

Review Article

Cutaneous leishmaniasis

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Abstract Leishmaniasis is a major world health problem, which is increasing in incidence. New cases of cutaneous leishmaniasis are being reported in Pakistan from previously non-endemic areas. This protozoal disease is transmitted by sandflies and may produce a variety of clinical pictures, including some rare and unusual presentations. Treatment is often delayed due to poorly managed cases, non-availability of laboratory facilities or appropriate drugs. Atypical presentations can sometimes perplex even the most experienced. Early diagnosis and treatment with correct dosage of antimony are essential for an effective outcome. This review focuses on the different aspects of cutaneous leishmaniasis with especial emphasis in context of Pakistan.

Key words

Cutaneous leishmaniasis, clinical presentations, treatment, diagnosis.

Introduction

Leishmaniasis is a spectrum of diseases ranging in severity from the usually benign cutaneous form to potentially life threatening visceral leishmaniasis. Transmission of the disease occurs through the bite of Phlebotomine sandflies infected with leishmania parasites. The localization or spread of the disease depends on the species of leishmania as well on the host immunity. Most forms of the disease are zoonotic - they are normally passed on from animals, and limited to areas where animals live, but some forms are anthroponotic - infecting only humans.¹ Of the 88 countries affected world-wide, all but 16 are developing, thus causing a major health and economic problem for these countries. It is estimated that approximately 1.5 to 2 million are infected each year with almost

350 million people at risk for the disease.²

Over the past few years leishmaniasis in Pakistan has increased at a considerable rate and has also extended its geographic distribution. Cutaneous leishmaniasis (CL) is endemic in Balochistan with scattered foci in Sindh, NWFP and Punjab.³ The lack of effective vector control and other prophylactic measures, due to feeble resources, poverty and illiteracy along with an expensive and prolonged treatment has made this disease a major health concern in Balochistan.

The cutaneous afflictions of leishmaniasis have been known since antiquity. Among the most ancient medical documents that probably refer to this condition as "Ebers Papyrus" in Egypt, date back to 2000 years BC.⁴ In 1885, Cunningham first reported organisms in macrophage from lesions of "Delhi Boil" in India.⁵ Although, Cunningham was the discoverer, the correct

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interpretation of the parasite was made by many others, including, Borovsky and Sir William Leishman.⁵

Geographical distribution

The geographical distribution of CL is mainly determined by the sandfly vectors. Human leishmaniasis has a very wide geographical distribution and range of climate and altitude. Leishmaniasis in its various forms is present in all continents except Australia and Antarctica⁵ and is endemic in 88 countries of the world including Asia, Africa, Southern Europe, Middle East and South America.² Cutaneous leishmaniasis in Pakistan has many scattered foci. On the one hand, it is found in the Northern hilly areas and on the other in Lasbella and Makran coastal areas in the extreme Southern part of the country, along with foci in Punjab (e.g. Multan, Mangla Dam etc.) and in NWFP (e.g. Bannu, D.I. Khan). The disease is endemic in Balochistan, with the maximum incidence reported from Sibbi, Chaman, Loralai, Kohlu, Duki, Khuzdar, Dera Bugti, Ziarat, Lehri, Nushki, Uthal, Turbat, Mand and the suburbs of Quetta.^{4,6,7}

Pathogenesis

Leishmania is a protozoan of phylum *Sarcomastigophora*, class *Zoomastigophora*, order *Kinetoplastida* and family *Trypanosomatidae*. The protozoan leishmania is an obligatory intracellular parasite, which exists, in two distinctive forms. In man and other hosts it occurs as a non-flagellar amastigote form, which are small, round to oval bodies measuring 2-5 μm . In culture and gut of sandflies the

flagellar or the promastigote form is seen which are motile slender organisms, measuring 10-15 μm with a single anterior flagellum.¹

