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Loxoscelism: Proposal of a New Protocol for Treatment

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Abstract

Loxoscelism is a rare but often underestimated cause of dermonecrosis in emergency departments. Different kinds of treatment are proposed in literature, but a shared management protocol is not yet available. We propose a therapeutic protocol considering a case which occurred in our emergency department, managed with the support of the Poison Control Center (PCC) and the Hyperbaric Unit. In particular, focusing on the risk of bacterial superinfection and necrotizing fasciitis, we suggest to consider the use of hyperbaric therapy.

Keywords: Loxoscelism; Clostridia; Spider fangs; Cutaneous loxosceles

Introduction

Loxoscelism is a syndrome induced by the bite of a spider of the Loxosceles species [1]. Brown spider envenomation is a cause of necrotizing skin lesion due to spider bites [2] and sometimes can provoke systemic complications, the diagnosis is often underestimated. In our case a patient was successfully treated with antibiotics, steroids and hyperbaric oxygen therapy. This contribution remarks the importance of a multidisciplinary approach in the event of dangerous spider bites.

Case Report

A 39 years old woman consulted the general practitioner on November, 4th 2014 because of a probable spider bite in the right zygomatic region. She was most likely bitten the previous day. The lesion was attributed to a spider bite because a spider was captured near the bed the next morning. The physician described a right periorbital edema with a probable necrotic area and a severe headache. Thus he prescribed amoxicillin and clavulanic acid 1g twice a day, betamethasone 1mg once a day and topical gentamicin sulfate with betamethasone valerate. During the following days the edema expanded and almost the whole right half of the face was affected. Moreover, the patient lamented a worsening headache, right ear pain, diarrhea (4-5 surges a day) and nausea. For these reasons the patient presented at Emergency Department on November 7th 2014. The physician could observe a right periorbital edema with a probable necrotic area of 0.5 cm in diameter. A retro-auricular welt, attributed to reactive lymphnodes and a reddening of the right half of the face were present. Meanwhile, the headache was worsening without rigor nucalis. Blood tests showed an increase of inflammatory markers and leucocytosis. Once the insect bite, headache, and diarrhea were diagnosed, a wide spectrum antibiotic therapy was instituted with ciprofloxacin 500 mg twice a day for 5 days, betamethasone 4 mg once a day gradually decreasing, loperamide, and pain killers when necessary. Symptoms did not regress and retro-bulbar pain appeared. The patient then contacted our Poison Control Center (PCC) for a toxicological opinion. The PCC, having consulted the Hyperbaric Unit, suggested she undergo hyperbaric treatment. The patient was examined by the Hyperbaric Unit physicians on November 12th 2014. During the examination the patient appeared awake, responsive, eupneic, with headache accompanied by a severe sense of retro-bulbar oppression without vision alterations and pain localized to the lesion. Two lesions, 4 mm wide in diameter, were present on the right eyelid and another one, partially secreting, 0.5 mm wide, in the right zygomatic region. The area appeared as a red-violaceous welt with pain at acupressure. No reactive lymph nodes were observed. We obtained an intralesional swab for microbiological analysis and we contacted an arachnologist by phone. According to the description, the spider was likely to be identified as a violin spider. Infection of soft tissues, skin necrosis, and ulcer were diagnosed, therefore hyperbaric oxygen therapy was indicated. On the same day the patient underwent hyperbaric treatment conducted according to the following profile: pressure descent rate 2 m/min up to a depth of -18 m, then: 30 minutes in 100% oxygen, 5 minutes in open air, 30 minutes in 100% oxygen, 5 minutes in open air, 30 minutes in 100% oxygen, and final ascension in oxygen reaching a depth of -3 m at a rate of 2 m/min. After the first treatment an impressive reduction of pain and edema was noted. The patient underwent another treatment the same day and other 4 treatments (twice a day for 2 days) using the same profile. Reduction of edema and pain at the lesion was observed again. Because of the persistent retro-bulbar pain, an magnetic resonance imaging (MRI) was deemed necessary in order to exclude the presence of inflammatory phlegmons. The MRI was carried out on November 14th 2014 and a mild increase of signal was attributed to a past cellulitis. On November 14th 2014 the cultural analysis showed a superinfection by Multi Resistant Staphylococcus haemoliticus. On the basis of the favourable results of the hyberbaric therapy another six treatments were performed, according to table 9 of US NAVY manual, 6th review. Eventually, using these treatments, the patient obtained a complete

resolution of symptoms and the regression of skin lesions. Only a small necrotic area was still cicatrizing.

