Cutaneous leishmaniasis

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Distribution

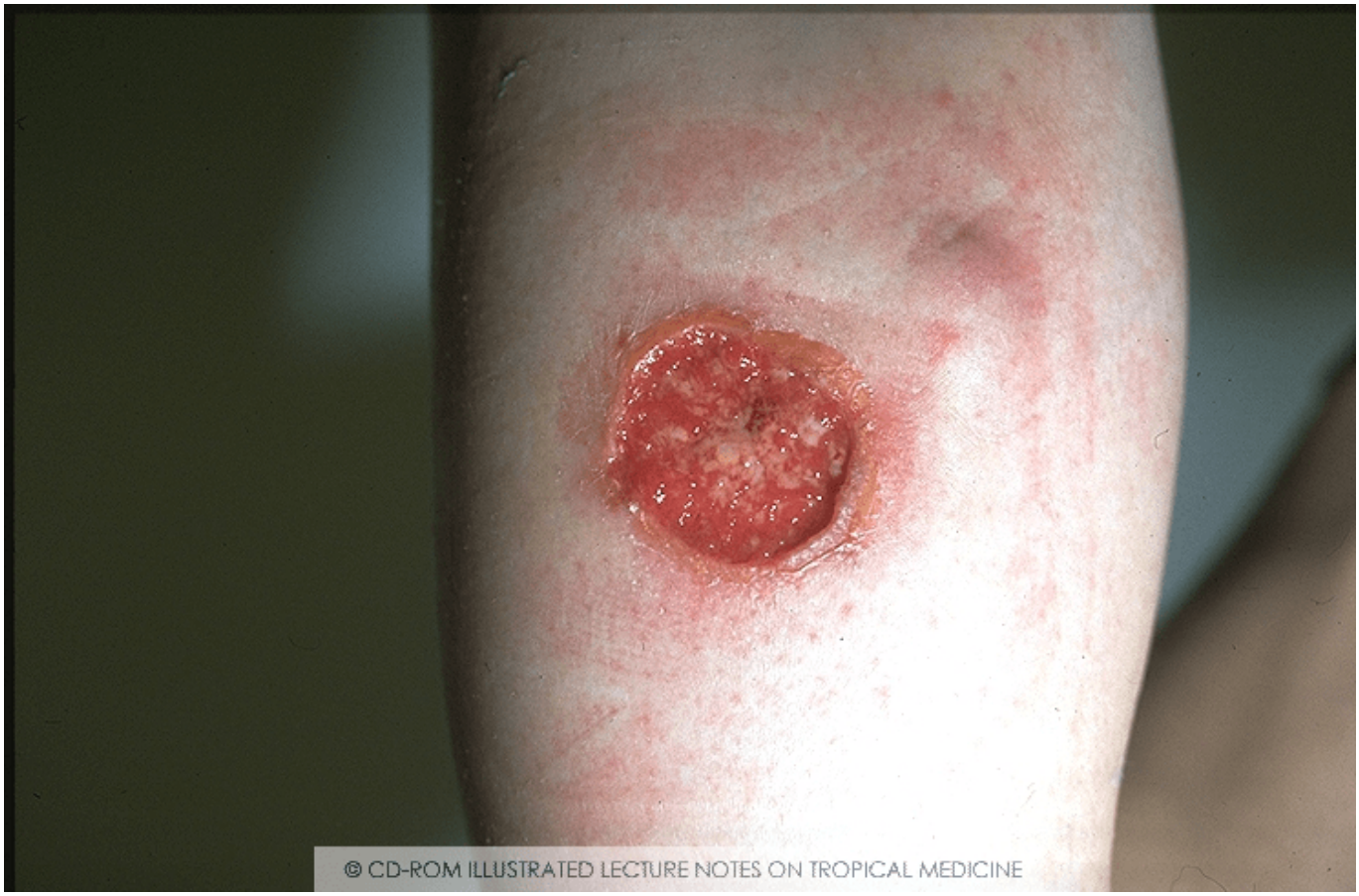
Approximately 90% of all cases of cutaneous leishmaniasis now occur in Iran, Syria, Saudi Arabia, Afghanistan, Algeria, Peru and Brazil.