Leishmania parasites are transmitted by phlebotomine sandflies, which are widely distributed in the tropics and other warm mainland areas. The sandflies live in dark, damp places, and are relatively weak flyers, with a range of only 50 meters from their breeding site. Unlike mosquitoes, they fly silently and their small size (2-3mm long) allows them to penetrate mosquito nets. They are most active in the evening and at night.⁸ There are some 600 species in five genera within the subfamily *Phlebotominae*, species in three genera, *Phlebotomus*, *Lutzomyia* and *Sergentomyia*, suck blood from vertebrates, only the former two transmit disease to man.⁹ Generally speaking the species biting man in the Old World will be *Phlebotomus* and in the New World *Lutzomyia*. The phlebotomine sandfly vectors for cutaneous leishmaniasis in Pakistan are *P. papatasi*, *P. sergenti* and *P. salehi*.^{4,10} Each species of leishmania favours one or more animal reservoir, except *L. donovani* and *L. tropica*, which are thought to be mainly, if not exclusively, anthropomorphic.¹¹ In zoonotic cutaneous leishmaniasis (rural, wet type) caused by *L. major*, the transmission of infection i.e. rodent-sandfly-rodent cycle is maintained in wild rodent/gerbil colonies. *Rhombomys opimus*, *Meriones spp.* and *Psammomys obesus* are the three major reservoir species of the rodents that maintain infection in most of central Asia, Middle East and North Africa.⁴ A number of rodent species have been implicated as being the animal reservoir hosts in Pakistan, these include,

Meriones hurriane or other species of gerbils, *R. opimus* and *Tatera indica*.^{4,10} Other rodents that might be important in this respect include, *M. P. M. crassus*, *M. lybicus erythrorus* and *Mus musculus*.⁶ Transmission of leishmania infection occurs almost exclusively through the bite of an infected sandfly; however, other possible modes of transmission reported are the direct transmission via skin contact of cutaneous leishmaniasis and congenital transmission in visceral leishmaniasis.⁵

Clinical features

The clinico-pathological picture of cutaneous leishmaniasis is variable and depends not only on the leishmania species but also on the immune status of the host. After an incubation period, mostly measured in months, but may range from a few days to over a year, lesions appear usually on the exposed areas of the skin, accessible to the vector and corresponding to the bite sites.¹² Clinical features of leishmaniasis, excluding visceral leishmaniasis, will be considered under the following headings.

1. Localized cutaneous leishmaniasis

Localized cutaneous leishmaniasis (LCL) in the Old World is caused by *L. major*, *L. tropica*, *L. infantum* and *L. aethiopica*, primarily by the former two. The LCL in the New World is caused by two independent species or "complexes" of parasites i.e. *L. braziliensis* and *L. mexicana*. With minor differences, the clinical lesions produced by all these species are similar.¹³ LCL usually affects the unclothed parts of the body at the site of sandfly bite. After an incubation period of less than two months in *L. major* and more than two months in *L. tropica* a

red furuncle-like papule appears.¹⁴ The papule gradually enlarges in size, over a period of several weeks, and eventually the lesion becomes crusted in the centre. When the crust is removed, a shallow ulcer is found, often with raised and somewhat indurated borders. Healing usually takes place in 2-6 months in *L. major* infection and 8-12 months in *L. tropica*. The healing is always with a scar that is typically atrophic, hyperpigmented and irregular (cribriform).¹³ Zoonotic cutaneous leishmaniasis due to *L. major* is the main type of leishmanial disease in Pakistan, except in Mirpur, Mangla Dam area, a spot in the extreme south of Balochistan and Afghan refugee camp in Timargara (Dir, NWFP) where cutaneous leishmaniasis due to *L. tropica* has been reported.^{7,15} A recently conducted study in Multan also identified *L. tropica* as the causative species.¹⁶

