Cutaneous leishmaniasis and its clinical spectrum. An overview from the Old World

Federica Dassoni

“A. Manzoni” Hospital, Lecco, Italy

Address for correspondence:
Federica Dassoni
“A. Manzoni” Hospital
Via dell’Eremo 9/11
23900 Lecco, Italy
E-mail: federica.dx@gmail.com

Summary

Cutaneous leishmaniasis is still considered by the World Health Organization (WHO) an uncontrolled disease, affecting nearly 100 countries in the Old World (Europe, Middle East, Asia, Africa) and in the New World (Central and South America). Depending on the species of Leishmania, host genetics, and immune factors, a spectrum of different clinical forms of the disease may develop, conventionally known as localized cutaneous leishmaniasis (LCL), mucocutaneous leishmaniasis (MCL), anergic diffuse cutaneous leishmaniasis (ADCL) and post-kala-azar dermal leishmaniasis (PKDL).

The range of clinical and immunological manifestations of leishmaniasis has been the subject of many studies in order to understand the host immune mechanisms that are playing a crucial role in the pathogenesis of this disease. The individual features are relevant in order to choose effective therapeutic interventions and to establish a prognosis. Therefore, the different forms of this disease should be kept in mind in endemic countries, as well as in immigrant populations and travellers. This review highlights the immunological-clinical correlation in the spectrum, with special reference to the disease in the Old World.

KEYWORDS: parasitic diseases; leishmaniasis.

Background

Cutaneous Leishmaniasis (CL), which was found in ancient Egyptian and Christian Nubian mummies from 2000 BC, described for the first time in the 9th century by Avicenna (Balkh sore), still remains a major world health problem. It is considered by the World Health Organization (WHO) an emerging and uncontrolled disease (1-3). Leishmaniasis is a widespread disease which is endemic in the “Old World” (Europe, Middle East, Africa, Central Asia, and India) and in the “New World” (Central and South America) (Figure 1). It is caused by several different species of an intracellular protozoa belonging to the genus Leishmania, which was identified in the early twentieth century, and is transmitted by the bite of an infected female sandfly (3).

Following infection of man by these parasites, there will be some individuals naturally resistant to this infection, and others with a different degree of susceptibility. Depending on the species of Leishmania, host genetics, and immune factors, a spectrum of clinical forms of the disease develops: the result of infection can vary from a chronic skin ulcer, nodule or plaque (cutaneous leishmaniasis, CL), to erosive mucosal disease with progressive facial disfiguring (mucocutaneous leishmaniasis, MCL), to generalized cutaneous lesions (anergic diffuse cutaneous leishmaniasis, ADCL), to a life threatening systemic infection with hepato-splenomegaly (visceral leishmaniasis, VL, also called kala azar, meaning “black fever” in Hindi) (4-8).

The aim of this review is to provide an update on the clinical and immunological spectrum of cutaneous leishmaniasis, with special reference to the disease in the Old World. Diagnostic and therapeutic options are also briefly showed.

Epidemiology

Leishmaniasis is a neglected vector-borne tropical infection that is considered to be a disease of the poor (1). Concentrated in developing countries in Southeast Asia, East Africa, and Latin America, it is also endemic in several Mediterranean countries (3, 9) (Figure 1). Distribution is also dependent on the ecology, climate changes and human behavior; urbanization, and introduction of agricultural projects into new areas, can increase leishmaniasis incidence (10). 1.5-2 million new infections are estimated each year, of which approximately two-thirds are represented by cutaneous forms. Leishmaniasis currently affects more than 12 million people in nearly 100 countries (WHO). The estimated annual global mortality due predominantly to VL is 20,000-40,000 (4, 11). The size
The population at risk is about 350 million (12). Despite the estimates of mortality and morbidity, leishmaniasis belongs to the group of neglected tropical diseases. Many species of *Leishmania* may infect humans (Table 1). However most of the parasites reside in zoonotic reservoirs, for example, *Leishmania* (*L.*) *infantum* in dogs and *L. major* in rodents. People living in proximity of reservoirs are at increased risk of becoming infected, and may become an anthropotonic

Table 1 - Species of *Leishmania* infecting humans and their clinical manifestations.