Clinical aspects

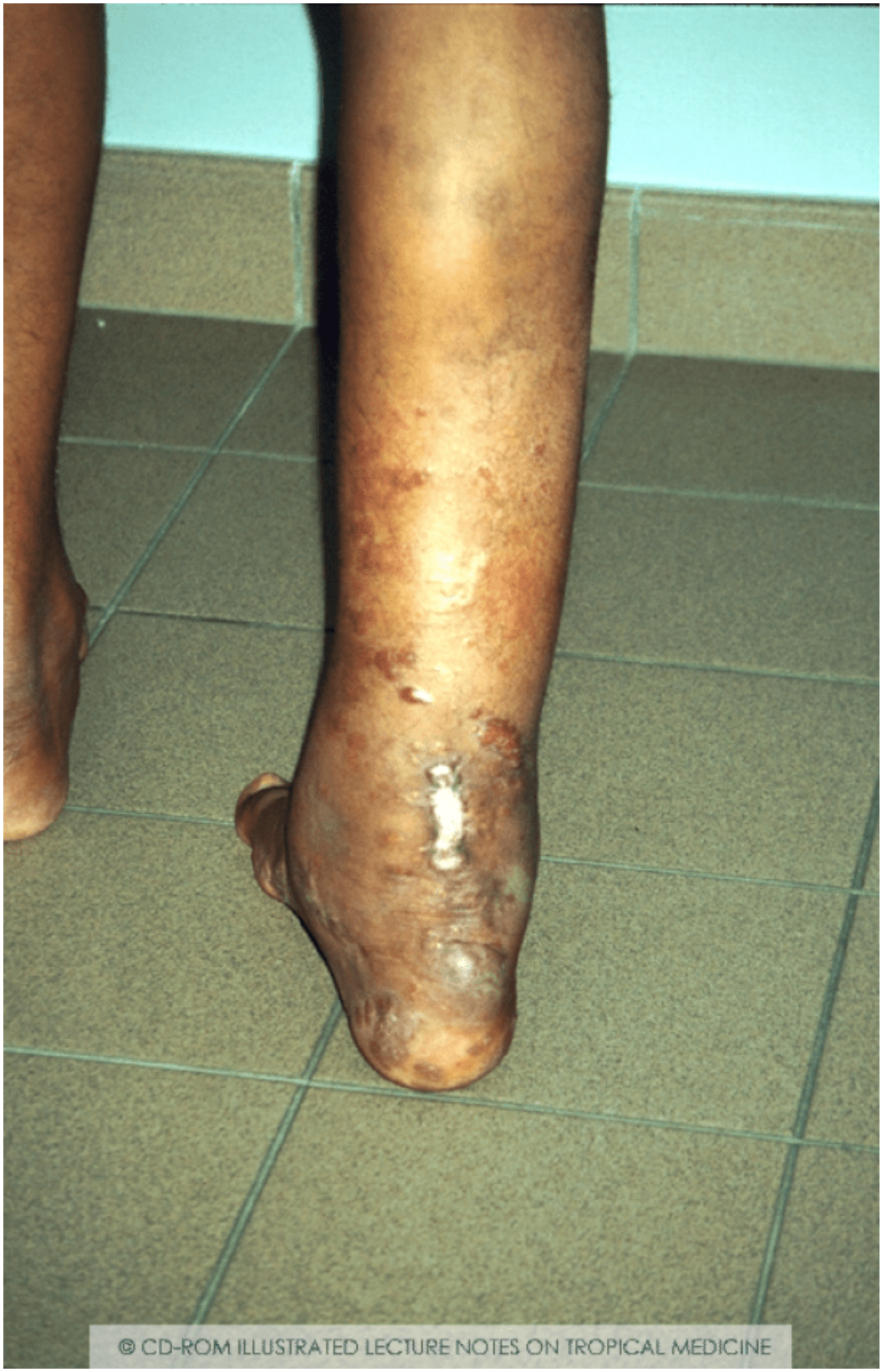
Various forms are clinically distinguished, the most important of which are:

1. Localised cutaneous leishmaniasis: skin ulcers that heal very slowly or nodular lesions, limited in extent and number. These chronic sores have regional names: clou de Biskra in Algeria and Aleppo boil in Syria.
2. Diffuse cutaneous leishmaniasis: cutaneous nodules and plaques that do not ulcerate but sometimes spread over the entire body.
3. Recurrent cutaneous leishmaniasis

"... After it is cicatrised, it leaves an ugly scar, which remains through life, and for many months has a livid colour. When they are not irritated, they seldom give much pain... It affects the natives when they are children and generally appears in the face, though they also have some on their extremities... In strangers, it commonly appears some months after their arrival. Very few escape having them, but they seldom affect the same person above more than once."



