [1,3,4].

Other *Loxosceles* species described as primary causes of loxoscelism in several world countries include: *L. reclusa* and *L. deserta* in North America, *Loxosceles* intermedia in Brazil, *Loxosceles gaucho* in Argentina and *Loxosceles rufescens* in Mediterranean countries and the Middle East [1,4].

These spiders are usually found at home in dark, undisturbed, hidden places with infrequent cleaning, behind furniture, bed headboards, among clothes that have not been used for some time, behind curtains, in cellars and little-used rooms, attics and similar places [5]. It is essential to inquire about these antecedents in the clinical history to specify the diagnosis, which is almost always clinical. Most patients only seek medical help when they have a bulla (Fig. 3), a slow healing wound or eschar, usually two to three weeks after the bite (Fig. 4).

The clinical manifestations of the bite are highly variable, most cases ranging from simple cutaneous irritation with localized edema to dermonecrotic lesions. Less frequently, it can cause severe systemic inflammatory reactions such as acute renal failure and disseminated intravascular coagulation or eventually death [5,6]. These spiders never attack humans spontaneously; rather, when encountered by human presence or movement, they try to hide in any dark and hidden area. Since most arachnids are nocturnal predators, it frequently happens that they are overtaken by daylight during their hunting trips, remaining still in places that are well lit, illuminated or exposed to view. This is the reason why the great majority of *Loxosceles* sightings happen during the day, in sinks, walls, showers, etc. It should be remembered that they are found in almost every house in the central sector of Chile if they are searched for with sufficient diligence.

When it occurs, the bite is always accidental and happens when someone involuntarily holds, pushes or crushes the spider between their clothes, shoes, garments directly under the skin; that is, it acts in self-defense by biting the skin.

The bite almost never produces immediate pain, furthermore, this usually goes unnoticed. Most frequently, patients notice it one or two days later, when they discover a bulla, an ecchymotic or discolored area on the skin (Fig. 5). This means that when suspicion arises, in most cases the culprit is not seen or found and when asessed by a doctor, the diagnosis is only presumptive. There are very infrequent cases in which someone puts on a shirt or pants and feels the bite of a specimen that had taken refuge inside before or at the arrival of the morning light and in some of those cases sometimes it is possible to find the spider crushed inside the clothes.

There is no consensus on treatment. For decades, Chilean Health Authorities recommended and used an antivenom derived from antibodies produced from horses and other mammals, but this was discontinued in 2016 due to the limited evidence and demonstrated effectiveness [6].

Symptomatic treatment is the most used and includes management through the use of non-steroidal anti-inflammatory drugs, narcotics or corticosteroids according to the patient's pain and the extent of skin damage the prevention of secondary staphylococcal infections and wound care through the application of local cold, elevation and immobilization of extremities [6-8]. In late and more advanced cases where there is presence of scabs and/or extensive necrosis (Fig. 6), surgical excision (Fig. 7-10), secondary healing and eventually direct closure of the wound may be necessary (Fig. 10,11). Ocasionally the use of grafts in extensive wounds or surgical reconstruction are also needed (Fig.9) [1,7,8].

The use of Dapsone, a polymorphonuclear inhibitor, has shown beneficial effects in reducing the inflammatory phenomenon and accelerating the recovery of skin lesions. Its use is conditioned by the need to rule out visceral involvement; therefore, its application is limited to after 48 hours if there are no signs of hemolysis [7-9]. Some authors propose measuring glucose-6-phosphate dehydrogenase levels, since deficiency of this enzyme may increase the risk of induced hemolysis [9,10]. It has also been proposed that the use of topical tetracyclines reduces ulceration through the chelation of divalent cations that inhibit sphingomyelinase-D; this would decrease the expression of MMP2 and MMP9, slowing the inflammatory response and the progression of dermonecrosis [11,12].