<table>
<thead>
<tr>
<th>Subgenus</th>
<th>Old World leishmaniasis</th>
<th>New World leishmaniasis</th>
<th>Viannia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td><em>Leishmania</em></td>
<td><em>Leishmania</em></td>
<td><em>Viannia</em></td>
</tr>
<tr>
<td></td>
<td><em>L. major</em></td>
<td><em>L. mexicana</em></td>
<td><em>L. braziliensis</em></td>
</tr>
<tr>
<td></td>
<td><em>L. tropica</em></td>
<td><em>L. amazonensis</em></td>
<td><em>L. guyanensis</em></td>
</tr>
<tr>
<td></td>
<td><em>L. aethiopica</em></td>
<td></td>
<td><em>L. panamensis</em></td>
</tr>
<tr>
<td></td>
<td><em>L. infantum</em></td>
<td></td>
<td><em>L. peruviana</em></td>
</tr>
<tr>
<td>Anergic diffuse cutaneous</td>
<td><em>L. aethiopica</em></td>
<td><em>L. amazonensis</em></td>
<td><em>L. shawi</em></td>
</tr>
<tr>
<td>Recidivs cutaneous</td>
<td><em>L. tropica</em></td>
<td></td>
<td><em>L. naiffi</em></td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td><em>L. aethiopica</em></td>
<td></td>
<td><em>L. lainsoni</em></td>
</tr>
<tr>
<td></td>
<td>(20)</td>
<td></td>
<td><em>L. lindenbergi</em></td>
</tr>
<tr>
<td>Mucosal</td>
<td><em>L. aethiopica</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(L. major)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(L. tropica)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral or viscerotropic</td>
<td><em>L. infantum</em></td>
<td>*L. infantum/chagasi</td>
<td></td>
</tr>
<tr>
<td>Post-kala-azar dermal</td>
<td><em>L. donovani</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td><em>L. infantum</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
reservoir. Examples of human reservoirs are cutaneous leishmaniasis (CL) caused by *L. tropica*, anergic diffuse cutaneous leishmaniasis (ADCL) due to *L. aethiopica* and VL caused by *L. donovani*.

In the Old World, up to 75% of CL cases is found in Brazil, Syria, and Afghanistan (3, 9). In European countries, only two *Leishmania* species are endemic: *L. infantum*, responsible for zoonotic cutaneous and systemic disease within the Mediterranean region, with a reservoir in the domestic dog; and *L. tropica*, causing sporadic cases of anthropogenic cutaneous disease (3).

### Immunological spectrum

Depending on the species of the infecting *Leishmania*, the parasite properties (pathogenicity, virulence), host (age, nutritional state), and the host cell-mediated immune response (which can be affected by genetic polymorphism), a spectrum of clinical forms of the disease develops. Clinical manifestations further vary by different endemic region (16). The individual features are relevant in order to choose effective therapeutic interventions and to establish a prognosis (3).

The bite of an infected sandfly may lead to no infection, subclinical or asymptomatic infection (especially in viscerotropic species), self-limiting lesions, localized cutaneous leishmaniasis (LCL), mucosal leishmaniasis (ML), mucocutaneous leishmaniasis (MCL), disseminated cutaneous leishmaniasis (DCL), anergic diffuse cutaneous leishmaniasis (ADCL) and visceral leishmaniasis (VL), also called "kala-azar", which is often followed by a dermal manifestation known as "post-kala-azar" dermal leishmaniasis (PKDL) (Table 2).

Overall, most clinically apparent infections remain localized in the skin or adjacent lymph nodes. Certain species escape to nasal/oropharyngeal mucosa, multiple cutaneous sites, or internal organs (kala azar). Dissemination is mainly, but not exclusively, dependent on parasite properties such as temperature sensitivity, tissue tropism, capacity of immune evasion and persistence in the host tissues (16).