Skin ulcer due to cutaneous leishmaniasis.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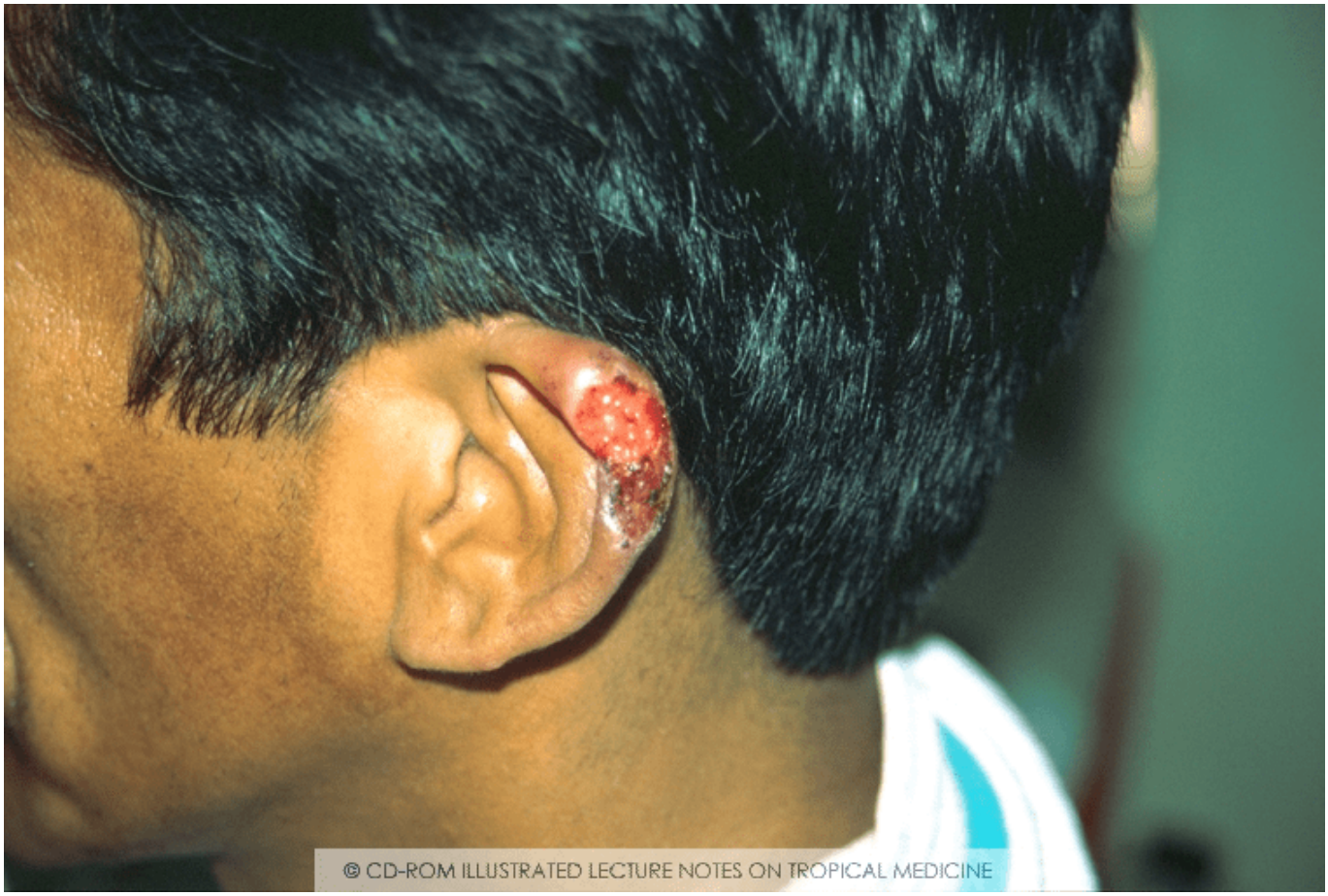
Diffuse cutaneous leishmaniasis. Infection with Leishmania aethiopica. Copyright ITM

