Leishmaniasis

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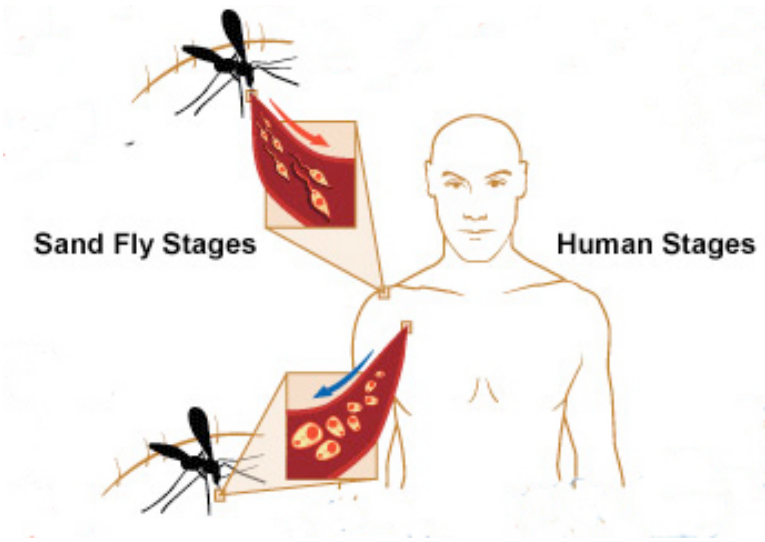
Definition

Leishmaniasis is a vector-borne disease that is caused by obligate intracellular protozoa, and that is characterized by both diversity and complexity. It is caused by more than 20 leishmanial species and is transmitted to humans by ~30 different species of phlebotomine sandflies. Leishmaniasis consists of three main clinical syndromes: cutaneous leishmaniasis (CL); muco-cutaneous leishmaniasis (MCL; also known as espundia); visceral leishmaniasis (VL; also known as kala-azar).

Transmission and life cycle of *Leishmania spp*

The transmission of *Leishmania spp* is possible thanks to the bite of infected female sandflies, genus *Phlebotomus* everywhere except in central and south America where the vector is belonging the genus *Lutzomyia* (morphologically very similar each other). The sources of infection usually are infected dogs and numerous rodent species. The sandfly feeding by an infected vertebrate ingests infected cells (macrophages) when it takes a blood meal and become able to transmit the infection to another host during the next blood meal. This is more evident and frequent in case of cutaneous form of leishmaniasis because infected macrophages are in the skin; but it is also possible in case of muco-cutaneous (less frequent) and visceral form (very rare) of leishmaniasis because of the possibility to found infected macrophages in blood circulation, that can be ingested by sandfly during meal. Only in case of infection by *Leishmania donovani*, responsible for visceral leishmaniasis in indian sub-continent, there is the possibility (rare) of human-to-human transmission of the infection through the byte of *phlebotomous argentips*. In all other form of leishmaniasis the transmission is from animal reservoir to human through sandfly bite.



The life cycle of *Leishmania* is simple and it involves two stages without sexual stage. In insect vector, the parasite takes a promastigote form (which is characterized by elongated, motile and an extracellular stage and is accumulated in the midgut and foregut), while in vertebrates the parasite is found in amastigote form (ovoid, nonmotile and intracellular stage, especially in dendritic cells and macrophages). During the vector's blood meal, the promastigote form is injected in the skin where, in 12-24h, will infect local macrophages and transform in amastigote form. After transformation, the amastigotes multiply within the macrophage and ultimately the macrophage

bursts releasing the amastigotes to infect other macrophages. This stage is chronic in nature and may continue for months to years and even for the life time without noticeable signs and symptoms, depending upon the host susceptibility and its immune status. The infected macrophages may remain localized to the skin, as in case of CL leading to ulcer formation, or may disseminate to other organs, as in VL (especially spleen, liver and bone marrow) or to the mucosa as in muco-cutaneous leishmaniasis (MCL). The sandfly feeding by an infected vertebrate ingests infected cells (macrophages with amastigotes) when it takes a blood meal; the amastigotes become promastigotes and will migrate to vector's midgut and foregut (in a variable period of 4-25 days). The infected sandfly is able to transmit the infection to another host during the next blood meal completing the transmission cycle. The incubation period for the appearance of clinical symptoms is usually three-six months.