Inflammatory satellite papules may develop around the primary lesion representing a reaction to local dissemination of the parasite or its antigenic products. These papules are smooth, 2-5 mm in size. They are located within 2 cm from the edge of the primary lesion or the nearest satellite papule. The pathology of the satellite papule is non-specific and amastigotes are usually not found.^{5,13} Sporotrichoid spread is also commonly seen in LCL. Solitary or multiple subcutaneous nodules occur proximal to the skin lesions, and usually along the axis between the skin lesions and the regional lymph nodes. These nodules usually measure 0.5-2.0 cm and are smooth, soft and mobile. They are sometimes triggered by antileishmanial treatment.^{12,17} Histology of these lesions may show amastigotes.¹⁸ In some cases cutaneous

leishmaniasis has been found to remain "active", i.e. with positive smears, for 24 months or even longer. Such cases have been designated "non-healing chronic cutaneous leishmaniasis".¹¹ Multiple lesions can be seen in LCL, the highest number of lesions reported for a single patient is 372.¹⁷ Rare sites for lesions include scalp, genital areas, eyelids, lips, nostrils, palmoplantar and paronychia.^{17,19,20} Leishmania parasites have also been found in rheumatoid nodules in a patient with rheumatoid arthritis, treated with methotrexate and prednisone.²¹ Atypical lesions may be seen in LCL, which include the hyperkeratotic psoriasiform lesions, eczematoid lesions, zosteriform pattern, warty lesions, erysipeloid lesions, keloidal and nodular lesions and acneiform lesions.^{13,17,22} Other atypical presentations reported are annular and chancriform lesions,¹⁹ angio-lupoid²³ and cold cellulitis.²⁴ Similarly, *L. chagasi*, the causative agent of visceral leishmaniasis in the Americas, has been associated with atypical cutaneous leishmaniasis.²⁵

2. Mucocutaneous leishmaniasis

Mucocutaneous leishmaniasis (MCL) is a serious and occasionally life-threatening form of leishmaniasis found mainly in the New World. *L. braziliensis braziliensis* is the most common etiologic agent. Smaller proportion of cases due to *L. b. panamensis* and *L. b. guanensis* also occur. Similar lesions can be produced by *L. aethiopica* in Africa.^{5,11,14} MCL begins with a cutaneous lesion that is identical to that of cutaneous leishmaniasis; however, rather than showing eventual resolution, the infection extends to the adjacent mucosa and cartilage of the upper respiratory tract. The disease leads to marked disfigurement and patients with

mucosal disease never heal spontaneously.²²

3. Diffuse (anergic) cutaneous leishmaniasis

Diffuse cutaneous leishmaniasis (DCL) is a polar form of cutaneous leishmaniasis characterized by largely disseminated nodules, abundance of parasites throughout the course of the disease, absence of parasite-specific cell-mediated immune response and a poor response to antimonial treatment. DCL may be caused by *L. m. amazonensis*, *L. mexicana* and *L. pifanoi* in the New World and by *L. aethiopica* in the Old World, but the disease caused by *L. m. amazonensis* in Central and South America is more common.⁵ DCL due to *L. major* has also been reported.²⁶ The disease usually begins with an initial primary lesion which disseminates to involve other areas of the skin. The lesions are often scattered over limbs, buttocks and face. There is no systemic involvement. Classically, the lesions of DCL do not ulcerate, but ulceration has been described in DCL.⁵

4. Leishmaniasis recidivans (chronic lupoid leishmaniasis)

Leishmaniasis recidivans (LR) is a distinctive form of chronic cutaneous leishmaniasis that is usually a complication of *L. tropica* in the Old World and less commonly *L. braziliensis* in South America.⁵ LR refers to the development of new lesions in the centre or periphery of a healed lesion of cutaneous leishmaniasis. Clinically, there is a central scar in which central or peripheral infiltrated papules and crusted inflammatory lesions develop that expand slowly, assuming a circular or arciform configuration.²⁷ The lesions frequently worsen in summer and may