Localised cutaneous leishmaniasis

After a bite by a sandfly infected with *L. tropica* (mainly urban infection), there is an incubation period of a few weeks or months, occasionally years. There is initially a small papule and usually only a single lesion, though sometimes there are several. This slowly spreads and can remain completely dry, become warty or nodular or develop into a painless, sharply delineated ulcer surrounded by a purplish raised border. Satellite lesions can occur. Spontaneous healing often occurs after 6 to 12 months, resulting in a depressed scar. Recurring cutaneous lesions – possibly with severe disfigurements – occasionally occur. There is usually immunity to any subsequent infection with the same organism. In infection with *L. major* (mainly rural infections, particularly from a rodent reservoir) the lesions are usually larger and develop more quickly, hence the name. There is a greater tendency to local spreading via the lymphatics and this has to be distinguished from sporotrichosis. The lesions will eventually spontaneously heal with scar formation. Clinical cure starts when macrophages become activated and start killing amastigotes. This is mediated via a T-helper cell type 1 (Th1) response. This immune reaction also prevents recrudescence of latent chronic infection. The Th1 response is accompanied by secretion of pro-inflammatory cytokines, such as interferon gamma and interleukin 12. If the immune response would be towards production of down-regulating cytokines (interleukin 4, 10, 13, TGF beta), macrophages will not be capable of eliminating the parasites, but tissue destruction will be limited.

In South America the lesions often have their own local names and clinical expressions. Hence in Peru they are called “uta” (a solitary ulcer or a few restricted lesions brought about by *L. peruviana*, frequently on the face). In Guyana they are known as “bush yaws” or (French) “pian bois” (*L. guyanensis*) with raspberry-like lesions that resemble yaws. In Yucatan, Mexico an ulcer on the ear (usually caused by *L. mexicana*) is known as “chiclero” ulcer.

A “chiclero” is a man who collects chicle-latex in the forest. During their activity in the plantations the workers can get bitten by *Lutzomyia olmeca* and as such are exposed to a high risk of contracting leishmaniasis, hence the term “chiclero ulcer”.



Chiclero ulcer on an ear (leishmaniasis). Photo Cochabamba, Bolivia

Diffuse cutaneous leishmaniasis

Diffuse cutaneous leishmaniasis is a diffuse affliction of the skin with extensive non-ulcerative nodules and is a very chronic disease. It is sometimes followed by chronic lymphoedema of an affected part of the body. This disease is poorly understood but is probably caused by a diminished resistance to the parasite. This immunosuppression is possibly brought about by the parasite itself. One of the supposed mechanisms of escape of *Leishmania* parasites is downregulation of the expression of major histocompatibility complex (MHC) class II molecules on the macrophages they colonise. In East Africa diffuse cutaneous leishmaniasis is often caused by *L. aethiopica* and in the New World frequently by *L. mexicana*.

If there are generalised cutaneous lesions the condition must be differentiated from lepromatous leprosy, keloids, neurofibromatosis and post kala azar dermal leishmaniasis (PKDL). Due to the low

resistance of the patient very numerous amastigotes are present and most skin smears are positive. Treatment is difficult as the patient's immune system itself is functioning poorly. DCL patients are anergic to leishmanial antigen. Patients with DCL have a predominantly Th2-type cytokine response. They have low concentrations of interferon gamma and interleukin 12. There is no tendency to self-cure. Differentiation from PKDL is important, as the latter can still be treated reasonably well. In Sudan 1 case of diffuse cutaneous leishmaniasis is found for every 100 cases of localised cutaneous leishmaniasis. The incidence varies greatly from district to district. It occurs frequently in South America, but in contrast to this it does not occur in India (or very exceptionally –eg in HIV patients).

Recurring cutaneous leishmaniasis

Recurring cutaneous leishmaniasis seldom occurs (Iraq, Iran). This disease, also known as leishmaniasis recidivans leads to significant tissue damage. Parasites are very difficult to detect in these very chronic lesions. Differentiation from cutaneous tuberculosis is important.

Diagnosis of cutaneous leishmaniasis

Attempts should be made to detect the parasite microscopically in a biopsy or smear from the edge of the wound. The biopsy should if possible, be divided up for pathology (seldom available, not very sensitive and is principally used more for exclusion of another cause) and cultures (bacteria, mycobacteria, fungi, *Leishmania*) and an impression preparation should also be made. Lesions on the face can be injected with 0.1 ml physiological saline and aspirated again while moving a small, thin needle back and forth in the skin. Serology is usually negative. Differential diagnosis includes ulcers due to mycobacteria, cutaneous diphtheria, tertiary syphilis, yaws, cutaneous carcinoma and deep or subcutaneous mycosis. Field sore (cutaneous diphtheria) and tropical ulcers are painful, particularly in the early phase.

Differential diagnosis of disseminated nodular and ulcerated lesion includes leishmaniasis, sporotrichosis, atypical mycobacteria and nocardiosis.

Treatment

The response to treatment varies according to the species. Drugs for systemic and topical treatment can be used. There is an urgent need for better and cheaper drugs.