The vector

The phlebotomine sandfly live in desert or semi-arid ecosystems but they are found throughout the world's intertropical and temperate regions; some species breed in peridomestic situations entering habitations. The vector density is varying seasonally because of sensitivity to climate variability of the vector. The female sandfly lays its eggs in the burrows of certain rodents, in the bark of old trees, in ruined buildings, in cracks of house walls, in animal shelters and in household rubbish, or in such environments where the larvae can find the organic matter, heat and humidity which are necessary for their development. The sandflies are small (approximately 2–3 mm in length) and soundlessly flying insects. The body and the small wings are very hairy and when at rest the insects hold their wings upright in a V-shape above them. They are poor flyers and have a flight range of a few kilometers, usually fly quite low and remain in the vicinity of their breeding ground. They are unable to fly in the presence of any wind produced by fan or ventilator also. They are usually most active at dawn and dusk. The female bite produces a rose-coloured papule surrounded by erythematous area about 10–20 mm in diameter. They can suck blood both from animals (cats, dogs, various rodents, cattle, birds and lizards, etc.) *etc.*) and human. Because of their small dimensions, they can get through standard mosquito nets. Mosquito-nets with a very fine mesh have the disadvantage that they make ventilation difficult, which is unpleasant in warm conditions.

Phlebotomous

Lutzomyia

Epidemiology

Leishmaniasis is endemic in 88 countries on five continents with a total of 350 million people at risk. Of the 88 endemic countries, 22 are in the Central and South America and 66 in the Old World. As declaration of disease is compulsory in only 32 out of 88 endemic countries, a substantial number of cases are never reported. Annually are estimated around 1.5 million new

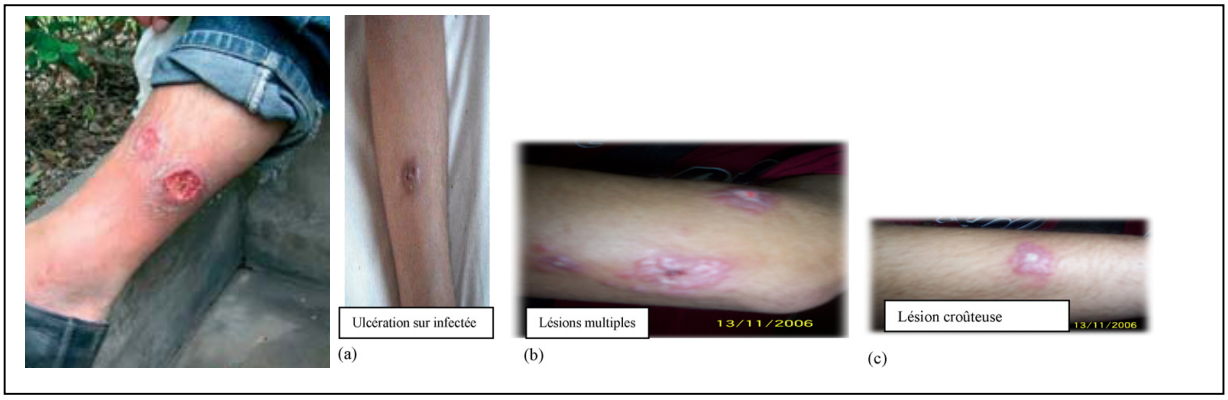
cases of cutaneous leishmaniasis (CL) and 500,000 cases of VL, with an estimated 12 million people presently infected worldwide. Annually there is an estimated of 50,000 deaths related to VL. More than 90% of the CL cases occur in Iran, Afghanistan, Syria, Saudi Arabia, Brazil, and Peru. Of the 500,000 new cases of VL, more than 90% are reported from India, Nepal, Bangladesh, southern Sudan and north-east Brazil. Despite this widespread geographic distribution, human leishmaniasis is often very focal within an endemic area, leading to 'hotspots' of disease transmission.

Clinical aspects

There is three clinical forms of leishmaniasis:

- **Cutaneous Leismaniasis (CL)**

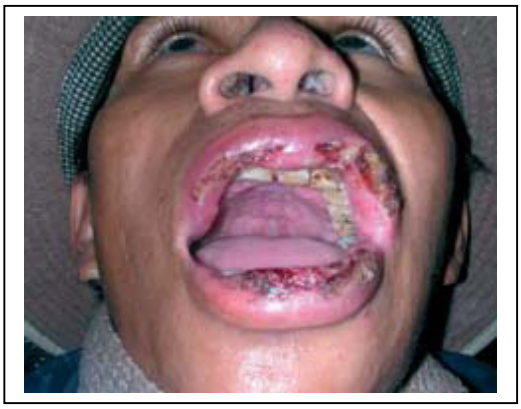
Cutaneous forms of the disease normally produce skin ulcers or nodules on the exposed parts of the body such as the face, arms and legs. The ulcers can heal spontaneously – although slowly – in immunocompetent individuals but causing scars. The disease can produce a large number of lesions - sometimes up to 200 - causing serious disability and invariably leaving the patient permanently scarred, a stigma which can cause serious social prejudice. Different species of *Leishmania* can infect the macrophages in the skin with variable clinical presentation and prognoses.