Discussion

Clinical aspects

Early signs and symptoms of cutaneous loxosceles are pruritus, burning pain, erythema and local induration [3]. Physicians are generally consulted 24 to 48 hours after the bite [4] and this often causes a delayed therapy. Different evolutions are possible: most Loxosceles envenomations provoke only a mild inflammatory reaction [5,6] and necrosis is unlikely to present if a lesion is absent 2 to 3 days after the bite [7]. Cutaneous loxoscelism with severe edemas occurs in 4%, while systemic loxoscelism is far more rare: less than 1% of necrosis induced by *Loxesceles reclusa* [8]. A serious lesion can increase in size and form a pustule while the erythema enlarges and becomes violaceous. A blue macule appears presenting zones of necrosis [3]. An eschar may form in 3 to 7 days [8]. Histopathology in loxoscelism is characterized by thrombosis, hemorrhage, inflammatory infiltrate, dermatitis and liquefactive necrosis [9]. This pattern is produced by the effects of toxins present in the venom. The venom contains various enzymes including collagenases, peptidases, hyaluronidases and Sphingomyelinase D [10]. Tambourgi et al. [11] demonstrated that the hemolysis inducted by Sphingomyelinase D is due to the activation of the complement. Moreover Sphingomyelinase D decreases the EGFR (epidermal growth factor receptor) expression, which is involved in wound repair [12]. Polimorphonuclear leukocytes (PMN) infiltrate and metalloproteinases are also involved in tissue damage [10]. In case of infections (typically Clostridia) other factors contribute to the damage: in fact Clostridia is known as a producer of alpha toxin that causes myolisis, haemolisis and coagulation disorders [13]. Conditions of hypoxia, not only promote anaerobic bacterial growth but also affect the efficiency of phagocytosis [13]. Moreover, tissue necrosis can reduce redox potential and thus facilitate bacterial growth[13]. Therefore, an early control of infection is crucial in patients at risk, in order to avoid the development of necrosis.

Signs like haemoglobinuria, haematuria and proteinuria [8], nausea/vomiting, fever up to 40.5C, chills, myalgias/arthralgias, thrombocytopenia, intravascular coagulation and also acute renal failure (due to rhabdomyolysis) are suggestive of viscerocutaneous loxoscelism; possible complications are pyoderma gangrenosum, pulmonary edema and systemic toxicity [14]. Pain out of proportion with respect to the clinical findings and that evolves in numbness in presence of crepitus [13] and grayish or black skin indicates necrotizing fasciitis. Diagnosis is usually clinical and based on anamnesis. When possible, the analysis of the spider by an arachnologist is useful since laboratory tests to confirm the diagnosis are not easily available. The worse complications can be detected monitoring haemoglobin, free haptoglobin, haemoglobinuria and LDH [4].

Computerized tomography (CT) and Magnetic Resonance (MR) can be useful when necrotizing fasciitis is suspected [15].

Therapy

Different kinds of treatment have been proposed in literature. However, none is currently supported by strong evidence [1]. RICE (rest, ice, compression, elevation), tetanus and diphteria immunization, anthistamines including cyproheptadine are generally considered reasonable first line treatments and useful in every poisonous insect bite [16]. Cyproheptadine is used to contrast the effect of serotonin on platelet aggregation and ischemia [2]. However, this treatment has been found useless in a controlled trial on white rabbits [17]. Antibiotics are frequently administered in order to avoid infective complications [4]. Considering the possible presence of Clostridia in the fangs of the spider, Penicillin G is probably the best molecule in case of *C. perfringens* infection, but erythromycin and tetracyclines are also possible alternatives [2]. The latter, in particular, besides their antibiotic properties, are known for their anti-inflammatory and immunomodulatory action, which could be useful in this setting. Using tetracyclines in envenomated rabbits, Paixao and Cavalcante et al. [12,18] observed a decreased expression of metalloprotases 2 and 9 and an avoidance of keratinocyte cell death. Intralesional or systemic glucocorticoids are commonly used in clinical practice [19] and, even if not recommended in cutaneous loxoscelism, could have some benefit in viscerocutaneous loxoscelism according to some authors [20,21].

Inhibition of PMN chemotaxis and the consequent reduction of skin necrosis are the rationale for the use of dapsone [22] although, even in this case, its use is not supported by strong evidence. Hobbs [22], in a randomized controlled animal laboratory experiment, compared the treatment with dapsone, dapsone and hyperbaric oxygen, and a control, finding no clinically significant difference in the three groups. In another study [23] dapsone was found to be able to reduce the size of the lesions in guinea pigs.

Hence, its use is still controversial and not free from adverse effects including hemolytic anemia. This could generate confusion because the venom itself can produce the same effect [24]. Anti-venom is also used for systemic loxoscelism, particularly in Brazil, where two sera are available: an antiloxoscelic serum against venoms of *L. gaucho, L. laeta* and *L. intermedia* and an anti-arachnidic serum [1]. Even though there is little evidence of its use, it has been found to be able to decrease necrosis in animal models [25]. Allergic reactions and serum sickness are among the possible adverse effects. Theoretically promising new therapies should include metalloproteinase inhibitor drugs [10].

