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Clinical picture and laboratorial evaluation in human loxoscelism

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ABSTRACT

Loxosceles spiders are found globally, especially in South and North America. In Brazil, approximately 10,000 cases of *Loxosceles* spp. spider bites are reported annually. Herein we analyzed 81 patients diagnosed as either cutaneous or cutaneous-hemolytic loxoscelism, in a geographical area where most accidents are caused by *Loxosceles gaucho*, and we report their clinical and laboratory data obtained during week 1 and 2 after the bite. Massive hemolysis was noticed in only 2 cases, but high serum bilirubin and LDH levels, suggestive of hemolysis, were noticed in 25 cases on admission. Anemia was not frequent (14.7%), and reticulocytosis was particularly noticed during week 2 (in 56% of patients). High D-dimer levels were suggestive of endothelial cell activation and intravascular thrombin generation, but thrombocytopenia was noticed in only 17.6% of patients in week 1. Acute kidney injury (AKI) only occurred in patients with massive hemolysis. The definitive diagnosis of overt disseminated intravascular coagulation (DIC) could not be established on admission. Fever was associated with the presence of hemolysis ($p = 0.03$). Altogether, these findings provide evidence that mild hemolysis is frequent in loxoscelism and suggest that AKI is uncommon, exclusively occurring in patients with massive hemolysis.

1. Introduction

The brown recluse spiders, *Loxosceles* spp, are found globally, especially in South and North America (Gertsch, 1961; Southcott, 1976; Gertsch and Ennik, 1983; Platnick, 2010). In Brazil, approximately 20,000 cases of spider bites are reported annually, and *Loxosceles* bites account for almost 50% of bites involving all venomous species. Three species have been mostly implicated in human envenomation in Brazil: *Loxosceles gaucho*, *Loxosceles intermedia* and *Loxosceles laeta* (Brasil, 2001). *Loxosceles* spp venoms have been demonstrated to produce cutaneous necrosis and, occasionally, hemolysis by multiple pathways. Sphingomyelinase D, a key component of *Loxosceles* venom (Forrester et al., 1978) activates complement, endothelial and epithelial cells, as well as endogenous metalloproteinases (Patel et al., 1994; Gomez et al., 1999; Tambourgi et al., 2000; Veiga et al., 2001; Tambourgi et al., 2005; Paixão-Cavalcante et al., 2006; Tambourgi et al., 2007). Clinical manifestations evoked by *Loxosceles* envenomation vary depending on the amount of venom injected, anatomic location of the bite, and host susceptibility, as well as on spider species, sex and age (Futrell, 1992; Gonçalves de Andrade et al., 1999; de Oliveira et al., 2005; McGlasson et al., 2007). Classically, loxoscelism have been classified into two forms: cutaneous and cutaneous-hemolytic (also known as systemic or viscerocutaneous loxoscelism). In cutaneous loxoscelism, patients manifest a slow-progression cutaneous lesion that may evolve into necrosis; this form can be associated with non-specific systemic signs, such as scarlatiniform or morbilliform rash, headache, malaise, nausea, vomiting and low-

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grade fever. The cutaneous-hemolytic form of loxoscelism–in which in addition to the cutaneous lesion, hemolysis is present – is much less common and seldom result in death; this type of loxoscelism is associated with acute kidney injury and disseminated intravascular coagulation (DIC) due to intravascular hemolysis (Futrell, 1992; Hogan et al., 2004; Isbister and Fan, 2011). Although the development of massive intravascular hemolysis is well recognized in cutaneous-hemolytic loxoscelism, no report has demonstrated the occurrence of mild hemolysis in cutaneous loxoscelism. In fact, few clinical reports have reported laboratory data from patients bitten by *Loxosceles* spiders, mostly of patients with cutaneous-hemolytic loxoscelism (Taylor and Denny, 1966; Hostetler et al., 2003; Zambrano et al., 2005; Dyachenko et al., 2006; de Souza et al., 2008; McDade et al., 2010). Herein, we report a prospective clinical and laboratory data survey of patients with definitive or presumptive diagnosis of either cutaneous or cutaneous-hemolytic loxoscelism admitted to Hospital Vital Brazil, Butantan Institute. Our findings suggest that mild hemolysis is frequent, and that it occurs in one-third of those patients.

