Cutaneous leishmaniasis

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Distribution

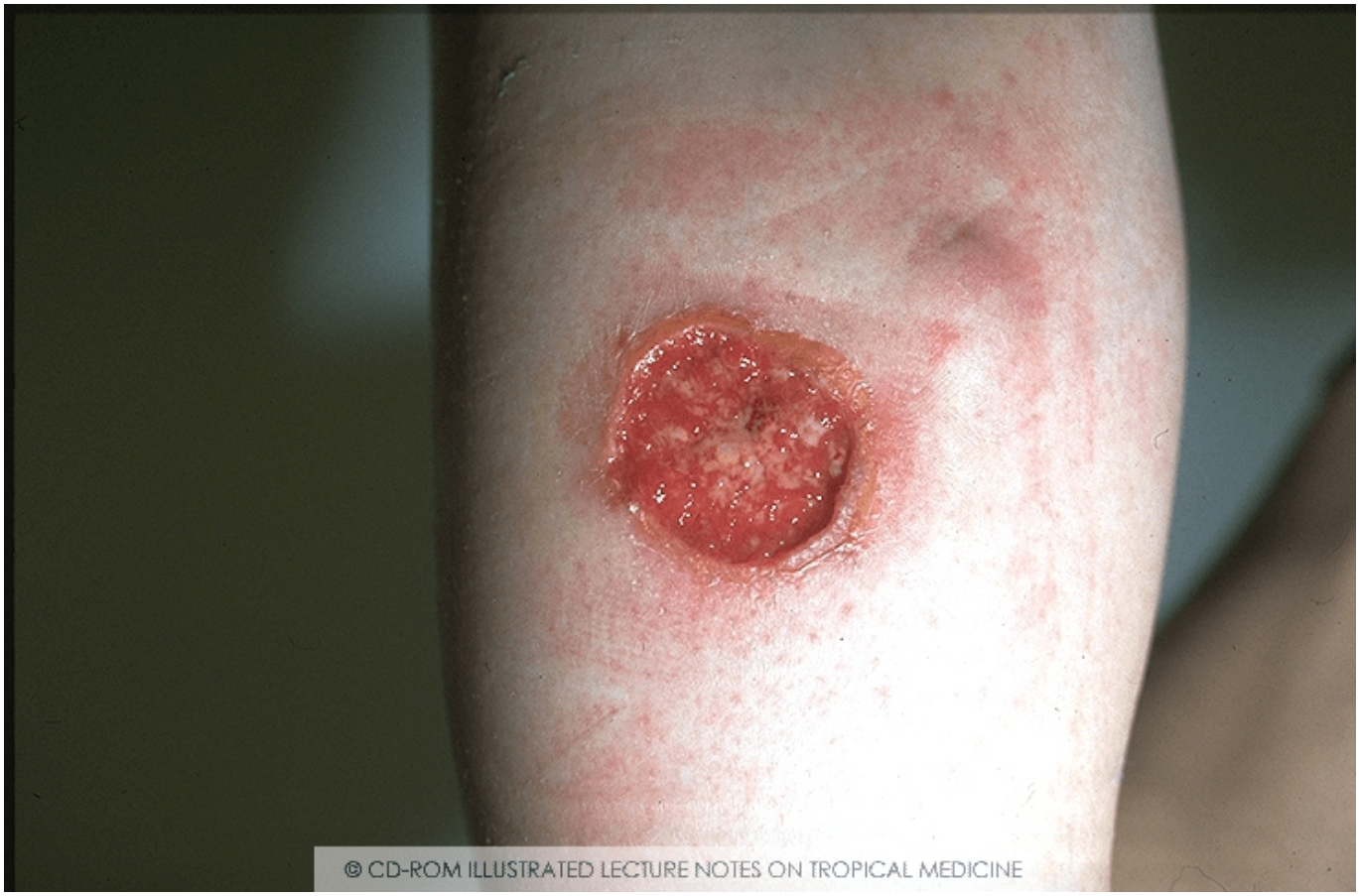
Approximately 90% of all cases of cutaneous leishmaniasis occur in Iran, Syria, Saudi Arabia, Afghanistan, Algeria, Peru and Brazil.