Role of hyperbaric oxygen therapy

There are various reasons supporting the use of hyperbaric oxygen therapy (HBOT) in anaerobic soft tissue infections [13]:

Efficiency of polymorphonuclears is indirectly improved in the presence of oxygen.

Some antibiotics have an increased activity when exposed to oxygen.

Anaerobic bacteria are directly hit by the toxic effect of oxygen.

Moreover, molecular oxygen, reacting with organic molecules, generates free radicals which are involved in bactericidal and bacteriostatic mechanisms [13].

Hyperbaric treatments reaching PO_2 over 30 kPa stop Clostridial alpha-toxin production thus preventing its systemic effects [26]. Hyperbaric oxygen must always be intended as complementary to other therapies (antibiotic, surgery, etc.) and cannot be recommended for use on its own in soft-tissue infections [13,15]. In vitro studies confirmed the bacteriostatic and bactericidal effect of hyperbaric oxygen on Clostridia, but not on quiescent spores [13]. Some authors consider hyperbaric treatment useful to deactivate the sulfhydryl

present in sphingomyelinase D [19]. Moreover, hyperbaric oxygen inhibits the production of toxins, stops the activity of theta toxin while not affecting the activity of the pre-formed alpha toxin [27]. A drop in pH, due to products of aerobic and anaerobic metabolism, is usually observed as a consequence of an infection and this favors anaerobic germs growth [15]. Host responses also benefit from an increased oxygenation: in fact phagocytosis is enhanced by oxygen, which is precursor of the bactericidal H_2O_2 [13]. Hyperbaric oxygen therapy can contrast leukocyte impairment and contributes to containing ischemia and the spread of infection [26]. The penetration of aminoglycosides through the cytoplasmic membrane and the bactericidal properties of fluoroquinolones decrease in anaerobiosis [13].

Several authors investigated on the effects of hyperbaric oxygen therapy in vivo with discordant conclusions [28]. Hobbs [22] compared four groups of piglets treated with dapsone, hyperbaric oxygen, dapsone in combination with hyperbaric oxygen, or no treatment and found an increase in the rate of reduction in induration between the treated groups and the control, although clinically insignificant. In a controlled trial [17] hyperbaric oxygen was compared with dapsone, cyproheptadine, and control in four groups of New Zealand white rabbits experimentally envenomated. There were no statistically significant differences in lesion size, ulcer size, and histopathologic ranking. However, other authors [3,8]found that hyperbaric oxygen therapy had a positive effect on animal models.

Maynor [3] confronted five groups of New Zealand white rabbits injected with venom. One group was left untreated, another one received only one immediate hyperbaric oxygen treatment (100% O_2), the next were administered 10 immediate hyperbaric oxygen treatments (100% O_2), another group received 10 48 hours delayed hyperbaric oxygen treatments (100% O_2), and the final group underwent 10 immediate hyperbaric treatments with normal inspired PO_2. The author found a decrease in wound diameter at 10 days ($p<0.0001$) in all treatments when using 100% O_2. He concluded that a hyperbaric oxygen treatment within 48 hours contributes to a reduction in size of wounds. Beilman [29] obtained similar encouraging results in guinea pigs.

Proposal for a protocol

Although there is little to no evidence reported in literature for the majority of the treatments, there is some data available for treatment of necrotizing fasciitis.

In the light of the review of literature exposed above and on the basis of the reported case, we propose a new protocol to support physicians in the choice of best treatment according to the clinical conditions presented by the patients. This protocol, at the moment, is not supported by clinical trials since designing a randomized trial in this area would be difficult at best primarily because of ethical reasons. It is, however, an attempt to rationalize the tendencies already in use in clinical practice by integrating the knowledge available on Loxosceles envenomations and on necrotizing soft-tissue infections, which have been demonstrated to be closely linked. Considering the demonstrated presence of bacteria such as Clostridia (including Clostridium perfringens)[30] in the spider fangs and the various treatments proposed in literature, we suggest a protocol based on the evaluation of clinical aspects and risks of infection calculated by using a score.

Protocol

According to our protocol the patient presenting with a suggestive anamnesis and signs/symptoms of spider envenomation should be evaluated for the presence of pain, edema, necrosis/ischemia.

Variable		Score
C-reactive protein	< 150 mg/L ≥ 150 mg/L	0 4
Total white cell count	< 15 per mm^3 15-25 per mm^3 > 25 per mm^3	0 1 2
Hemoglobin	>13.5 g/dL 11-13.5 g/dL < 11 g/dL	0 1 2
Sodium	≥ 135 mmol/L < 135 mmol/L	0 2
Creatinine	≤ 1.59 mg/dL > 1.59 mg/dL	0 2
Glucose	≤ 180 mg/dL > 180 mg/dL	0 1

Table 1: Modified from C.-H. [31].