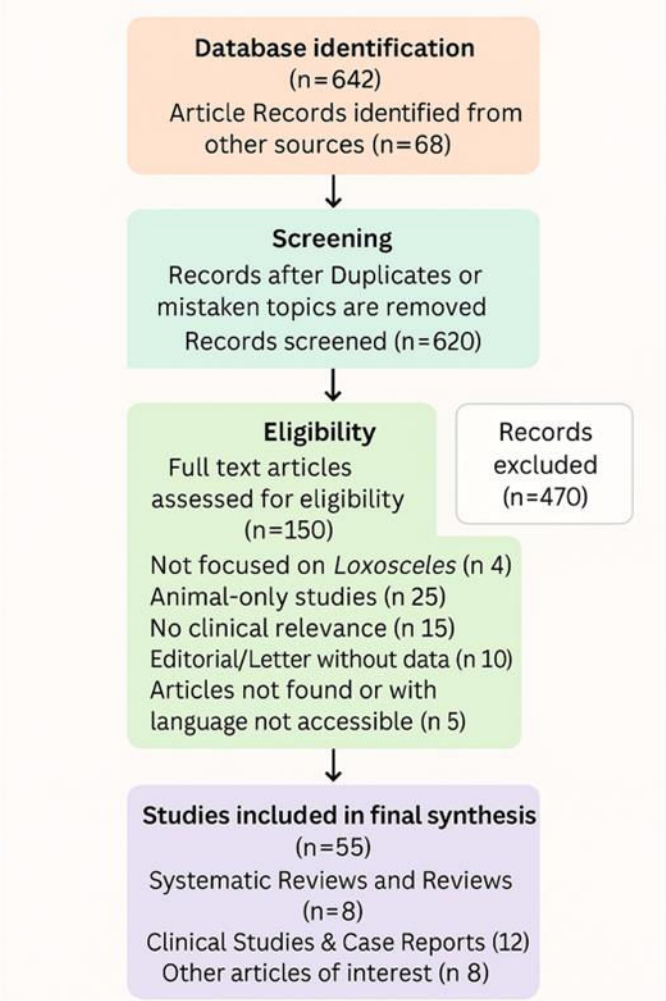
Methodology

For this review, an extensive search of the literature through Pubmed/Medline, Toxnet, Lilacs and clinicaltrials.gov for 2005 to 2025 period. Out of those searches, the resulting articles were handled in Endnote®, so relevant papers could be selected. Most articles were case reviews and have no interests for our purpose. The final selection is included in the bibliography section. A Prism flow diagram is shown below for clarity.

The clinical cases were those selected from the Clinica La Parva´s medical database, stored in Nopali clinical software for Apple IOS. Out of 50k medical records over a 10 year period, there were 19 cases of patients with *Loxosceles* spider bite diagnosis. Seven of them had at least four months follow up during their evolution, three were taken as examples, so the spontaneous improvement is shown here, as one that required surgical reconstruction and complete follow up.

Photographs were taken with Nikon® cameras and Iphone® series 14 or latter.

Bibliography Flow Diagram



Nature of *Loxosceles laeta*

It belongs to the genus *Loxosceles*, order *Araneida*, suborder *Labidognatha* and within South America, *L. laeta* species is the most widely distributed and although several other species are known, it appears to be the most lethal [1,4-6,13]. Its adult size is between 1 to 5 cm with extended legs (Fig. 1,2). The female is distinguished from the male as the latter has a narrower body and thinner legs (Fig. 1,2) [6,13]. Visually, two segments are distinguished: cephalothorax and abdomen. It is brownish-coffee in color and its body is covered by abundant hairs and setae, in vertical, horizontal and oblique disposition. On the tarsi, the hairs fulfill tactile functions to detect irregular or textured surfaces, which allows them to find points of support to move. On smooth surfaces such as glass, with no rugged or rough areas, these spiders have great difficulty climbing them.

The cephalothorax has a design that resembles the shape of a violin, hence its nickname "violinist spider". It has three pairs of ocelli or eyes that are arranged in a triangle and not four, which distinguishes them from other genera.

The chelicerae (Fig. 12) are responsible for the bite and inoculation of the venom and also fulfill key functions in feeding and defense, are connected to venom glands located in the cephalothorax. Each chelicera consists of two main parts: the basal segment, where the venom glands are stored, which is more robust and is firmly held to the cephalothorax and a mobile fang, a terminal segment, sharp and curved, which perforates the skin or cuticle of the prey. There are other spider species inhabiting Chilean homes, but they are harmless (Fig. 14).

Loxosceles laeta mates and reproduces mainly in spring and summer and during these periods is that they are most commonly

seen by humans. It is characterized as a solitary spider and spends its life hidden from light; therefore, it is usually found in dark, silent and little-visited places. The most frequent places in a house where they hide are behind bedheads, furniture, pictures, curtains, corners, closets, among clothes and even inside shoes [5-7]. These are very relevant data in the clinical interview: the location where it occurred, since if a patient reports that the biting event was outdoors, in the garden, among bushes or on a sunny day, it makes *Loxosceles* very unlikely as the cause of suspicious lesions; the number of lesions, since it is usual for the spider to bite only once and not several times in the same or different sites. These data can help both confirm and rule out Loxoscelism from other differential diagnoses such as bacterial infections of the skin, insect bites, vasculitis, hypersensitivity reactions, autoimmune diseases or other alternatives [16]. The natural predator of *Loxosceles* is another home spider, *Scytodes globula* called "tiger spider" (Fig. 12,13), which looks weak and flimsy, however, secretes a glue-like fluid that paralizes even large specimens of *Loxosceles*. We also have personally observed live parasites within the abdominal cavity of *L laeta* females, never described before, although ignore the parasitic species or their rol as predators (Fig 14).

Clinical Presentation and Classification

The clinical presentation is classified into Systemic Loxoscelism (SL) and Cutaneous Loxoscelism (CL), which is subdivided into Edematous Cutaneous Loxoscelism (ECL) and Necrotic Cutaneous Loxoscelism (NCL) [6,7]. Clinical manifestations depend on the amount of venom inoculated and intrinsic patient factors such as allergies, hypersensitivity, atopy, age, obesity, diabetes, smoking, connective tissue diseases and autoimmune factors. The site of the bite also plays a role, with areas with more adipose tissue being the most compromised due to fat necrosis that can be extensive.

SL occurs in 10-15% of reported cases and is the most lethal due to intravascular hemolysis, which usually reaches a peak 48 hours after the bite. This can be detected by a significant drop in hemoglobin levels, hematuria, an increase in lactate dehydrogenase and bilirubin plasmatic levels. Patients who are at greater risk of developing LS are pediatric patients, who are more susceptible to developing severe hemolysis, acute renal failure, disseminated coagulopathies and even patient death.

