Clinical Presentation of Cutaneous Leishmaniasis caused by *Leishmania major*

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**Keywords**
Clinical polymorphism · Cutaneous leishmaniasis · *Leishmania major*

**Abstract**

*Background/Aims:* The diagnosis of cutaneous leishmaniasis (CL) is based on the microscopic detection of amastigote, isolation of the parasite, or the detection of *Leishmania* DNA. Nevertheless, since these techniques are time consuming and not usually available in many endemic countries, the diagnosis remains clinical. Consequently, such disease may be overlooked because of its similarity to other skin diseases. The aim of this study is to describe the clinical polymorphism of CL caused by *Leishmania major*. **Methods:** A cross-sectional survey was carried out on 166 patients. Diagnoses were made by both microscopic examination of stained tissue-scraping smears and PCR. The *Leishmania* species was identified by restriction enzyme analysis of the ribosomal internal transcribed spacer 1 region. The clinical polymorphism was analyzed only for patients with a positive diagnosis for CL and *L. major* as the identified species. **Results and Conclusion:** Of the 166 patients, 75 patients fit the inclusion criteria. Twelve different types of CL caused by *L. major* were defined. The most common type was the ulcerocrusted form followed by the papulonodular form and the impetiginous form. The ulcerated, mucocutaneous, lupoid, and sporotrichoid forms were less common. The eczematiform, erysipeloid, verrucous, psoriasiform, and pseudotumoral types were represented by a single case. Zoonotic CL caused by *L. major* can simulate many other skin diseases, which may lead to a significant spread of this disease and increases in morbidity and drug resistance. This large polymorphism may be the result of a complex association between the genetics of the parasite and the immune response of the host.

**Introduction**

Cutaneous leishmaniasis (CL) is a protozoan skin infection caused by species of the genus *Leishmania* and transmitted by the bite of infected female phlebotomine sandflies [1, 2]. According to the World Health Organization (WHO), 350 million people are currently at risk of acquiring the infection. It is endemic in 88 countries worldwide, including Central and South America, Africa, and...
Asia, and Southern Europe. The worldwide incidence of CL is 1.5 million cases per year [3–5].

Although the WHO has designated leishmaniasis as one of the 15 most neglected tropical diseases, the global morbidity due to leishmaniasis remains underestimated due to misdiagnosis and inadequate reporting guidelines [6].

The first sign of CL is a tiny erythema at the site of a sandfly bite, which then develops into a papule and nodule. The lesion becomes ulcerated in 2 weeks to 6 months, after which the lesions heal spontaneously. Although CL is mild and not life threatening, its disfiguring lesions and scars can severely affect the social and psychological functioning of the affected individuals, causing anxiety, depression, decrease in body satisfaction, and low quality of life [7–9].

The diagnosis of CL is usually based on specific clinical features and parasitological investigations, including microscopic examination of the stained skin-scraping smear, PCR, and isolation of the parasite by culture on specific medium. Unfortunately, these laboratory investigations are not always available in routine daily practice and are expensive and time consuming. Consequently, in many endemic regions, the diagnosis of CL is mainly clinical. Also, it is important to highlight that CL has very different clinical manifestations depending on the condition of the host’s immunity and the species of parasite [2]. A wide spectrum of differential diagnoses is possible, including actinomycetoma, Buruli ulcer, ulceroglandular tularemia, cutaneous anthrax, cutaneous tuberculosis, paracoccidioidomycosis, pyoderma gangrenosum, squamous cell carcinoma, basal cell carcinoma, cutaneous lymphoma, impetigo, psoriasis, leprosy, sporotrichosis, and *Mycobacterium marinum* [1, 2]. Delayed and incorrect diagnoses of CL may cause the significant spread of this disease and consequent increases in morbidity and drug resistance.

The species responsible for Old World CL are *L. tropica*, *L. killicki*, *L. ethiopica*, *L. arabica*, *L. gerbilli*, *L. turanica*, *L. infantum*, and *L. major*. The last one is the most prevalent species isolated from the cutaneous lesion in the Old World with a wide geographical distribution from West Africa to Central Asia [10].