- **Muco-cutaneous Leishmaniasis (MCL)**

In mucocutaneous forms of leishmaniasis, lesions can lead to partial or total destruction of the mucous membranes of the nose, mouth and throat cavities and surrounding tissues. These lesions are usually seen months or years after a first episode of cutaneous leishmaniasis, when the macrophages of the naso-oropharyngeal mucosa become colonized. *L. braziliensis* is responsible for most cases of MCL.

These disabling and degrading forms of leishmaniasis can result in victims being humiliated and cast out from society.



- **Visceral Leishmaniasis (VL) or "Kala-Azar"**

  Visceral leishmaniasis is characterized, after an incubation period of 3-6 months, by irregular bouts of fever, substantial weight loss, swelling of the spleen and liver, anaemia, leucopoenia, thrombocytopenia and loss weight. If left untreated, the fatality rate in developing countries can be as high as 100% within 2 years. Usually children under 5 years and immunocompromised patients are more frequently affected by the disease VL is caused by the *Leishmania donovani* complex – *L. donovani sensu stricto* in East-Africa and Indian sub-continent and *L. infantum* in Europe, North Africa and Latin America..

Diagnosis

The diagnosis, especially for visceral leishmaniasis, can be difficult in absence of epidemiological criteria. In case of suspect of leishmaniasis, a bone marrow aspirate (for VL) or cutaneous biopsy (for CL and MCL) must be done for a direct research of the parasite by microscopic observation. General laboratory and serologic analysis can support the diagnostic suspicion before direct microscopic observation of the parasite. An immunological assessment can be useful for understanding the presence of an eventual immunodepression facilitating the progression of disease (especially in case of VL).

Therapy

The cutaneous and muco-cutaneous leishmaniasis can be heals spontaneously or with local treatment of the lesions. On the contrary visceral leishmaniasis needs an anti-parasitic treatment with expensive and potentially toxic drugs (pentavalent antimonials, liposomal amphotericine B) that must be administered intravenously in hospitals with supervision of a specialist in infectious diseases. Recently a new oral drug (miltefosine), not yet available in many European countries, has been introduced with good rate of cure. If timely done, the treatment can be curative in 100% of cases.

Prevention

The prevention of the leishmaniasis needs:

- Vector control measures:
  - Indoor residual spraying (IRS) of insecticides: Insecticides include products such as organochlorines (DDT and dieldrin), organophosphates (malathion), carbamates (propoxur) and synythetic pyrethroids (permethrin and deltamethrin). For several months, the insecticide will kill all susceptible insects. Considering the seasonal transmission of leishmaniasis in many endemic countries, the timing of spraying is important, together with the alternant use of different insecticide for reducing the risk of insect-resistance. Spraying of DDT (the most effective and safe insecticide for IRS) in the indoor human dwellings including the roof structure should be done. It should also cover animal shelters (especially cow-sheds) and other structures in peridomestic situations as sandflies have been recovered both from human as well as animal dwellings.
  - Insecticide impregnate bednets (ITNs): ITNs are one of the most effective methods of reducing man-vector contact in intra and peridomiciliary transmission of

vector-borne diseases. Bednets could thus be a useful tool in VL control, however, in order to be physically sandfly-proof bednets need to have a finer mesh (>200 holes/inch^2) than those used against malaria mosquitoes. The insecticides most used for bednets are synthetic pyrethroids (permethrin, deltamethrin, lambda-cyhalothrin), which combine the properties of low to moderate mammalian toxicity, low volatility and high insecticidal activity.

- Personal protection: through application of repellents/insecticides to skin or the use of adequate habits for reducing sandfly biting.

- Elimination of reservoirs: can be done destroying rodents burrows, killing infected dogs and giving to non-infected dogs deltamethrin-impregnated collars (to be changed every six months) that can confer to them protection from the majority of sandfly bites for about six months.