Clinical aspects

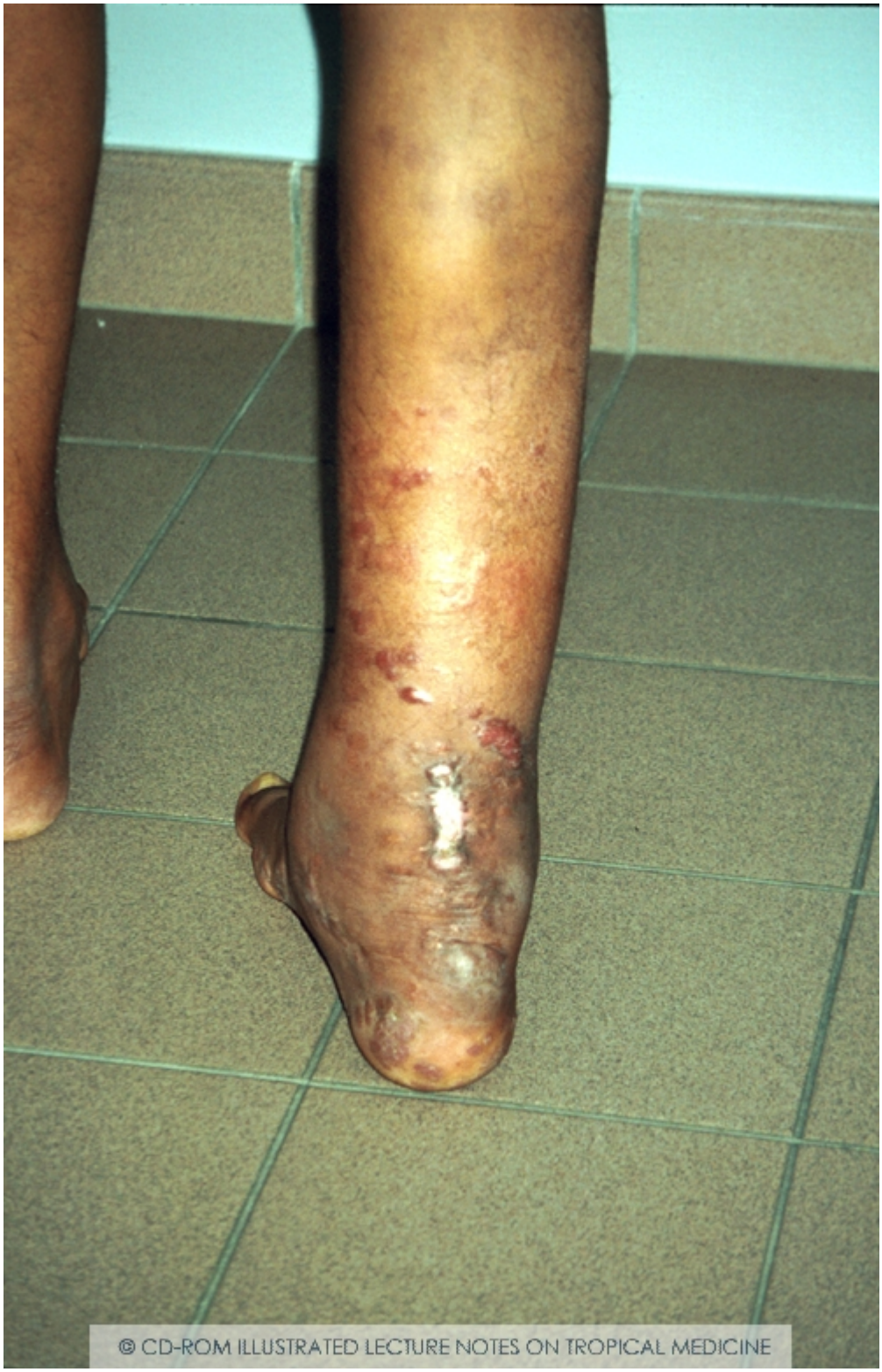
Various forms are clinically distinguished, the most important of which are:

1. Localized 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 cicatrized, it leaves an ugly scar, which remains through life, and for many months has a livid color. When they are not irritated, they seldom cause 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. Copyright ITM