The protocol should be applied within 48 hours after the bite. Beyond 48-72 h, necrosis is unlikely to present [7] without any other accompanying signs, and that would render the treatment excessive even if not invasive. Blood samples should be drawn at admission to determine the value of the LRINEC score [31] that includes: C-reactive protein, total white cell count, haemoglobin, sodium, creatinine, glucose. This score has been demonstrated to be predictive of necrotizing fasciitis even in clinically early cases [31]. The maximum

score is 13, a score ≥ 6 is suggestive, and a score ≥ 8 is highly predictive of necrotizing fasciitis (Tables 1 and 2).

Low Risk	Medium Risk	Evolving Risk	Very High risk
No necrosis	No necrosis	Ischemia	Ischemia
Neglectable pain	Mild pain	Severe pain	Severe pain
Neglectable edema	Mild edema	Severe edema	Severe edema
LRINEC SCORE <6	LRINEC SCORE <6	LRINEC SCORE >6	LRINEC SCORE ≥8
Swab if possible	Swab if possible	Swab if possible	Swab if possible
Basic therapy	Basic therapy	Basic therapy	Basic therapy
		Hyperbaric oxygen therapy TAB. 9 U.S. NAVY REV. 6 2 sessions/day for 2 days. Then repeat evaluation If compartment syndrome 2 sessions/day for 5 days after fasciotomy	Hyperbaric oxygen therapy TAB. 2.8 ATA 90 min. 2 sessions/day for 3 days then TAB. 9 US NAVY 1 session/day for at least 10 days
	CT or MRI	CT or MRI	CT or MRI
		Consider surgical evaluation	Recommended surgical evaluation
Blood samples for viscerocutaneous loxoscelism	Blood samples for viscerocutaneous loxoscelism	Blood samples for viscerocutaneous loxoscelism	Blood samples for viscerocutaneous loxoscelism
CT: Computerized Tomography, MRI: Magnetic Resonance Imaging			

Table 2: A stratification of risk and a consequent treatment is possible according to the following scheme.

Basic therapy includes: antihistamines, antibiotics (wide spectrum), steroids (according to clinical conditions); check tetanus and diphteria immunization.

Blood samples for viscerocutaneous loxoscelism include: free haptoglobin, haemoglobinuria, LDH.

Note: Increased depth of HBOT in case of Clostridia infections are documented in literature [15]. The kind of hyperbaric treatment is suggested according to the US NAVY tables for necrotizing fasciitis.

According to the Karolinska Institute [26] patients with fasciitis or myositis must be treated at 2.8 bar pressure for 110 minutes, 2-3 times/day in the first 24 hours, then 1-2 times/day depending on clinical improvement. In case of infection by Clostridia a more aggressive HBO treatment is appropriate, sometimes even before surgery, depending on clinical conditions.

Obviously, when the characteristics of the lesions allow it, we recommend collecting a sample using a tampon and requesting an antibiogram to guide the choice of the most suitable antibiotic. In case the patient is admitted within 48 hours since the bite, the evolution should be monitored through blood tests administered after 1-2 days. If, instead, the patient is admitted later than 48 hours since the bite, then the blood tests should be performed when no improvement of the condition is observed in 72 hours.

Even if in our case the respect of the timing proposed in our protocol was not possible, the prognosis after treatment was favourable. The time lapse of 48 hours since the bite for the application of the protocol is in fact intended also to avoid excessive treatment when the risk of necrosis is yet decreased.

Conclusions

Loxoscelism should be considered a possible cause of skin necrosis even if rare. The main steps in the management of a similar case are:

Recognizing the damage as a bite (and identifying the spider when possible), looking for skin necrosis, pain and edema, Calculating the risk of infection (using the score and obtaining a swab) setting a therapy according to the case seriousness.

Basic therapy procedures are useful for all patients and include: rest, ice, compression, elevation, tetanus and diphteria immunizations, antihistamines and steroids in particular cases with severe edemas. Antibiotic therapy, when possible, should be based on the results of the swab, however we emphasize the need of an early active therapy targeting *Clostridium spp*. HBOT can be performed, with preventive and therapeutic intent, by following the tables reported in the protocol derived from the evidence available on its use in necrotizing fasciitis.

CT or MR imaging can be a useful diagnostic tool in presence of mild pain and edema and both recommended either in serious cases or whenever phlegmons are suspected. A surgical evaluation should always be considered in patients at medium and high risk. Tests for viscerocutaneous loxoscelism must be performed in order to detect the negative evolution in time.

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