Knowing the clinical polymorphism of the cutaneous lesion caused by this widely distributed species of *Leishmania* is crucial for physicians for an accurate clinical diagnosis. Up to now many studies have focused on the description of the clinical features of cutaneous leishmaniasis in several foci in the world [11–16]. However, so far very few studies have identified the parasite and assigned a clinical polymorphism to a species of *Leishmania*. Indeed, Karamian et al. [17] have described the clinical features of 6 CL cases infected with *L. major* and 3 cases infected with *L. tropica*. Hammami-Ghorbel et al. [18] described mucosal leishmaniasis in 7 CL cases infected with *L. infantum* and 2 cases infected with *L. major*. The other

![Flowchart of Material and Methods.](image-url)
investigations have studied the clinical polymorphism within an endemic focus without an accurate identification of the \textit{Leishmania} species. Thus, this study describes the clinical polymorphism of cutaneous leishmaniasis from patients infected with \textit{L. major}. The study was carried out within an endemic focus of zoonotic cutaneous leishmaniasis in Tunisia. Diagnosis of CL was made by both microscopic examination of stained scraping smears and PCR. Identification of \textit{Leishmania} species was carried out using a PCR-RFLP technique.

\section*{Materials and Methods}

For further details, see the supplementary materials (for all online suppl. material, see www.karger.com/doi/10.1159/000456543) [19–22] (Fig. 1).

\section*{Results}

A total of 172 samples were collected from patients with 1 or more cutaneous lesions suggestive of CL. Out of these, 68 and 79 samples were positive using direct microscopic examination and PCR-ITS-1 (internal transcribed spacer 1), respectively. Analysis of the PCR-positive samples by RFLP revealed that 2 patients were infected by \textit{L. infantum}, 2 patients with \textit{L. killicki} (synonymous with \textit{L. tropica}) and 75 patients with \textit{L. major}. Only the clinical and epidemiological features of the last group were analyzed and discussed.

Thus, among the total number of CL cases caused by \textit{L. major}, 39 were females and 36 were males, with an age range of less than 1 year to 70 years. All patients had lesions over exposed parts of the body. Indeed, the most commonly affected sites were the upper limbs (36%) followed by the lower limbs (33.33%) and face (30.66%). The duration of the disease varied from 10 days to 3 months.

Based on the clinical morphology of the lesion, 12 clinical forms were observed from the 75 cases of zoonotic CL caused by \textit{L. major}. These forms varied from a mild papulonodular lesion of less than 1 cm in diameter to more serious, extensive, and complicated forms (Table 1).

The ulcero-crusted form was the most common (\(n = 29, 38.66\%\) of \textit{L. major} CL cases) and occurred mainly in the lower extremities. It is usually characterized by a painless ulcer with a well-demarcated raised border covered with a brownish scab (Fig. 2a, b). The second form was the papulonodular form that constituted 16\% of all \textit{L. major} CL cases. It consists of an erythematous smooth and superficial papule with infiltrated borders. Its size varied from 0.3 to 1 cm. The most common site of involvement was the face (50\%). Sometimes, the nodular lesion was surrounded by small papules (Fig. 2c, d).

The third form of \textit{L. major} CL was the impetigenous form (13.33\% of zoonotic CL cases), which occurred most