2. Patients and methods

Patients ($n = 81$) with definite or presumptive diagnosis of either cutaneous or cutaneous-hemolytic loxoscelism–who had been admitted to Hospital Vital Brazil, Butantan Institute, São Paulo, Brazil, during 2004–2006 –were included in this study. Epidemiological and clinical information –such as sex, age, time interval between bite and admission, clinical signs and symptoms–administered treatment, occurrence of complications, and laboratory data were collected and evaluated. Definite diagnosis was accomplished based on identification of the agent associated with a skin lesion showing features compatible with loxoscelism evolution. Presumptive diagnosis of cutaneous loxoscelism was carried out in patients who exhibited (a) a characteristic lesion associated with (b) compatible epidemiological history, (c) a characteristic time-course of loxoscelism lesion and, sometimes, (d) non-specific systemic symptoms and signs. The characteristic lesion of cutaneous loxoscelism, usually present in the first 2–3 days after the bite, is manifested by a painful macula, whose color is a mingling of violaceous (which does not blanch upon diascopy) and pale areas, sometimes indurated, and which is frequently surrounded by an erythematous area. Serous and/or hemorrhagic blisters can be observed. Patients admitted later may manifest dry necrosis or an ulcer with sharply defined rim and tissue of granulation (Futrell, 1992; Isbister and Fan, 2011). Thus, that clinical presentation could not be attributable to any other etiology. Cutaneous-hemolytic loxoscelism was defined when intravascular hemolysis was suspected, irrespective of local reaction severity. One case report of a patient included here with massive hemolysis has been published elsewhere (de Souza et al., 2008).

2.1. Treatment

Polyvalent antivenom for *Loxosceles* sp, *Phoneutria* sp and *Tityus* sp (soro antiaracnídico, SAA, Instituto Butantan) was administered to patients in the early stage of cutaneous loxoscelism, who manifested neither necrosis nor ulcer on admission (Pauli et al., 2009); on the other hand, antivenom treatment was prescribed to all patients with cutaneous-hemolytic loxoscelism. Antivenom was given intravenously and the number of vials varied according to envenomation severity: 05 vials for cutaneous loxoscelism, and 10 vials for cutaneous-hemolytic loxoscelism (Brasil, 2001). The classification of severity was based on clinical manifestations on admission. Prednisone (40–60 mg/day, or 1 mg/kg/day for children) was administered for 5–7 days.

2.2. Laboratory analyses

A previous study showed that patients seldom arrive prior to 24 h at the hospital, but in different time periods thereafter (Malaque et al., 2002). Thus, in order to standardize the analysis of results, blood samples collected in different time periods after arrival were grouped according to the time period they were obtained: week 1 (days 1–7) or 2 (days 8–14) after *Loxosceles* sp bite. Blood samples were obtained at Hospital Vital Brazil, and sent to Hospital Universitário (University of São Paulo, São Paulo-SP) to be analyzed in automated equipments. Hematological (complete blood count), hemostatic [fibrinogen assay, activated partial thromboplastin time (aPTT), prothrombin time (PT), D-dimer assay] and biochemical [serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, urea, creatinine, C-reactive protein (CRP), lactate dehydrogenase (LDH), creatine kinase (CK), Na^+ and K^+)] tests were carried out, regardless in which day the blood samples were collected. If several laboratory results from blood samples collected over the two-week period were available, the most altered ones were included in the analysis. Presumptive diagnosis of intravascular hemolysis was suspected when jaundice was present and/or serum levels of total bilirubin (TB) were higher than 1.0 mg/dL and indirect bilirubin (IB) higher than >0.7 mg/dL. Serum creatinine levels were considered abnormal when values were higher than 1.3 mg/dL.

2.3. Statistical analyses

A database of this pooled information was constructed and statistical calculations were performed using the softwares Epi-Info 6.04c (CDC, Atlanta, GA, USA) and Stata™ 8.0. Comparisons between proportions (χ^2 test or Fisher's exact test), means or medians (Student's *t*-test or Mann–Whitney's rank sum), whenever was appropriate, or determination of correlation among variables were performed using Stata™ 8.0 and Sigmastat™ 3.5. Whenever necessary, data transformation was undertaken to obtain homocedasticity and normal distribution. Differences with $p < 0.05$ were considered statistically significant.

3. Results

A total of 81 patients with loxoscelism were included in this study. The median age was 36 years (range: 3–75 years; 7.4% less than 14 years old), and no gender difference was observed (female/male: 49.4%/50.6%). In 14 cases (17.3%),