Parasite species determine the localization and some of the clinical features of the disease, as they have developed successful strategies for surviving the antimicrobial activities of their host cell, and maintaining them in a deactivated state.

At the same time, the immunocompetent host responds with both innate and acquired mechanisms (cell-mediated immunity/CMI or DTH). These inflammatory responses mediate disease expression and may or may not produce the desired clinical result: asymptomatic infection, or self-healing disease (16).

Under optimum conditions, macrophages are eventually activated to a leishmanicidal state largely governed by intact T-helper cell-type 1 (Th1) response. This complex response involves antigen-presenting dendritic cells, responding CD4+ T cells, and secretion of pro-inflammatory cytokines, including IL2, IL12, IL17, interferon γ, and tumor necrosis factor (TNF). This same Th1 response also prevents recrudescence of latent, chronic infection (16).

Host immune factors determine disease patterns and severity, in a way similar to the concept of shifting immune profiles in leprosy (17, 18).

### Infection

The female sandfly vector (belonging to the genus *Phlebotomus* spp. in the Old World, and *Lutzomyia* spp. in the New World) becomes infected during blood meals on infected hosts (humans or animals) when it ingests macrophages infected with amastigotes. In the sandfly’s midgut, the parasites differentiate into promastigotes. In the procyclic stage promastigotes present species-specific lipophosphoglycan (LPG) on their surface, which protects them from proteolytic digestive enzymes and allow them to attach to the insect gut; here the promastigotes divide and multiply (13).

Characteristics of the intravascular cycle are used to define the subgenus group: *Leishmania* (which attach to the midgut) and *Viannia* (hindgut) (14, 15). Infective metacyclic leishmania promastigotes are regurgitated when the sandfly takes a subsequent bloodmeal on the host’s skin; they are then phagocytized quickly by macrophages and transform into amastigotes.

*Leishmania* is an obligate intracellular parasite in mammals. Amastigotes multiply in infected macrophages or dendritic cells in various tissues, depending on the species of *Leishmania* and host factors. The varying organ specificities together with the host’s immunity are responsible for the phenotypic manifestations of the various forms of leishmaniasis.

Three types of transmission cycle are observed in human infections:

1. a primarily zoonotic reservoir of wild animals isolated from human residence; humans become infected only as trespassers (e.g. *L. guyanensis*, *L. panamensis*, *L. aethiopica*, etc.);
2. a primarily zoonotic reservoir of (peri)-domestic animals close to human residence (e.g. dogs in *L. infantum*);
3. a primarily human reservoir (e.g. *L. tropica* and *L. donovani*).

Transmission independent of the sandfly vector is rare and accounts for congenitally acquired leishmaniasis, or infection through needle-sharing or prick or cut accidents, and transfusion-acquired infections (3).

### Immunological spectrum

Depending on the species of the infecting *Leishmania*, the parasite properties (pathogenicity, virulence), host
Clinical spectrum of cutaneous leishmaniasis. A review

Starting from one end of the spectrum to the other end, we consider the characteristic of the different clinical presentations of CL (pictures are shown in Table 2).

**Mucocutaneous leishmaniasis (MCL)**

In this form of the disease, necrosis of the nasopharyngeal and oral mucous tissue is associated with a strong T cell immune response, with exacerbated delayed-type hypersensitivity (DTH) to \textit{Leishmania} antigens (5). Scanty parasites are found in samples. MCL, also called \textit{espundia} in South America, is a severe and occasionally life threatening form of leishmaniasis. \textit{L. braziliensis} and \textit{L. panamensis} in the New World, and \textit{L. aethiopica} in the Old World, are the most common etiologic agents. Few cases of MCL with a favorable course caused by \textit{L. tropica} are described (20).