CL is the most frequent and least severe. It is subdivided into Edematous Cutaneous Loxoscelism (ECL) and Necrotic Cutaneous Loxoscelism (NCL). ECL only occurs in 5% of cases and consists of the mildest version where the manifestations are reduced to the presentation of edema and superficial bullae without necrosis. Necrotic Cutaneous Loxoscelism is the most frequent and occurs in 80% of cases. Although NCL is characterized by the presence of the livedoid plaque (Fig. 8), whose characteristic is central necrosis, this may take at least 48-72 hours to appear and is not always present when the affected person consults, which makes diagnosis even more difficult.

Pathophysiology of *Loxosceles Venom*

It is constituted by several toxins among which proteolytic and cytotoxic enzymes stand out. The best known and studied are Phospholipase-D and Sphingomyelinase-D, which activate several inflammatory and apoptotic intracellular signaling pathways, so the cutaneous-necrotizing, hemolytic, vasculitic and coagulant effect is attributed to them. It is interesting to note that several components of the venom are very similar to those found in the venom of some snakes [14-17].

Sphingomyelinase-D: It is the most studied component of *Loxosceles venom*, to which the effects of dermonecrosis, vasculitis, coagulation and hemolysis are attributed.

This enzyme hydrolyzes sphingomyelin, a phospholipid found mainly in cell membranes; its hydrolysis generates Ceramide-1-Phosphate and Choline. This process initiates a chain of events as a consequence as follows:

- *Structural alteration of the plasma membrane:* by hydrolyzing phospholipids, the organization and function of membrane proteins with their respective receptors and enzymes are altered; in response, the Matrix Metalloproteinases (MMPs) are activated, such as MMP-2, MMP-9 and MMP-7, which proceed to the degradation of MEC, specifically fibronectin and fibrinogen, contributing to the propagation of the venom and dermonecrosis [16-18]
- *Generation of Ceramide-1-Phosphate:* Ceramide-1-Phosphate is a sphingolipid that regulates numerous biological functions. In the context of Loxoscelism, it acts as a perpetrator of damage, playing the role of apoptotic mediator and inducer of inflammatory responses, altering vascular permeability and in turn increasing the inflammatory response.
- *Activation of Lysophosphatidic Acid Receptors (LPA):* Sphingomyelinase-D can also hydrolyze Lysophosphatidylcholine (LPC) to generate Lysophosphatidic Acid (LPA). In the context of Loxoscelism, it acts as prothrombotic, inducing platelet

aggregation, endothelial hyper permeability and pro-inflammatory responses that explain the pathogenesis of cutaneous-visceral loxoscelism [17,18]

- *Activation of Cellular Signaling Pathways:* Sphingomyelinase produces proteolysis and cytolysis and can activate several intracellular signaling pathways, including the MAP Kinase (MAPK) pathway, involved in the inflammatory response and apoptosis [16-18]
- *Phospholipase-D:* Phospholipase-D (FLD) is one of the most important toxins in the venom as it exacerbates the inflammatory response responsible for local and systemic effects through the following pathological events
- *Induction of Pro-Inflammatory Cytokines and Chemokines:* IL-6, IL-8, CXCL1/GRO-α and CCL2/MCP-1 in fibroblasts, which in turn stimulates the migration of monocytes to the site of the bite. This exacerbated inflammatory response is a key component in the pathogenesis of skin lesions [15]
- *Platelet Aggregation and Hemolysis:* events that trigger acute renal failure and the effects of cutaneous-visceral Loxoscelism.
- *Hyaluronidases:* Enzymes that facilitate the diffusion of the venom through the tissues by degrading hyaluronic acid in the Extracellular Matrix (ECM) [19]

Colagenases

The presence of collagenases in *Loxosceles* venom has been documented in studies showing the degradation of collagen in experimental models in mice where it was observed histologically: acute inflammation with edema, thrombi and vasculitis, increased levels of mast cells and their degranulation and apoptosis in giant cells. In addition, degradation of collagen type I and III was observed [20,21]. These data may explain the difficulty in the repair of the ulcer observed in CL in humans and the relevance of collagenases in the pathogenesis of Loxoscelism.

Manifestations of Cutaneous Loxoscelism

Cutaneous Loxoscelism typically progresses from an initial asymptomatic phase, painless or with very few specific symptoms, through a progression phase with the appearance of pain and changes in the appearance of the lesion, to a necrosis phase and finally a resolution phase.

1. *Initial Phase (0-6 hours):* Edema, Flictenae and erythema can be appreciated (Fig. 4-9); in rare cases, the mark of the chelicerae is even visible. At the time of the bite, there is generally no pain or it may be undetectable. It is believed that the appearance of pain may be related to progressive ischemia after the first hours [7,22]

2. *Progression Phase (6-72 hours):* During this period, local pain may increase progressively. The lesion can evolve to a purplish or blue plaque, irregular, surrounded by an erythematous halo, with indurated swelling in the affected and immediately neighboring area. In some cases, a central hemorrhagic blister and an irregular ecchymotic center may develop, accompanied by extensive inflammatory edema (Fig. 5,6)

3. *Necrosis Phase (3-7 days):* At this stage, the lesion progresses to a necrotic ulcer. Cutaneous necrosis is a characteristic of cutaneous Loxoscelism, although it is not always present and is not exclusive. There are other pathologies that present with necrosis. The ulcer may be surrounded by a pale border and an area of inflammation (Fig. 12,13) [7,22,23]

4. *Resolution Phase (weeks to months):* Healing of the lesion through progressive deposition of granulation tissue, deposition and retraction of collagen, resulting in healing by secondary intention, can take several weeks. In uncomplicated cases, the lesion may heal completely without leaving large scars. However, in more severe cases, surgical reconstruction may be necessary to treat the necrotic ulcer (Fig. 10,11) [7,22-24]

Figure 1: *Loxosceles laeta* male.

