

The Immune System in Foetal Death After a Spider Bite: Case Report with Literature Review

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Abstract

Loxoscelism is caused by the bite of a spider belonging to any of the *Loxosceles* species. We analyse the case of a pregnant woman, 35 weeks into gestation, who was accidentally bitten by a *Loxosceles rufescens*, in June 2015. She was treated with corticosteroids and antihistamines. After 36 hours of the bite, the patient went to Hospital having felt a lack of foetal movements. Foetal death was diagnosed and the woman was admitted for induction of labour. The autopsy stated as the cause of foetal death to be the presence of umbilical vein thrombosis and sub-funicular placental infarction. We propose that the activation of the thrombosis, in the case of this pregnancy was triggered by events linked directly with the venom of the spider. This venom possesses chemical components sufficient to activate the complement cascade which is closely linked to the coagulation system, and indirectly affected by the inflammation of the allergic response in a previously sensitized patient.

Keywords: Allergy; Cytokines; Complement and clotting; Inflammation; Loss pregnancy to term; *Loxosceles rufescens*

Introduction

Loxosceles rufescens is a cosmopolitan spider characterized by its cytotoxic venom and urban distribution [1]. It is nocturnal. Its mobility is reduced at temperatures below 15° Celsius which concentrates its maximum activity to the months of May, June and July, when its population increases. This spider lives in warm areas of the Mediterranean including Spain, France, Greece and Turkey (Figure 1) [2-5]. It is not an aggressive spider; it only attacks if it feels threatened, which can happen when handling clothes in whose folds, these arthropods have been hiding. There are two types of well defined loxoscelism: a) cutaneous loxoscelism is a clinical condition, limited to the tissue which develops skin necrosis and disfiguring ulcers, and has a good prognosis and b) systemic loxoscelism with visceral involvement, alterations of the coagulation, fever, dehydration, hypotension and shock, which is less frequent, but can be severe and even fatal. These two clinical variants are commonly present in around 84% and 16% of cases, respectively [6,7]. The amount and the content of the venom produced by the spider depend on several associated factors, such as the specimen, size, gender, nutritional state and age of the spider. All these represent important factors contributing towards the severity of the loxoscelism [8,9]. In the case of the *Loxosceles rufescens* its venom contains a complex mixture of biologically active substances, including sphingomyelinase D (MSD), Phospholipases-D (PLD), Astacin-like metalloproteases, Hyaluronidase, ICK-insecticide peptide and a TCTP-histamine releasing factor [10], developed to block the vital physiological and biochemical functions of the victims. Specifically, the biological properties of the PLD have been reported by numerous authors using SDS-PAGE analysis and chromatography methods showing: massive inflammatory response with neutrophils infiltration and complement activation, platelet aggregation, immunogenicity, oedema and increased permeability of the blood-vessel wall [11,12]. The MSD induces activation of the alternative pathway of the complement, of polymorphonuclear cells, platelets and vascular thrombosis. MSD also results in an increased expression of E-selectins, IL-8, GM-CSF and ceramides, thereby increasing the inflammatory reaction and the thrombotic disorders of the blood [5,13]. The metalloproteases induces erythrocytes lysis [14]. The power of hyaluronidase lies in its ability to spread toxins through the tissues [10]. The morbidity and mortality rates due to loxoscelism remain unknown in our country, due to the rarity of the clinical entity and the difficulty

of diagnosis, when patients fail to see the spider and to retrieve it. In the majority of the cases (68%) [15], a presumptive diagnosis is given, based on appearance of the lesions. There are two treatments for the envenomation of *Loxosceles*: one is the conservative local treatment with ice, corticoids, antihistamines, anti-inflammatory analgesics and later reconstructive surgery, used in the cases of cutaneous loxoscelism, such as dermonecrosis; the other treatment option is the specific treatment with serum therapy, in which an anti-serum (horse-derived with whole isotype IgG anti-venom) produced with *Loxosceles* venom, is administered to the victims after undergoing a spider bite, used for all patients with viscerocutaneous loxoscelism [10]. Although there are very few hospitals, in Spain, that have the anti-venom serum, the effectiveness of the treatments described in the international literature has been widely debated, and a definitive treatment has yet to be established [16,17]. The host immune system, challenged by the spider venom, would defend itself with a local inflammatory reaction, involving the activation of the complement and coagulation system, the release of TNF-alpha and other pro-inflammatory cytokines by keratinocytes, more immediate hypersensitivity reaction, in which helper T cells (Th2), immunoglobulin E (IgE), mast cells, and eosinophils are involved. The risk of developing an allergy reaction increases with the number of bites received over one's lifetime [18]. This is due to the existence of similar chemical components, highly conserved, in the toxins within the species [7]. The aim of the present study is to analyse and explain, using the clinical and laboratory data of the case report and a review of the literature, the implications that the immune system could have in the generation of umbilical vein thrombus and foetal death, in a pregnant woman who has been bitten by a spider.