ulcerate. The lesions tend to resist treatment and become chronic.¹³

5. Post kala-azar dermal leishmaniasis

Post kala-azar dermal leishmaniasis (PKDL) is a rare sequel to visceral leishmaniasis that has been apparently cured after adequate treatment. There is a significantly higher PKDL rate (69%) in those who receive inadequate and irregular treatment of kala-azar than in those who are treated with stibogluconate 20 mg/kg daily for 15 days (35%). It is caused by *L. donovani* and *L. aethiopicus* in the Old World, primarily by the former and is endemic in East Africa and India.^{5, 28} In India, the rash of PKDL occurs in 20% of patients and appears 1-2 years after recovery, as hypopigmented macules markedly similar to the lesions of lepromatous leprosy.¹⁴ Erythematous macules develop next and finally, after a variable period of months or years, nodules replace the hypopigmented and erythematous macules.⁵ The rash is progressive over many years and seldom heals spontaneously. Cases of PKDL are more resistant to treatment, requiring higher doses of systemic medication.¹⁴

6. Other clinical aspects

L. tropica was found to be the causative organism in several cases of visceral leishmaniasis in American soldiers returning from Saudi Arabia (viscerotropic leishmaniasis). The clinical features consisted of high-grade fever, malaise, intermittent diarrhea and abdominal pain. Skin lesions did not occur.⁵ Skin involvement in visceral leishmaniasis has been poorly documented. Co-infection by the human immunodeficiency virus (HIV) has resulted in the development of atypical

forms of visceral leishmaniasis with an increased incidence of cutaneous involvement, and skin findings may be the earliest sign of the disease. The reported cutaneous lesions include a psoriasiform eruption, papulonodular lesions, erythrodermic pattern,²⁹ linear brown macules,³⁰ dermatomyositis-like eruption, a polymyositis-like syndrome³¹ and leishmania parasites in biopsy of a fibrous histiocytoma and skin tattoo.³⁰

Diagnosis

The clinical picture of cutaneous leishmaniasis can be greatly altered by superadded infection or a badly managed treatment, which can cause difficulty in diagnosis and delay in treatment. A rapid method of diagnosis in CL is by obtaining smears from the lesions and examining it under a microscope, after staining with Giemsa or Leishman stain. Different methods can be used for making a smear i.e. impression or touch preparation, slit skin smear, scalpel scraping by using a dental broach or by fine needle aspiration. It is recommended that the sample should be taken from the edge of the active lesion, as far away from crusting, ulceration and secondary infection as possible.³² However, others have recommended dermal scrapings from the bottom of the ulcers yielding a positive result in over 90% of cases.³³ Fine needle aspiration cytology can be used an initial, easy to perform and relatively less painful procedure with good positive yield.³⁴

The histological picture in cutaneous leishmaniasis differs according to the stage of infection and the clinical type. A consistent finding is a moderate to heavy

dermal infiltrate of lymphocytes, plasma cells and macrophages. In about 80% of cases, epithelioid cell granulomas with giant cells and a rim of lymphocytes are present. In all histopathological examinations it is important to search for amastigotes, which are diagnostic.³⁵ Several different culture media have been used to isolate leishmania, including Novy-McNeal-Nicolle medium (NNN), modified Evan's medium, Tobie's modified NNN medium and Schneider's insect medium. The incubation temperature is usually around 25°C. The cultures may be positive in 3-8 days, but may take as long as 4 weeks.³⁶ A new microcapillary culture method has shown higher sensitivity and rapid growth of promastigotes as compared to the traditional culture methods.³⁷ There are cases of cutaneous leishmaniasis on record, due to both *L. major* and *L. tropica*, in which leishmania parasites have been grown successfully from blood of the patients.³⁸

