



Review

Atypical presentations of cutaneous leishmaniasis: A systematic review



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ABSTRACT

Cutaneous Leishmaniasis (CL) is endemic in 88 countries, showing relevant prevalences. The aim of this study was to perform a systematic review on atypical lesions of CL around the world, addressing clinico-epidemiological, immunological and therapeutic aspects. A search of the literature was conducted via electronic databases Scopus and PubMed for articles published between 2010 and 2015. The search terms browsed were “cutaneous leishmaniasis”, “atypical” and “unusual”. Based on the eligibility criteria, 34 out of 122 articles were included in the final sample. Atypical lesions may include the following forms: erythematous volcanic ulcer, lupoid, eczematous, erysipeloid, verrucous, dry, zosteriform, paronychia, sporotrichoid, chancriform and annular. In any cases, they seem to be another disease like subcutaneous and deep mycosis, cutaneous lymphoma, pseudolymphoma, basal and squamous cell carcinoma. The lesions have been reported in the face, cheeks, ears, nose, eyelid, limbs, trunk, buttocks, as well as in palmoplantar and genital regions; sometimes occurring in more than one area. The reason for clinical cutaneous leishmaniasis pleomorphism is unclear but immunosuppression seems to play an important role in some cases. There are no established guidelines for the treatment of atypical cutaneous leishmaniasis. However, pentavalent antimonials remain as first line treatment for all forms of leishmaniasis even for HIV-infected patients and atypical forms. Finally, to diagnose an atypical lesion properly, the focus has to be on the medical history and the origin of the patient, comparing them to the natural history of leishmaniasis and always reminding of possible atypical presentations, to then start searching for the best diagnostic method and treatment, reducing the misdiagnosis rate and, subsequently, controlling the disease progression. Thereby, contributing for breaking the transmission chain of the parasite, due to early correct diagnosis which, in turn, contributes to reduce the prevalence.

1. Introduction

Leishmaniasis collectively refers to various clinical syndromes caused by obligate intracellular protozoa of the genus *Leishmania*, that is transmitted by the sandfly (Ayatollahi et al., 2015; Karami et al., 2013). It is a vector-borne zoonosis, with dogs, rodents, wolves, and foxes as common reservoir hosts and humans as incidental hosts (Ayatollahi et al., 2015; da Silva et al., 2014). Approximately 1.5 million new cases are documented each year and more than 350 million people live in areas of active parasite transmission (Dassoni et al., 2013).

Cutaneous leishmaniasis (CL) is one of the four different forms of the disease and the most common form (Alhumidi, 2013); being a major public health problem in 88 countries with an endemic behavior (Dassoni et al., 2013; Oryan et al., 2013). The other three clinical

forms include: visceral leishmaniasis (or Kala-azar); mucocutaneous leishmaniasis; and diffuse cutaneous leishmaniasis (DCL) (Shah et al., 2010; Talat et al., 2014). Diffuse cutaneous leishmaniasis is relatively rare and usually associated with mucous membrane involvement (Dassoni et al., 2013).

In an endemic area, it is necessary for the physician to be aware that any atypical lesion, especially chronic form, should be investigated for cutaneous leishmaniasis (Ayatollahi et al., 2015). Be attentive to the clinical examination, investigate if the patient lives in endemic area or traveled to an endemic area can facilitate the diagnosis.

There have been reports of some atypical lesions of CL around the world. These lesions can mimic many other diseases and confound the physicians, which may delay the precise diagnosis, submitting the patients to unnecessary treatments, worsening the picture, and contributing to the transmission chain of the parasite. However, there is a

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lack of studies addressing specifically this issue. In this scenario, we aimed to perform a systematic review of the literature on atypical lesions of cutaneous leishmaniasis, addressing the clinic-epidemiological, diagnostic and therapeutic features of these uncommon lesions.

2. Material and methods

The present study represents a systematic review of literature. The searches were conducted via the international electronic databases Scopus and PubMed, on March 20th, 2015. The search terms browsed in the databases were “cutaneous leishmaniasis” (Medical Subject Headings – MeSH), “atypical” and “unusual”, with 5-year time limit (2010–2015).

In order to reduce the risk of bias of individual studies, where a title or abstract seemed to describe a study eligible for inclusion, the articles were entirely examined to assess their relevance based on the inclusion criteria. Three independent researchers (CM, LC, GS) carried out a three-step literature search. Any discrepancies among the three reviewers who, blind to each other, examined the studies for the possible inclusion were resolved by the senior author (ML).

The article analysis followed previously determined eligibility criteria. The studies must have met all the following criteria for inclusion: (1) manuscripts written in English; (2) articles addressing atypical lesions of cutaneous leishmaniasis; and (3) prospective or retrospective observational (analytical or descriptive), experimental or quasi-experimental studies, or case report. Considering the scarce of data about atypical manifestations of CL, and that the cases are publicized in the literature mainly as case reports, we decided to include this type of publication in our search in order to better explore the uncommon lesions. The full text of the selected articles (sample) were obtained directly from the aforementioned databases, when freely available, or through Coordination of Improvement of Higher Education Personnel (CAPES) Portal of Journals, a virtual library linked to Brazil's Ministry of Education and subjected to content subscription.