Figure 2: *Loxosceles laeta* female. Wine cork to compare size.

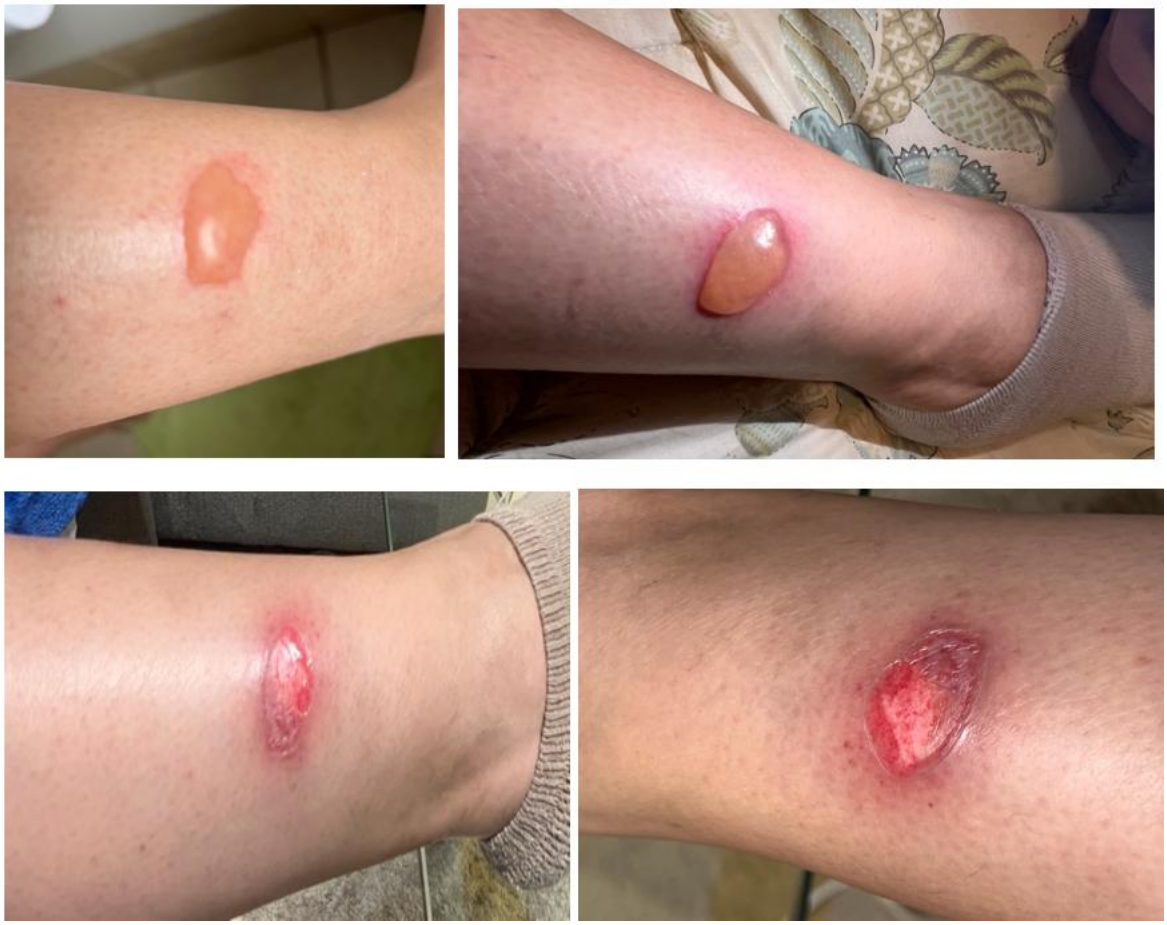


Figure 3: Early stage of bite of *L. laeta,* bulla at 2, 5 and 14 days.