In the Old world, mucosal lesions are rare but may be caused by any species, especially in the immunosuppressed. In the “New World” form, single or multiple primary cutaneous lesions may heal spontaneously, and later secondary mucosal leishmaniasis may develop, caused by metastasis to the oral and upper respiratory tract mucosa by hematogenic spread. Instead, in the Old World, MCL is caused by lymphatic contiguous spread. It starts with a cutaneous or mucocutaneous lesion which, rather than showing eventual resolution, extends to the adjacent cutis or mucosa and cartilage of the upper respiratory tract (21). The disease leads to marked disfigurement and patients with mucosal disease never heal spontaneously; this shows how the CMI is exacerbated causing tissue damage, but not effective to control the infection.

**Leishmaniasis recidivans (LR)**

The recidivans lesion is the result of a peculiar host reaction in which the cellular immunity, with or without...
treatment fails to sterilize the lesion despite the presence of exaggerate hypersensitivity.

LR is a distinctive form of chronic CL, caused usually by L. tropica and L. aethiopica in the Old World, and less commonly by L. braziliensis in the New World. It refers to the development of new lesions in the center or periphery of a healed lesion of cutaneous leishmaniasis. The new lesions may be infiltrated papules and/or crusted inflammatory lesions, which expand slowly, assuming an arciﬁrm configuration. It is also called relapsing leishmaniasis and appears similar to lupus vulgaris, with scarring and new lesions at the periphery (Figure 2). Although not as destructive as lupus vulgaris, LR may persist and spread for many years and is notoriously resistant to treatment (5, 20, 22).

Localized cutaneous leishmaniasis (LCL)

At the middle of the spectrum, LCL with one or multiple nodular/ulcerated skin lesions is the most frequent form of the disease (5).

Classically, weeks to months after the bite, a papule or nodule develops at the site of the bite, which is usually located on the exposed skin of the face, the arms or the legs. In most patients this grows slowly and becomes ulcerated in the course of weeks to months. The ulcer may be covered by a crust, which usually drops off to reveal, typically, a relatively painless ulcer. Secondary bacterial infection should be suspected if the lesion is painful and/or shows purulent discharge. The ulcer may be dry or exudative. Localized cutaneous leishmaniasis (LCL) in the Old World is caused by L. major, L. tropica, L. infantum, and L. aethiopica. It often heals spontaneously over months to years, depending on the causative species, leaving an atrophic hyperpigmented scar. Lesions may be single or multiple (multicentric CL), and satellite lesions may occur as well as lymphatic “sporotrichoid” spread (nodular lymphangitis).

In some cases CL remains active (with positive smears), for more than a year. Such cases are described as “non-healing chronic cutaneous leishmaniasis” (23).

LCL can be further divided into three main forms: nodular, including papules and plaques, nodulo-ulcerative, and ulcerative. These forms may appear singly or as overlapping features. Some uncommon and unusual features are also described, namely verrucous, vegetative, infiltrated, psoriasiform, lupus-like, rhynophymatous, zosteriform lesions and others, making LCL a polymorphic disease (20) (Figure 5).

Borderline disseminated cutaneous leishmaniasis (BDCL)

Together with cases of LCL, between the two poles of MCL and ADCL, a few patients may present disseminated forms which have been referred to as BDCL, and in which it has been possible to determine the location of primary skin lesion(s) and the secondary ones (5, 24).

The process of dissemination may take place in 2-3 months or more, when tens to hundreds erythematous papules and/or ulcerated cutaneous lesions may appear. Macrophages and parasites are scarce in the samples. This form has been described only from the New world, mainly due to L. (V) braziliensis.
Anergic diffuse cutaneous leishmaniasis (ADCL)

Diffuse cutaneous leishmaniasis (DCL) is a polar form of cutaneous leishmaniasis characterized by disseminated nodules and/or infiltrated plaques and/or hypopigmented macules and scars, an abundance of parasites throughout the course of the disease, the absence of parasite-specific cell-mediated immune response, and a poor response to treatment. ADCL is may be caused by *L. amazonensis*, *L. mexicana* and *L. pifanoi* in the New World, and by *L. aethiopica* in the Old World. It may be seen in other species in congenital, HIV- and transplant-related immunosuppression. The disease usually begins with an initial primary lesion, which disseminates; lesions are scattered on limbs, buttocks, and face including mucosal membranes. They progress slowly and become chronic. Relapse after treatment is a rule. There is no systemic involvement. Abundant macrophages and amastigotes are found in the lesions (20).