We adopted the following exclusion criteria: (1) repeated articles in different databases; (2) non-original studies, including editorials, reviews, prefaces, brief communications, and letters to the editor; (3) full text not available; (4) author's name not disclosed; and (5) out of context. Each paper in the sample was read in its entirety, and data elements were then extracted and entered into a spreadsheet that included authors, publication year, description of the study sample, and main findings.

Thus, to provide a better analysis, the next phase involved comparing the studies and grouping, to facilitate our study the results regarding the studied subject were classified into four categories: characteristics of the atypical lesions, epidemiological features, immunological aspects, and considerations on treatment of the atypical forms.

To achieve a high standard of reporting we have adopted “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) guidelines (<http://www.prisma-statement.org/>).

3. Results

Initially, the aforementioned search strategies resulted in 109 references in Scopus and 57 references in PubMed. Forty-four of them were repeated in the two databases and were counted only once. After this, there were 13 different references counted in PubMed, ending in 122 articles to be analyzed. After analyzing title, abstract and text according to the eligibility criteria, 34 articles were included in the final sample (Fig. 1). From this total, 30 (88.23%) are case reports and 4 (11.76%) are case series (Table 1). Table 1 shows the main findings of the sample, including information such as gender, age, geographic location, aspect and duration of the lesions, etiological agent, differential diagnostic and treatment.

4. Discussion

4.1. Characteristics of the atypical lesions of CL

The classic initial clinical sign of the CL is the appearance of small papules and an erythematous nodule, which may be single or multiple, usually located in an exposed region of the tegument where, after a few months, it develops into ulcers, the most common presentation (63%–91% of cases), with indurated raised outer borders, regular contours and a cross-grained background with or without a seropurulent exudate (Adriano et al., 2013; Siah et al., 2014). Commonly, CL skin lesions have a wide variety of forms: round or oval; erythematous base, infiltrated and firm in consistency; well-defined, high edges; reddish background and coarse granules (Hepburn, 2003; Neitzke-Abreu et al., 2014).

In general, based on the studies selected, atypical lesions have included the following forms: erythematous volcanic ulcer, diffuse, eczematous, lupoid, verrucous, dry, zosteriform, nodular lesions, erysipeloid, sporotrichoid, annular (resembling a ringworm infection), paronychia, palmoplantar, and psoriasiform (Doudi et al., 2012; Faber et al., 2003; Iftikhar et al., 2003; Kafaie et al., 2010; Momeni and Aminjavaheri, 1994; Oryan et al., 2013; Raja et al., 1998; Ramot et al., 2014). Chancriform and annular were also reported in genital lesions (Faber et al., 2003; Iftikhar et al., 2003; Momeni and Aminjavaheri, 1994; Raja et al., 1998). It has also been reported leishmaniasis recidivans, in which small nodules develop around a healed scar; angiolupoid cutaneous leishmaniasis of the face, resembling lupus erythematosus; vegetating lesions with a papillomatous aspect and a soft moist consistency; and verrucous lesions with a dry rough surface, presence of small scabs and peeling (Hepburn, 2003; Neitzke-Abreu et al., 2014).

Clinically, localized cutaneous lesions may resemble other skin conditions, such as: blastomycosis, sporotrichosis, diverse fungal skin infections, cutaneous anthrax, eczema, lepromatous leprosy, tuberculosis, *Mycobacterium marinum* infections, basal and squamous cell carcinomas (SCC), and infected insect bites (Akilov et al., 2007; Bari and Rahman, 2008; Ceyhan et al., 2008; Dassoni et al., 2013; de Brito et al., 2012). Syphilis has been also reported in the differential diagnosis (Neitzke-Abreu et al., 2014; Talat et al., 2014).

When the plaque lesions of CL are located on the face: systemic lupus erythematosus, discoid lupus erythematosus, lupus vulgaris, cutaneous lymphoma and erysipelas are in the differential diagnosis (Akilov et al., 2007; Bari and Rahman, 2008; Ceyhan et al., 2008; Dassoni et al., 2013; de Brito et al., 2012). Although erysipelas-like presentation of CL is rarely reported, its clinical features include erythematous infiltrative ill-defined plaque over the face covering the nose and both cheeks (David and Craft, 2009; Robati et al., 2011). The papulonodular form clinically may resemble sarcoidosis, acne rosacea or acneitis (Douba et al., 2012).

Sometimes, there are multiple erythematous nodules mimicking cutaneous lymphoma or pseudolymphoma. The typical microscopic findings are mixed inflammatory infiltrate with many histiocytes and granuloma formation containing Leishman-Donovan bodies (Alhumidi, 2013; Murray et al., 2005).

Ramot et al. (2014) have reported a case which three similar additional lesions were found on the right upper chest, forming a seemingly dermatomal distribution of lesions, leading to the clinical impression of herpes zoster. Similarly, Kafaie et al. (2010) reported a case with a zosteriform and multidermatomal lesion, around a scar tissue on the left lower part of the back, flank, and abdomen with papules, and pseudovesicular lesions on an erythematous background. These cases demonstrate the importance of including herpes zoster in the differential diagnosis. Furthermore, since dermoscopy can be easily utilized to diagnose this condition, dermatologists in endemic areas should be familiar with its typical dermoscopic features. Regarding differential diagnosis, Kafaie et al. (2010) have also mentioned lupus

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