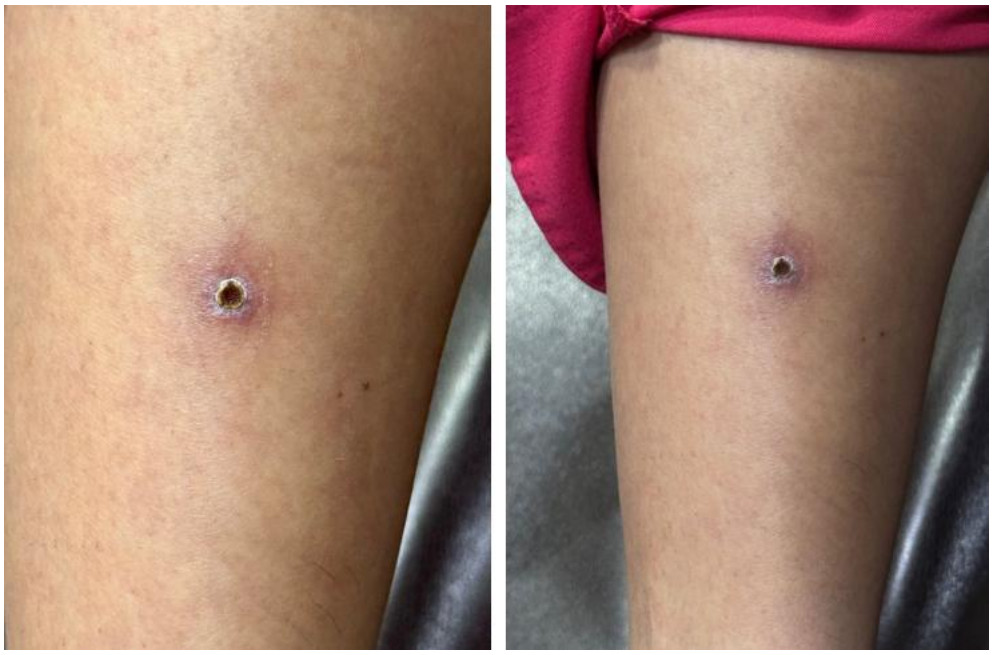


Figure 4: Eschar stage of bite of *L. laeta*, at 25 days.

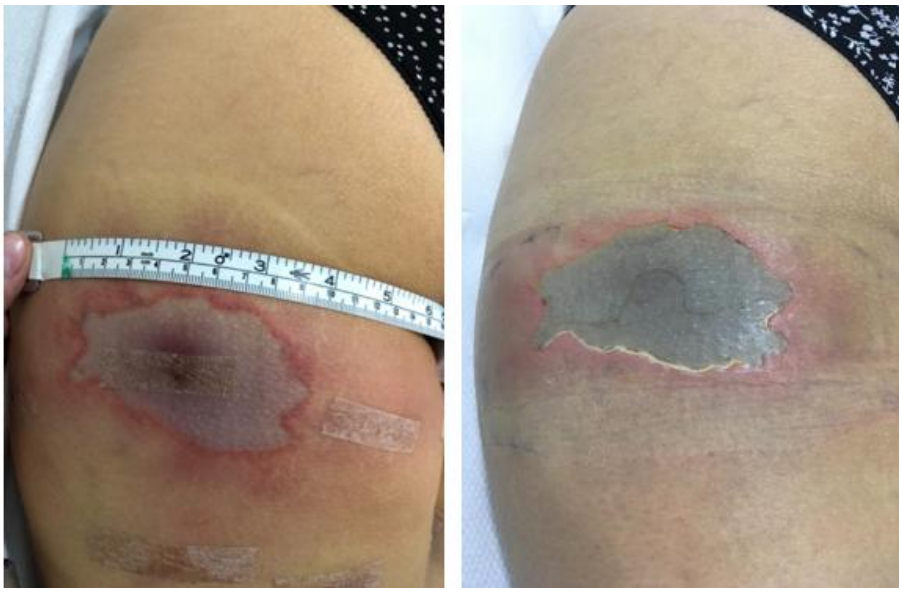


Figure 5: *Loxosceles laeta* bite on an upper thigh, 12 days evolution.

Figure 6: *Loxosceles laeta* bite, on an upper thigh, 19 days from diagnosis.

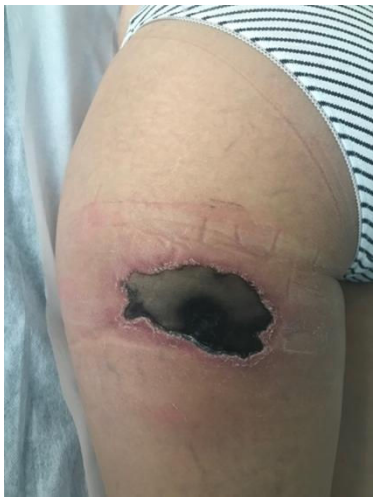


Figure 7: *Loxosceles laeta* bite, 22 days from diagnosis.