Post kala-azar dermal leishmaniasis (PKDL)

PKDL may appear after an episode of VL, independent of whether this is treated, partially treated or not treated (25). Hypopigmented macules, skin colored to erythematous papules or nodules develop, usually starting around the mouth from where it spreads to other parts of the body depending on severity (Figure 3). It is mainly seen in Sudan and India where it follows treated VL in 50% and 5-10% of cases, respectively (26). Though any organism causing kala-azar can lead to PKDL, it is most often associated with *L. donovani* which gives different disease patterns in India and Sudan. PKDL usually follows VL after 0-6 months in Sudan and after 2-3 years in India, though it may develop more than 10 years after VL. In the Indian variant, nodules enlarge with time and form plaques which rarely ulcerate. Nodules in the African variety often ulcerate as they progress. African PKDL may heal spontaneously; the Indian variety always needs treatment, being at the end of the spectrum at the “anergic” pole (polyparasitic disease). Identification of post-kala-azar dermal leishmaniasis (PKDL) is important because it demands long and toxic treatment and because PKDL patients may serve as a reservoir for visceral leishmaniasis (VL) (4).

Leishmaniasis and HIV coinfection

HIV and leishmania coinfection causes atypical, extensive and treatment-resistant leishmaniasis (Figure 4). Coinfection by the human immunodeficiency virus (HIV) has resulted in the development of atypical forms of visceral leishmaniasis with an increased incidence of cutaneous involvement. In VL-endemic areas, HIV infection raises the risk of contracting VL at least 100-fold, and VL accelerates HIV replication and progression to AIDS (4, 20). Cutaneous forms of leishmaniasis are also often atypical and resistant to therapy.

Diagnosis

There are several methods of laboratory diagnosis of leishmaniasis, based on the presence of parasites or their DNA in the tissues (3, 27). These include parasite detection by microscopic examination from scraping, histology, culture and successive isoenzyme analysis for identification, or molecular biology-based
assays for detecting the parasite DNA (polymerase chain reaction [PCR]). Culture and different species-specific PCR tests are more sensitive, but may be applied only in advanced centers and are not currently practical in developing countries (16, 28). PCR techniques show high sensitivity when applied to skin biopsy or smear samples. They are now commonly used in travelers, when species identification is needed to guide treatment. Leishmania DNA can be found in successfully treated cases up to years after treatment. Therefore, in complex relapsing cases culture and cytology or histology remain the preferred diagnostic methods as they detect viable parasites. Histopathology is an important tool in CL, even when parasite in the lesions are scanty. Generally the microscopy shows a diffuse dermal infiltrate of histiocytes, lymphocytes, plasma cells and neutrophils with a hyperplastic epidermis. The parasites however are pathognomonic. LCL may have an infiltrate with characteristics of an epithelioid cell granuloma and few parasites, correlating with well-developed CMI. More generalized leishmaniasis may reveal a dermal infiltrate of vacuolated macrophages full of amastigotes, with the appearance of a macrophage granuloma. PKDL demonstrates a mixture of chronic inflammatory cells; these can be arranged as a macrophage- or epithelioid cell-granuloma (4). Serological diagnosis is the technique more commonly used for VL (3, 27); it is rarely used for CL because of low sensitivity and specificity. When considering MCL however serology can be helpful, especially since few parasites will be found on direct examination or culture and rising antibody titers may herald relapse. PCR has been found to be the most sensitive diagnostic technique also in MCL.