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Type & Size of & Duration of & Distribution & Cases, n (\%) \\
& lesion, & lesion, & upper & lower & face \\
& mm & months & limbs & limbs & \\
\hline
Common clinical forms & & & & & \\
Ulcero-crusted & 5–60 & 0.5–4 & 14 & 12 & 3 & 29 (38.66) \\
Papulonodular & 5–20 & 0.5–4 & 3 & 3 & 6 & 12 (16) \\
Impetigenous & 5–40 & 0.3–1 & 3 & 0 & 7 & 10 (13.33) \\
Ulcered & 10–30 & 1–2 & 2 & 5 & 1 & 8 (10.66) \\
Mucocutaneous & 5–50 & 0.5–1 & 0 & 0 & 5 & 5 (6.66) \\
Lupoid & 30–40 & 1–3 & 1 & 1 & 1 & 4 (5.33) \\
Sporotricoid & 20–50 & 1 & 2 & 1 & 0 & 3 (4) \\
\hline
Uncommon clinical forms & & & & & \\
Eczematiform & 30 & 2 & 1 & 0 & 0 & 1 (1.33) \\
Erysipeloid & 70 & 2 & 0 & 1 & 0 & 1 (1.33) \\
Verrucous & 20 & 2 & 0 & 1 & 0 & 1 (1.33) \\
Psoriasiform & 50 & 2 & 1 & 0 & 0 & 1 (1.33) \\
Pseudotumoral & 30 & 1 & 0 & 1 & 0 & 1 (1.33) \\
\hline
Total & & & & & \\
27 & 25 & 23 & 75 (100) \\
\hline
\end{tabular}
\caption{Clinical forms and epidemiological features of cutaneous leishmaniasis caused by \textit{Leishmania major}}
\end{table}
commonly on the face. It consisted of a superficial lesion that clinically resembled impetigo. The lesions were round-shaped and squamo-crusted with a grainy center. This form was mainly noted among children aged between a few months and 10 years (Fig. 2e).

The ulcerated form, also called the wet or rural type, was detected in 8 patients of our studied group which represented 10.66% of the zoonotic CL cases. It most commonly affected the upper and lower extremities and presented clinically with an early infiltrated ulceration with an inflammatory peripheral bead (Fig. 2f, g).

Interestingly, *L. major* was also found to be responsible for mucocutaneous lesions which affected the mucous membranes of the lip and the nose. Five patients (6.66% of the zoonotic CL cases) presented this clinical form, 3 with lesions on the nose and 2 with lesions on the lips (Fig. 2h).

The lupoid form comprised 4% of all cases of zoonotic CL due to *L. major*. Clinically, it is characterized by a
slowly enlarging erythematous and infiltrated plaque. Indeed, the lesion began as multiple erythematous papules that later coalesced to form an infiltrated plaque covering a large part of the skin and closely resembling *Lupus vulgaris*. Sometimes, several apple jelly nodules were formed. This form occurred in both the extremities and the face (Fig. 2i, j).

The sporotricoid form constituted 4% of the zoonotic CL cases. It was characterized by the development of subcutaneous nodules and indurated nodes around the CL lesions, along the path of the proximal lymph node chains as a result of the local and regional lymphatic spread of the parasite. Thus, a beaded cord appearance of the lymphatic vessels was displayed in the vicinity of the CL lesions (Fig. 2k). In our series, this clinical form was observed exclusively in the upper and lower extremities.

We have also reported 5 other unusual forms of cutaneous leishmaniasis, each represented by a single case (1.33% of zoonotic CL cases each): (i) an eczematiform lesion was observed on the hand of a 10-year-old girl; it was characterized by a pruritic erythematous plaque clinically resembling allergic contact dermatitis (Fig. 3a); (ii) the erysipeloid form was observed in a 47-year-old woman involving the dorsal surface of her foot; the lesion was not ulcerated and was characterized by a diffuse erythematous infiltrate over the foot (Fig. 3b); (iii) a verrucous lesion occurred over the lower limb of a 14-year-old girl; clinically, it was characterized by a protruding lesion with a rough and hyperkeratotic surface resembling warts and tuberculosis verrucosa cutis (Fig. 3c); (iv) a psoriasiform CL lesion was observed on the elbow of a 34-year-old man; it was characterized by an infiltrated plaque on the elbow covered with whitish and dry scales simulating psoriasis (Fig. 3d); and (v) the pseudotumoral form was observed on the leg of an 11-year-old boy; clinically, it is characterized by a macaroon-shaped lesion with an embossed proliferation simulating squamous cell carcinoma and amelanotic melanomas (Fig. 3e).