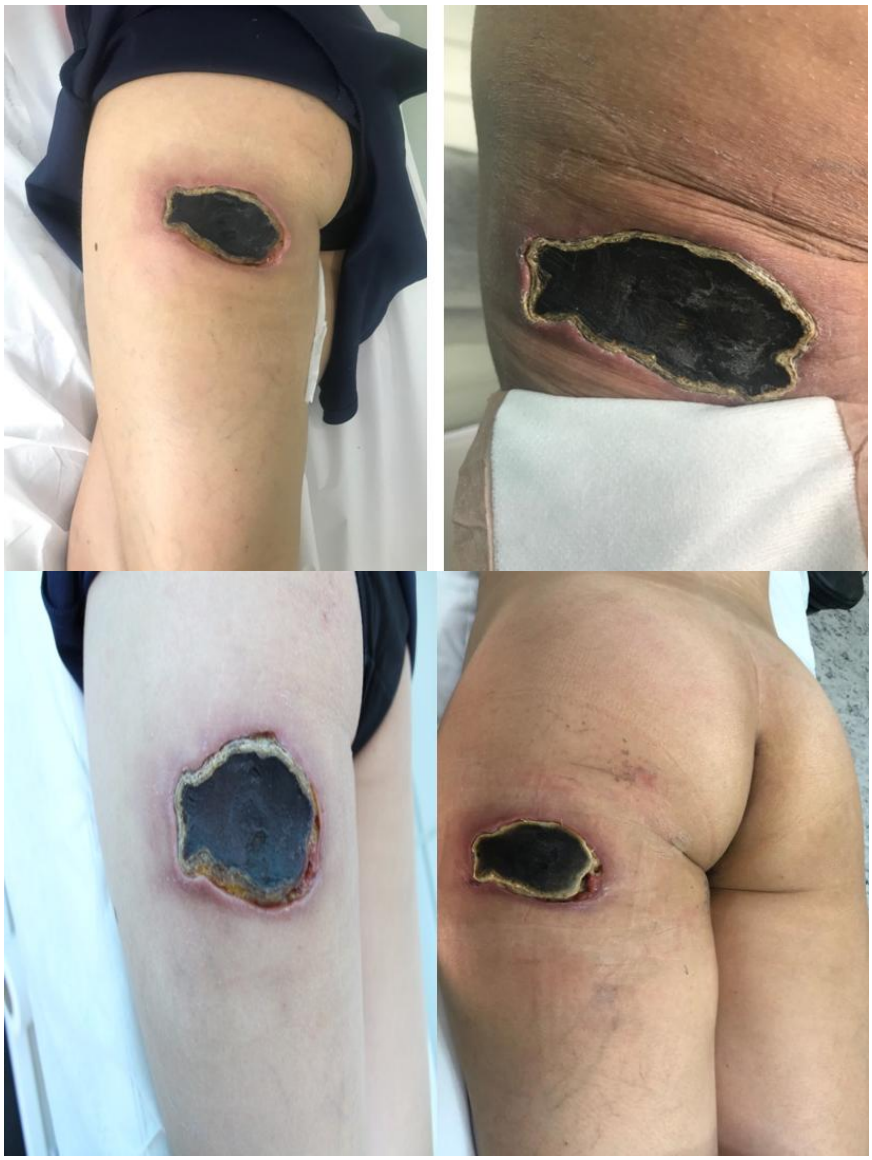


Figure 8: *Loxosceles laeta* bite, 35 days of evolution.

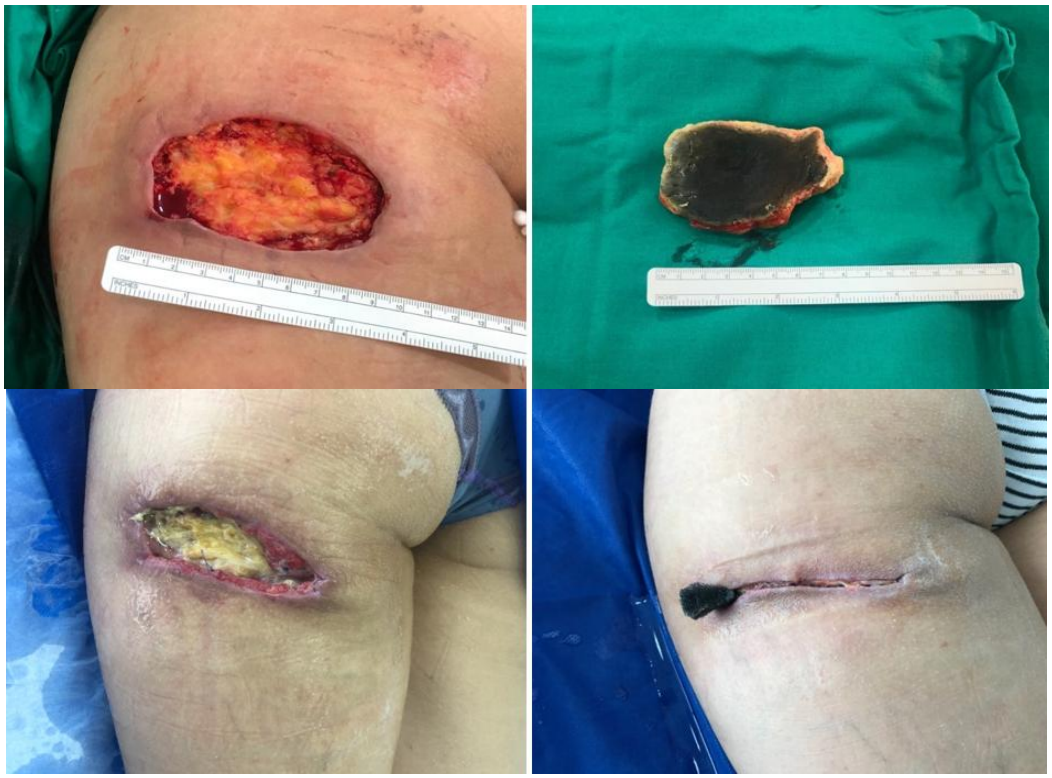


Figure 9: *Loxosceles laeta* bite, surgical excision of necrotic plaque, wound healing through secondary intention and later new surgical revisión. Its interesting to see the thickness of necrosis, which involves even the subcutaneous fat.