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Figure 1: Mediterranean countries where you can find spiders *Loxosceles rufescens*.



Figure 2: Ten days before the accident by spider bite, the patient underwent a routine ultrasound; it does not visualized fetal problems or in the blood vessels.

Case Report

We report the case of a 36 years of age Spanish woman who was pregnant (35 weeks into gestation), by means of *in vitro* fertilization (IVF). Background checks on the patient previous to the IVF treatment showed that there were no genetic, autoimmune or fertility problems. The problems of fertility seem to have been due to structural alterations in the husband's spermatozoa. On questioning, the woman emphasized that there was no family history of repeated miscarriages or foetal losses, that she was not a drug user, and that she drank no alcoholic beverages, had taken no medications, except those specifically for the pregnancy, had not been exposed to hazardous chemicals (as far as she knew), and she had not recently been travelling. The patient indicated that she had spent her childhood in a rural environment suffering, on various occasions, from insect stings and bites/stings from other animals (wasps, tiger gnat, dog fleas, etc.). Hence, she has a medical history of different forms of acute allergic reactions requiring either a visit to the emergency department or hospital admission having been diagnosed as allergic to insects. The evolution of the pregnancy remained normal as corroborated by various ultrasounds (Figure 2). When she was in the 35th week of gestation she was accidentally bitten by a spider of the genus *Loxosceles*, of the *rufescens* species (Figure 3), at the top right-hand-site of her neck, in the month of June 2015. After this bite, she was immediately taken to the Primary Care Center where she was treated with corticosteroids and antihistamines. Despite early treatment, a blister appeared on the site of the sting surrounded by an erythematous perimeter (Figure 4). There was also a low-grade fever described as a

generalized heat, headache, chills, burning pain, difficulty in lateral movements of the neck and an extreme generalized scarlatiniform exanthema. No respiratory problems or oedema in the oral mucosa were presented. After 36 hours of the bite, the patient went to the Maternal Hospital since no foetal movements could be felt. She was send directly to be monitored in the emergency obstetrics department where was diagnosed with foetal death and was admitted for induction of labour. The physical evolution of the patient, after the foetal loss, was favourable, although once discharged from the Hospital she presented a haemoglobin of 103 g/L (118-157) and a haematocrit of 0.296 L/L (0.35-0.47). The symptoms of the bite disappeared in a few weeks and without consequence, except for the emotional pain of the loss foetal (Figure 5). The autopsy report of the foetus and placenta stated the presence of umbilical vein thrombosis and sub-funicular placental infarction as the cause of foetal death. In September 2015, three months after the foetal loss, the patient returned to the hospital to be examined. The results of the laboratory tests, including complete blood count, liver and renal function chemistries, immunoproteins analysis, urinalysis and coagulation functions analysis, were all within normal limits, except the C5 of the complement proteins 15.80 mg/dl, in the range (4-15) and the reptilase time of 23 seconds, range (15-22). Thrombophilia was also dismissed as a possible cause.

Discussion

Pregnancy itself presents a factor of hypercoagulability, as a physiologically adaptive mechanism to prevent post-partum bleeding.



Figure 3: A) The spider retrieved by husband of the patient was identified, using binocular magnifying glass, as *Loxosceles rufescens* by the Environmental Health Service of the Regional Government of Andalusia. It was not possible to determine the sex of the spider due to the bad state which arrived at the laboratory. B) *Loxosceles rufescens* adult spider, typical from Mediterranean area.

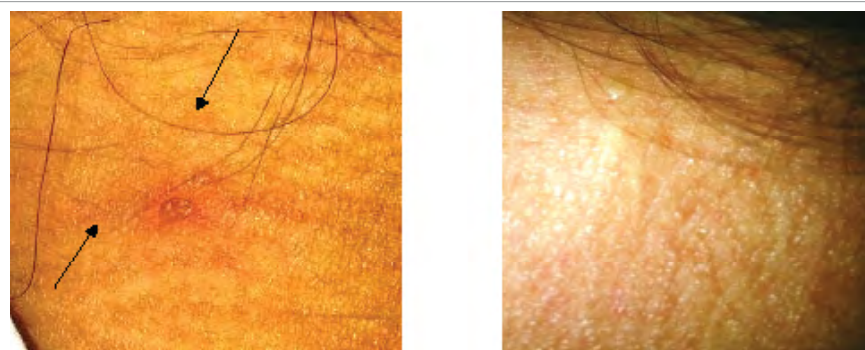


Figure 4: Skin lesion, in the area of the spider bite, on the upper region right neck when the patient was admitted in the Hospital. Blister surrounded by a small erythematous perimeter, accompanied by tiny blisters in the vicinity.