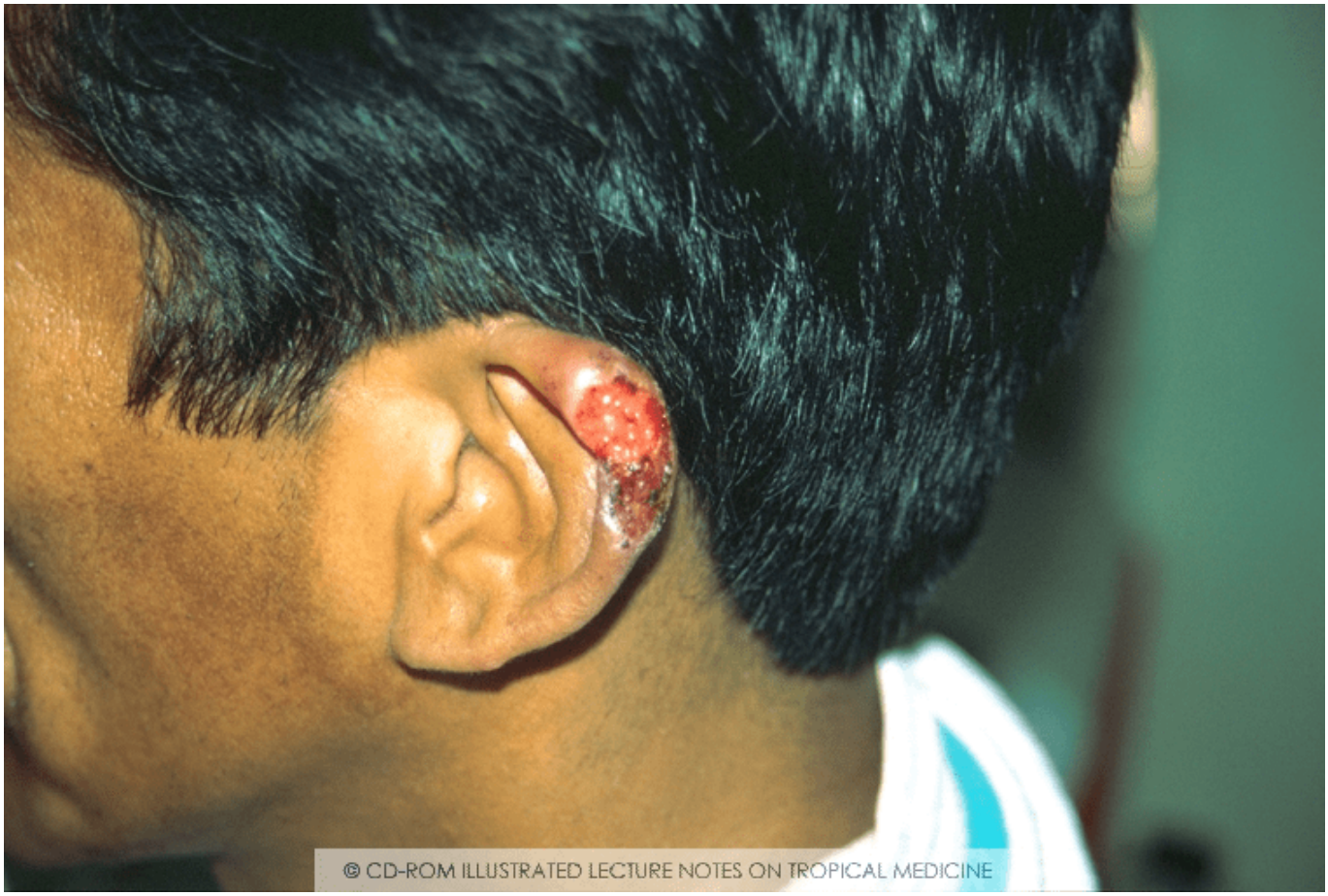
Diffuse cutaneous leishmaniasis. Infection with Leishmania aethiopica. Copyright ITM

Localized 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 spread locally 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 the secretion of pro-inflammatory cytokines, such as interferon-gamma and interleukin 12. If the immune response would be towards the 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 (bubblegum) in the forest. During their work 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 skin affliction with extensive non-ulcerative nodules and a chronic disease. It is sometimes followed by chronic lymphoedema of an affected body part. 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 supposed mechanism of escape of *Leishmania* parasites is the downregulation of the expression of major histocompatibility complex (MHC) class II molecules on the macrophages they colonize. In East Africa, diffuse cutaneous leishmaniasis is often caused by *L. aethiopica* and in the New World, frequently by *L. mexicana*.

If there are generalized cutaneous lesions, the condition must be differentiated from lepromatous leprosy, keloids, neurofibromatosis and post kala azar dermal leishmaniasis (PKDL). Due to the patient’s weak immune response, 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 diffuse cutaneous leishmaniasis case is found for every 100 cases of localized 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 diagnoses include 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 diagnoses of disseminated nodular and ulcerated lesions include 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. The presence of mucosal lesions or spread to lymph nodes
2. New World cutaneous leishmaniasis, except localized 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. Applying local heat via a CO_2 laser or an infrared lamp (40°C to 42°C for 12 hours), but heat-induced skin bullae can occur.
3. Ointment with 15% paromomycin: twice daily application is advised for a duration of 20-30 days.
4. Skin infiltration with pentavalent antimony with a fine needle. Blanching of the lesions should be obtained. Treatment is repeated every 5-7 days, generally 2-5 times, sometimes more.

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.
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).

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 has to be continued for at least 4 months after the disappearance of the parasites from the skin is an acceptable guideline here. Good results were obtained with amphotericin B.

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