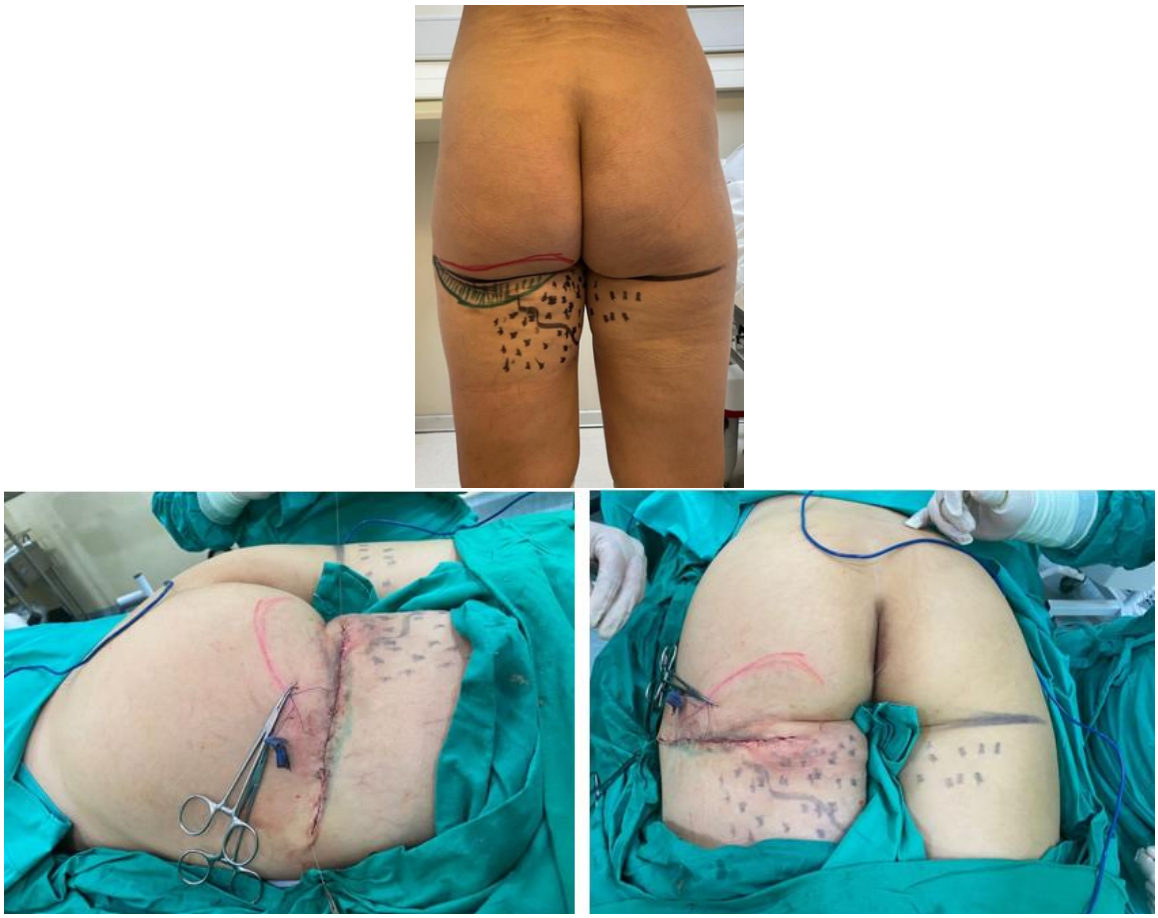


Figure 10: *Loxosceles laeta* bite scar, surgical planning and revisión at 7 months. These surgical procedures are needed to recover the aesthetic.

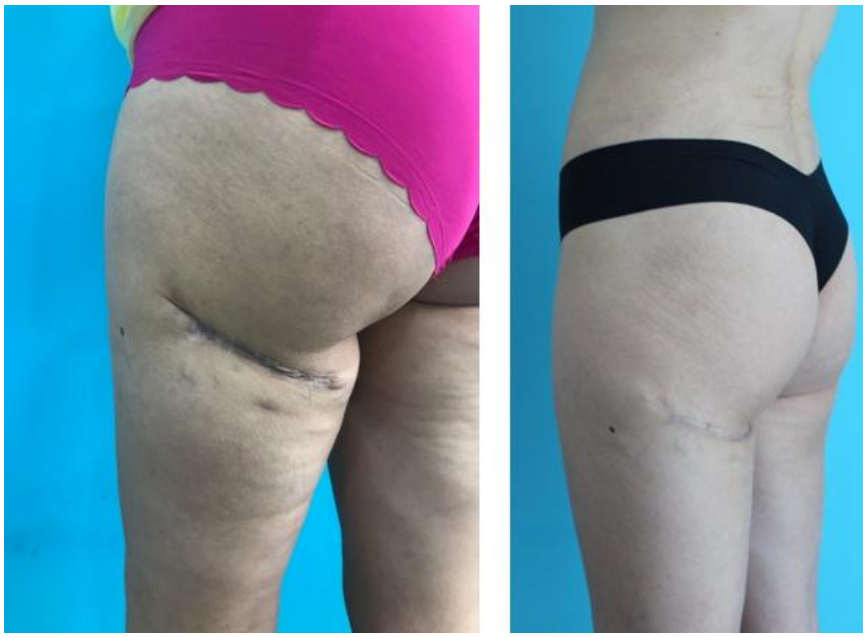


Figure 11: Healed *Loxosceles laeta* bite, at 3 (left) and 12 (right) months of evolution after surgical excision and reconstruction.