Indications for local treatment

1. lack of risk of developing mucosal lesions
2. Old World cutaneous leishmaniasis
3. small, single lesion
4. absence of spread to lymph nodes

Indications for systemic treatment

1. presence of mucosal lesion or spread to lymph nodes
2. New World cutaneous leishmaniasis, except localised Leishmania mexicana infection
3. lesions unresponsive to local treatment

Overview topical treatment of cutaneous leishmaniasis

1. physical methods: cryotherapy (liquid nitrogen) for 15-20″, repeated 2-3 times with an interval of e.g. 3 weeks. Blistering will occur.
2. application of local heat via a CO_2 laser or an infrared lamp (40°C to 42°C for 12 hours) has been used, but heat-induced skin bullae are common.
3. ointment with 15% paromomycin and 12% methylbenzethonium chloride in soft white paraffin (e.g. Leishcutan® ointment). Urea can be added as a keratolytic. Twice daily application is advised for a duration of 20-30 days.
4. skin infiltration with pentavalent antimony with a fine gauge needle. Blanching of the lesions should be obtained. Treatment is repeated every 5-7 days, in general 2-5 times, sometimes more.
5. imiquimod crème (Aldara®). This immunomodulator activates macrophage killing of Leishmania amastigotes, but is best used in combination with systemic meglumine antimonate. Experience with this drug is limited.
6. treatment with antimonium plus topical recombinant human granulocyte-macrophage colony stimulating factor (GM-CSF) has been described. GM-CSF (molgramostim = Leucomax®) was diluted for topical use to a concentration of 10 µg/ml. It was applied 3 times weekly for 3 weeks (1-2 µg/cm2/lesion). In vitro, GM-CSF has been shown to activate macrophages that kill *Leishmania* pathogens. Intralesional injection of GM-CSF (400 µg) has also been shown to reduce the healing time of leishmania ulcers.
7. Application of topical 5-aminolaevulinic acid (a porphyrin-prcursor), followed by two laser irradiations, which photoactivates the compound. It is expected that very little scar tissue would form, so for aesthetically important places, this might become first choice treatment, if the clinical studies confirm this expectation.

Overview systemic treatment of cutaneous leishmaniasis

1. Pentavalent antimonials (meglumine antimoniate [85 mg Sb/ml, IM] or sodium stibogluconate [100 mg/ml, IM or filtered IV] can be given parenterally for extensive skin lesions. For unknown reasons, the incidence of herpes zoster is increased about 10 times during IV treatment with IV Pentostam relative to the incidence in the normal population. Cases of cutaneous leishmaniasis not treated with antimony do not have an increased incidence of herpes zoster.
2. Pentamidine. First line against *L. guyanensis* (French Guyana). Several treatment schemes exist and the cure rate is dose-dependent. Some short-courses use 1200 mg as a total dose. In Guyana 3 mg/kg/day every other day is often used (4 injections).
3. Imidazoles, triazoles. Infections caused by *L. major* can be successfully treated with oral fluconazole 200 mg/day for 6 weeks (cure rate of 80%). Ketoconazole 600 mg per day x 28 days is moderately effective for *L. mexicana,* but much lower against *L. braziliensis*. Treatment with ketoconazole is sometimes complicated by hepatotoxicity, abdominal pain and nausea. Itraconazole (Sporanox®) gave good results in initial studies but this was not seen in the field.
4. Miltefosine. Not yet widely available, but allows oral therapy.
5. Amphotericin B and its liposomal formulations (IV).
6. Allopurinol. Not as monotherapy, but in combination with e.g. pentavalent antimony for *L. panamensis*.

Treatment of diffuse cutaneous leishmaniasis (*L. aethiopica*)

The treatment of diffuse cutaneous leishmaniasis caused by *L. aethiopica* is problematical, as this parasite is less sensitive to Glucantime®. Pentamidine can be used against *L. aethiopica*. A dose of 4 mg/kg/week which has to be continued for at least 4 months after disappearance of the parasites from the skin is an acceptable guideline here. Parenteral aminosidine sulphate is another therapeutic possibility. This is an antibiotic that is obtained from *Streptomyces chrestomyceticus*. It is an aminoglycoside and is thus potentially nephro- and ototoxic. It is chemically identical to paromomycin, which is obtained from a related *Streptomyces* strain. The compound is not resorbed from the intestine. Recurrences are frequently seen with aminosidine given as monotherapy. Aminosidine is however synergistic with stibogluconate and a permanent remission can be obtained with the combination of aminosidine with Glucantime® or Pentostam®. The dose is 14 mg/kg/day IM to be continued for up to 60 days after all parasites have been eliminated. The total treatment period takes 6 months or more. Good results were obtained with amphotericin B.

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