**Discussion**

Cutaneous leishmaniasis is a widely distributed vector-borne disease that is never fatal, even if without any treatment. It can be manifested as a nonspecific form that can mimic many other skin disorders. Many unusual lesions caused by *Leishmania* never come to the attention of physicians living in nonendemic areas. In fact other
conditions to consider in the differential diagnosis of leishmaniasis include fungal (chromoblastomycosis), bacterial skin infections (rhinoscleroma), viral (Orf), inflammatory diseases (psoriasis), malignant neoplasms (metastases), and ulcers (traumatic ulcers). Early diagnosis as well as treatment play an important role in the healing process to avoid disfiguring lesions and ugly scars resulting in a disturbance of psychological functioning and a decrease in the quality of life of the affected individuals [7–9]. Pentavalent antimonials, including N-methylglucamine antimonate (Glucantime®) and sodium stibogluconate (Pentostam®), remain the first line of treatment. These drugs act via inhibition of adenosine triphosphate synthesis. Nevertheless, due to their adverse effects such as myalgia, arthralgia, renal failure, leukopenia, anemia, thrombocytopenia, and cardiotoxicity [23, 24], other local alternatives have been implemented. Currently, cryotherapy is increasingly used for the treatment of cutaneous leishmaniasis, demonstrating a similar efficacy with the pentavalent antimony [25]. Another kind of treatment is currently available involving the application of heat, thermotherapy, demonstrating a greater safety and lower cost, especially in the case of contraindications to systemic treatment [26].

In the absence of parasitological and molecular diagnosis in many endemic foci, an accurate clinical diagnosis of CL may lead to a significant decrease in its morbidity and drug resistance.

Although L. major is the main species responsible for Old World CL worldwide, to the authors’ knowledge, a very limited number of studies have investigated and explored the clinical spectrum of CL caused by this Leishmania species. Indeed, many studies have described the clinical polymorphism of cutaneous leishmaniasis without any isoenzymatic or molecular identification of the causative species. In 2012 a retrospective study was carried out by Douba et al. [27], studying the clinical spectrum of CL in the region of Aleppo, Syria, an endemic focus of chronic CL caused by L. tropica. Thus, 3 clinical forms and 5 subtypes were observed with the papulonodular and plaque forms as the most common ones. Nevertheless, no identification of the parasite was done. Many other studies have explored the clinical forms of cutaneous leishmaniasis in different foci in the world such as West China, Iran, Burkina Faso, Colombia, and Middle Eastern countries [11, 28–31]. In Tunisia, Masmoudi et al. [32] have studied the different clinical aspects of CL in some zoonotic CL foci of the Centre and the South of the country. The ulcer-crusted form was the most predominant form (54.9%) followed by the sporotrichoid and lupoid forms with 18.6 and 15.7%, respectively. Nevertheless, no identification of the parasite was made during this investigation.

Among the few studies describing the clinical polymorphism of Old World CL caused by the L. major species (by an accurate identification of the parasite), Oryan et al. [33] described the clinical morphology of 21 L. major CL cases with the focus on Iran. This is the largest sample of L. major cases published so far. Thus, 6 different clinical forms were noted. The erythematous form was the most common, followed by the cutaneous, sporotrichoid, verrucous, and nodular forms.

Accordingly, among all the studies conducted on the clinical polymorphism of CL caused by L. major, the current study has the largest sample size. As the outcomes reveal, L. major had a large spectrum of clinical forms. The ulcer-crusted form was the most common, followed by the papulonodular, impetigenous, and ulcerated aspects. Other unusual forms of lesions were also reported. Our results are in concordance with those already published in Tunisia. Indeed, Masmoudi et al. [15, 32, 34] have described 11 clinical forms of CL in zoonotic foci in Central and South Tunisia. The ulcer-crusted form was the most predominant (54.9%), followed by the sporotrichoid form (18.6%) and the lupoid form (15.7%).

This clinical polymorphism of CL caused by L. major seems to be rather high, which could reflect the complexity of the disease, involving several factors related to the parasite (virulence, parasitic load, and the presence of other pathogens), the type and duration of the clinical lesion, the geographic location, the disease reservoir, and the host’s immune status [35, 36].