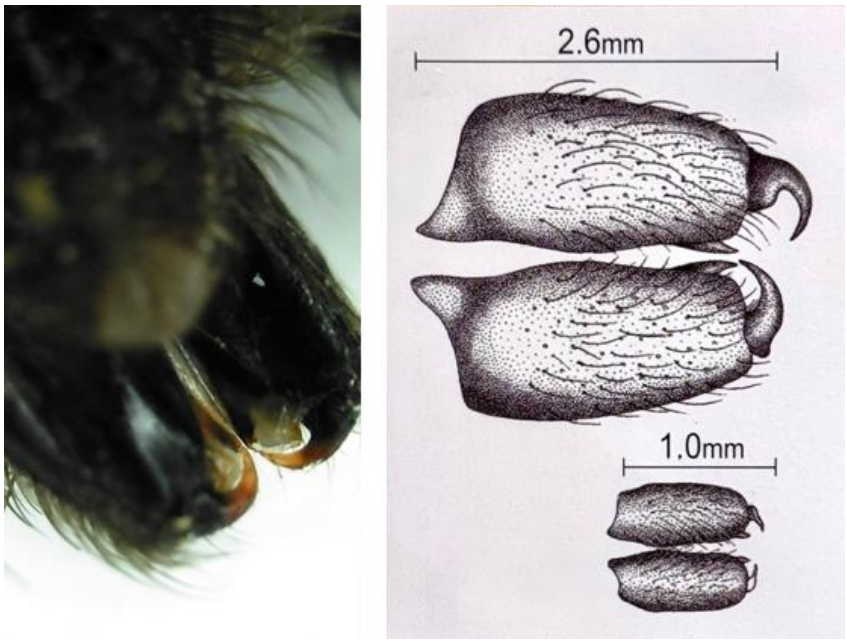


Figure 12: Chelicerae of *L. laeta* female.

Figure 13: *Scytodes globula* female spider carrying eggs and a *Scytodes* male. This is the main predator of *Loxosceles* within houses.

Figure 14: A Previously unknown parasite found inside a female of *Loxosceles* abdomen.

Figure 15: Other two species of harmless spiders found in chilean households. Their habitat is outside houses, usually humid enviroments in gardens.

New Therapeutic Strategies

Recent advances in the treatment of Loxoscelism have explored several innovative strategies that include:

1. *Use of Autologous Fibroblasts (AF)*

This method has shown promising results in stabilizing the necrotic process and improving ulcer healing, although more studies are required to confirm its efficacy. In this case, AFs were used to treat a skin ulcer; the necrotic process was stabilized with Dapsone, but ulcer healing was not achieved until fibroblasts were applied. Three weekly applications of AF at a concentration of 100,000/cm² were performed on a biocompatible polymeric matrix [25]

2. *Recombinant Phospholipases-D*

Another line of research focuses on the development of immunological strategies. Mutated recombinant phospholipases have been investigated as antigens to develop new therapies against Loxoscelism. These antigens have shown potential to neutralize the toxicity of the venom, including sphingomyelinase activity and nephrotoxicity, which could decrease or cushion both cutaneous and systemic manifestations [26]. This is an experimental treatment and should be considered as an early human trial

3. *Monoclonal Antibodies*

Monoclonal antibody fragments specifically targeting the Sphingomyelinases-D of the venom have been designed with the aim of neutralizing dermonecrotic activity. These antibody fragments have been humanized and optimized to improve their structural stability and antigen-binding capacity, showing potential as a safe and effective alternative treatment [27,28]. There is no need to say that it´s too early to validate them for every patient and at this stage I would consider only for severe cases with multi systemic involvement. Furthermore, there is always the chance of an unexpected immune response that could harm the patient. Another important consideration is the high cost involved in these novel treatments. These advances reflect a multidisciplinary approach to addressing Loxoscelism, although it is important to note that many of these treatments are still in

experimental phases and require further research for their widespread clinical application. In all likelihood, during the coming years, due to the advent of pathophysiological models based on artificial intelligence, we will see new discoveries and better understanding of the mechanisms to protect patients who have suffered bites.

Discussion

Loxosceles is a genus that is distributed throughout the world; more than 150 species are known, out of which *Loxosceles laeta* is of greatest medical importance and public health relevance in Chile.

Detailed knowledge of the nature of this spider and the physiological manifestations are fundamental for correct diagnosis and treatment. Given that there is still no consensus regarding emergency treatment and during its evolution, the molecular study of *Loxosceles venom* is imperative for new therapeutic alternatives.

Conclusion

Although there are limitations on this review, we feel that it represents a good understanding of the management at present. Furthermore, a photographic follow up of some typical cases and one that required reconstructive surgery are a teaching tool for emergency department physicians.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Neither of authors have financial interests nor benefits on this study.

Consent of Patients

All patients allowed use of the clinical photographs included here through a consent form.

Acknowledgments

Laboratory photos were taken at the Medical Laboratory in Clinica La Parva, Santiago de Chile.

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