Therapy

Many are the treatment options for CL (29), although their reported efficacy is extremely variable. Treatments that work for one species of leishmania and in one geographical area may not work for another species in another geographical region. This is the result of the parasites intrinsic and the patient's genetic variability (30). Treatment choice is usually based on local or personal experience and availability of drugs. Out of the WHO guidelines (29), local guidelines are being developed in different countries (4, 31, 32) as there is no international consensus. Moreover, guidelines specifically made for travelers and directed to different species are being produced by different international groups, including the European LeishMan consortium (4, 33). Treatment choice for CL depends on several factors: the species of parasite; the size, number and localization of the lesions; the risk of lymphatic spread or dissemination; the immune status of the host; cost and availability of the treatment; risk-benefit ratio; and patient preferences. Old world CL lesions caused by *L. major* and *L. tropica* often self cure within 4 to 15 months (16). In these cases, CL is treated to accelerate cure, reduce scarring especially at cosmetic sites (face, joints) and to prevent dissemination (e.g. mucosal disease) or relapse. Sometimes a "wait-and-see" approach with just local wound care is justified. Treatment can be local (topical or intralesional), oral, or parenteral. Local treatment is usually the first choice in Old World cutaneous leishmaniasis, with the exception of CL caused by *L. aethiopica* because of the risk of developing mucosal lesions and ADCL. New World CL is usually treated systemically because of the theoretical future risk of developing MCL. Here *L. mexicana* is the exception, as it may be treated locally. Widely accepted treatment options are:

Local (alone or, more commonly, in combination):
- Cryotherapy
- Topical paromomycin sulphate
- Intralesional pentavalent antimony (with or without cryotherapy)
- Thermotherapy

Systemic:
- Pentavalent antimonials (IV, IM)
- Pentamidine (IV, IM)
Amphotericin B and liposomal amphotericin B (IV)
- Miltefosine (oral)
- Antifungal azoles (oral)

New developments

Several plant products are in various stages of research and development (4). A promising new development is the use of human antimicrobial peptides (AMPs) which have powerful broad-spectrum antimicrobial activity with distinctive modes of action and are considered as promising therapeutic agents (defensines) (34).

Prevention

To date no leishmania vaccine has been successful.

Systemic drugs used for treatment are toxic and can’t be used as prophylaxis. Protection against leishmaniasis can be achieved by using protective clothing, impregnated bednets (sandflies can pass through normal mosquito nets because of their size), and insect repellents. Residual spraying of houses with long-lasting insecticides can reduce transmission. In some areas the intermediate host has to be eliminated (3, 4).

In endemic countries, prevention and control are based on early diagnosis and treatment, vector control, disease surveillance, and education of the community.

Conclusions

Leishmaniasis is a major health problem worldwide. Major risk factors of Leishmania distribution are socioeconomic conditions, malnutrition, population mobility, and environmental and climate changes (3).
Old World CL may be considered a bipolar disease. On one end of the spectrum is the classical self-healing sore with an effective parasiticidal mechanism. On the other end of the spectrum is the diffuse cutaneous leishmaniasis (ADCL), in which metastatic cutaneous lesions develop and the patient rarely, if at all, spontaneously develops immunity to the parasite. The spectrum of clinical and immunological manifestations of leishmaniasis has been the subject of many investigations in attempts to fully understand the host immune mechanisms that are playing a crucial role in the pathogenesis of the disease.

The individual features are relevant in order to choose effective therapeutic interventions and to establish a prognosis. Therefore, attention to the different forms of this disease should be paid in endemic countries, as well as in immigrant populations. Spurred by global warming, mass migration and rapid urbanization, cases are being reported in previously unaffected areas.

The European Union has been receiving an estimated 20 million migrants having arrived in the past 15 years (3). Therefore, leishmaniasis should be considered in the diagnostic assessment of immigrants or travelers who could have been exposed to the parasite in endemic areas, even if exposure occurred several months or years before (35).

Treatment is often toxic and ineffective, drug resistance is a threat and supplies may be limited. Experimental vaccines show promise (4), yet a long way needs to be covered before effective immunization for leishmaniasis becomes a reality.

Acknowledgement

No financial support declared, no conflict of interest declared.

Special thanks to Prof. Aldo Morrone, who allowed me to dedicate my work to people living in developing countries; and to Prof. Ben Naafs for his support, teaching and presence in times of need.

References

(12):1829-34.