Several investigations have suggested that the genetic variability observed among L. major isolates is correlated with different clinical manifestations [37, 38]. Thus, the high clinical polymorphism and the detection of an unusual clinical picture suggest the involvement of a highly aggressive isolate of L. major, as described in Afghanistan and Uzbekistan [39, 40]. In Iran, Oryan et al. [33] have reported a high genetic polymorphism of L. major and correlations between the geographical origin and the clinical manifestations of the disease. Nevertheless, Yazidi et al. [41] reported that Tunisian L. major isolates are highly polymorphic despite inducing a similar clinical picture and belonging to the same geographical origin.

Another factor that could be involved in the pathogenicity process of Leishmania is the infection of the parasite with viruses. Indeed, Zangger et al. [42] connected the aggressive phenotype of L. guyanensis to the presence of Leishmania RNA virus (LRV) in the parasite, showing that LRV could be responsible for elevated parasitemia,
destructive hyperinflammation, and an overall exacerbation of the disease. Also, Hajjaran et al. [43] have demonstrated the presence of LRV in an *L. major* isolate, which supports the large clinical polymorphism observed in our study.

The clinical polymorphism can also be explained by the variable susceptibility of each patient [2]. In fact, the clinical presentation and evolution of leishmaniasis is the result of complex interactions between the parasite and host immune response. Ultimately, the outcome of infection depends on the ability of host macrophages to effectively kill the intracellular parasite. In 1998, Louzir et al. [44] reported that the unfavorable clinical outcome of CL was positively associated with high IL-10, IL-12, and IFN-γ mRNA expression. Also, Kumar et al. [45] demonstrated that the levels of parasite burden and IL-4 were distinctly correlated in various clinical forms of CL due to *L. tropica*.

In immune-suppressed patients with HIV/CL coinfection, lesions were sometimes more severe with unusual presentations like the lepromatous and kaposian nickname forms [11].

In conclusion, our study emphasizes that cutaneous leishmaniasis caused by *L. major* exhibits a large clinical polymorphism and consequently should be included in the differential diagnosis of many common and uncommon dermatological diseases such as actinomycetoma, cutaneous anthrax, pyoderma gangrenosum, squamous cell carcinoma, basal cell carcinoma, impetigo, psoriasis, and leprosy. This finding could be the result of a complex association between the genetics of the parasite and the immune response of the host. In order to better understand this complex process, further studies should focus on *L. major* characterization from patients presenting an unusual clinical morphology of the cutaneous lesion.

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**Key Message**

This article presents an overview of the clinical polymorphism of cutaneous leishmaniasis caused by *L. major* in Tunisia.

**Acknowledgments**

The authors thank all the patients who agreed to participate in our study and all the staff of the regional hospital of Nasrallah, Kairouan (Mr. Abdeslam Hadadi, Mr. Jalel Mejbri, Mrs. Cherifa Ayadi, Mrs. Mariem Selmi, and Mrs. Hajer Azouzi), the Centre of Hygiene and Basic Health Care Kairouan (Dr. Imen Brahem Chrayti and Mr. Nacer Gallali), and the directors of the Basic Health Care of Kairouan (Dr. Amara Jemli and Mr. Youssef Hajjaji), who helped us to accomplish this work. We are also grateful to the dermatologist Dr. Monia Youssef for her valuable comments.

**Statement of Ethics**

All patients or their legal representatives provided written informed consent. The study was conducted in accordance with the protocol approved by the ethics committee of the Fattouma Bourguiba University Hospital, Monastir.

**Disclosure Statement**

The authors have no conflict of interest.

**Funding Sources**

This study was simultaneously supported by a grant from the EMRO/TDR Small Grants Scheme for Operational Research in Tropical and Other Communicable Diseases (No. SGS14/23) and the Ministry of Higher Education and Scientific Research, Tunisia. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Leishmania major Clinical Polymorphism

DOI: 10.1159/000456543

Dermatology 2016;232:752–759

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