Figure 5: Favorable evolution of the lesion in the neck, by spider bite, a week after the bite.

However, when combined with additional underlying hypercoagulable states, the risk of thrombosis or embolism may become substantial. During pregnancy, the maternal immune system must perform a dual function: on the one hand, it must be able to tolerate the semi-allogenic foetus while simultaneously protecting the mother and the foetus against external pathogens or injury. This requires a finely regulated balance between immune activation and tolerance [19]. The venom of the spider, inoculated in the neck of our patient, was an assault on local tissues with the activation of an acute inflammatory reaction, attraction of neutrophils and the degranulation of the skin mast cells [9,20]. Mast cells are cells of the immune system that are present in the skin and

mucosal epithelium and rapidly secrete pro-inflammatory cytokines and lipid mediators in response to infections and other stimuli [21]. These cells contain abundant cytoplasmic granules filled with various inflammatory mediators that are released when the cells are activated. These cells are dedicated to organising emergency inflammatory processes, in a few seconds, thanks to their proximity to the blood vessels. They can be activated by both immunological and non-immunological means, thereby eliciting the generation of a series of internal signalling pathways. These pathways include the activation of nuclear transcript factor NF- κ B, which plays a key role in inflammation and defensive immune response [21]. Mast cell products also provide defence against helminths and are responsible for symptoms of allergic diseases [21]. The substances present in the venom of the spider [10] would generate the activation of the alternative pathway of complement proteins, which are closely linked to the coagulation system. Complement effectors directly enhance coagulation. These effects are supplemented by the interactions of complement with other inflammatory mediators that can increase the thrombogenicity of blood [22-24]. On the other hand, the mast cells and the release of endogenous mediators such as pro-inflammatory cytokines (TNF- α , IL-1, IL-6, IL-4, IL-5, ..), nociceptive and vasoactive mediators (prostaglandin D2, platelet-activating factor PAF, ..) and arachidonic acid derivatives (leukotrienes, especially LTC4), among others, may produce a reduction in the flow, venous stasis, increased amounts of blood and local vasodilatation, thereby amplifying the inflammatory response [8,24]. The actions of *Loxosceles* venoms on the blood vessels and the circulation have yet to be studied in depth, especially in the

case of pregnant women. There are very few cases collected regarding loxoscelism in pregnant women in the world: five cases published in 1991 that responded well to conservative treatment, in the form of a low-dose of prednisone [25]; and only a single case of systemic loxoscelism in 2014, which evolved favourably, but the use of specific anti-venom was necessary as was an early caesarean to save the mother and the child [26]. In another case of loxoscelism, this time from Italy, a young man who had previously been sensitized, generated a thrombus in the coronary artery, without any other previous risk factor or known vascular pathologies [27]. In an animal model, the administration of MSD, a component of the venom of the spider, produced a clinical picture similar to toxic shock, accompanied by a strong release of pro-inflammatory cytokines including TNF-alpha, IL-6, IL-10 and nitric oxide that finally activated phospholipase A2 and platelet aggregation [28,29]. It has been demonstrated that animal venoms, for instance those of bees, wasps, ants, snakes and fishes can induce changes in the microcirculation such as activation coagulation factors and protein C that generate systemic coagulopathy, intense haemorrhagic lesions, migration of inflammatory cells and tissues damage [30-32]. The venom of *Loxosceles* presents immunochemical reactivity crossed with the venom of other species and probably with the venom of other animals [8,31]. There is no relationship between the magnitude of the local lesion and the production of haemolysis. Not all bites in humans and animals lead to necrotic or systemic lesions, everything depends on the individual susceptibility to the venom [12]. Therefore, the pregnant woman, in our case, is a sensitized patient (previously exposed to the allergen and high production of IgE linked to the FcεRI of the mast cells). The presence of scarlatiniform exanthema in distant sites of the bite is a sign of a generalized systemic reaction that was able to affect the vessels of the umbilical cord and generate the foetal death.

We found a clear cause-effect relationship between the bite of the spider and the foetal loss. The combination of these two clinical conditions: a) the chemical composition of the venom of the spider bite, with the ability to activate the complement proteins and the coagulation system; plus b) the defence of a maternal immune system previously sensitized with different forms of acute allergic reaction, were probably jointly responsible for the generation of the umbilical vein thrombosis and foetal death. It is possible that individually these situations would not have altered the coagulation system sufficiently to have provoked such a reaction, but this unique conjunction of entities, by means of mechanisms that remain largely unknown, could have been the triggers of the foetal death by thrombosis.

Ethical Statement

No research animals were involved with any material reported in the manuscript. All components of the submitted manuscript have been gathered with integrity, and permission of the patient and her husband was granted for reporting the case, and no breaches of confidentiality were made.

Conflict of Interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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