Immunodiagnosis, where available, may help in the diagnosis of CL. These can be divided into those tests that detect and measure antibodies in serum, and those that detect specifically activated T lymphocytes. The tests for cellular immunity include, leishmanin skin test, lymphocyte proliferation assay and macrophage migration inhibition test, among others.^{11,39} A variety of serodiagnostic methods are available and are in widespread use for the detection of antileishmania antibodies. The direct agglutination test uses promastigotes as the antigen, in which clumping of cells provides an easily visible indication.⁴⁰ Other serological tests include, gel diffusion and counter current electrophoresis test, Fluorescent antibody test, immuno-

peroxidase test and immunofluorescent test.³⁹ Polymerase chain reaction is a sensitive and specific method of diagnosis and has the added advantage of species determination.⁴¹

Treatment

There is no single, widely accepted treatment regimen for cutaneous leishmaniasis. This is partly due to the broad clinical spectrum of the disease, as well as the fact that many lesions of localized cutaneous leishmaniasis heal spontaneously. A simple guideline to follow is to try the topical methods or safer systemic compounds for the treatment of simple sores and reserve the systemic use of pentavalent antimonials for the more problematic sores. The problematic sores can be defined as those occurring over the face or other vital areas, sores where scarring would be disabling or disfiguring, lesions over cartilage, larger lesions, lymphatic involvement and sores that will not heal easily e.g. over the lower leg or over a joint.^{14,42}

1. Parenteral pentavalent antimony compounds

The standard therapy, and the only chemotherapeutic agent with a clearly favourable therapeutic index, is the pentavalent antimony compounds. Two therapeutically equivalent products are available: sodium stibogluconate (Pentostam®) and meglumine antimonate (Glucantime®).⁴³ The drugs appear to inhibit amastigotes glycolytic activity and fatty acid oxidation.⁵ The recommended daily dose at present is 20 mg/kg/day of elemental antimony, which is more effective than the

older, lower dosage regimens. The drug can be given both intramuscularly and intravenously in a single daily dose.³⁶ In American CL, 20mg/kg/day for 20 days is an appropriate course curing over 90% of cases in a single course. Shorter courses may be adequate for Old World disease.⁸ Indeed, in a recent randomized double-blind trial, sodium stibogluconate at a dosage of 20 mg/kg/day for 10 days was therapeutically equivalent and less toxic than the standard 20-day course.⁴⁴

Toxicity is common, and appears dose related, most patients develop malaise, anorexia, myalgia and arthralgia after 14 days treatment.⁸ Other side effects include local skin reactions, vomiting, transient elevation of liver enzymes, chemical pancreatitis, abdominal discomfort and occasional anemia, leukopenia and thrombocytopenia. Changes in the ECG may develop and include T wave inversion, ST segment elevation or depression and prolongation of QT interval. Prolongation of the corrected QT interval and concave ST segments are considered ominous signs.^{5,43,45} Nephrotoxicity (acute renal failure) and erythema nodosum have been reported.⁴⁶ Treatment should be monitored but in most cases these abnormalities settle rapidly once treatment is stopped. Lesions become less indurated, flatten, then reepithelialise as they respond to treatment. However, healing continues after treatment has stopped so the need for additional treatment should be delayed for 4-6 weeks.⁸

Ways to deliver antimony compounds orally is in experimental stages.⁴⁷ Immunotherapy has also been investigated as a modality of treatment,

where a vaccine against cutaneous leishmaniasis is combined with the antimonial salts.⁴⁸

2. Physical modalities

Cryotherapy is a cheap and easily performed method of treatment. Cryo-applications can be performed with either cotton tipped applicator dipped in liquid nitrogen, a liquid nitrogen cryoprobe or with a CO₂ cryosurgical machine. A 30-120 seconds application is performed or until the formation of ice-ball reaching 2 mm outside the lesion margin. Cryotherapy combined with intralesional antimonials is more beneficial and superior to either cryotherapy or intralesional antimonials alone. Other physical modalities include, local heat therapy using heated pads or an infrared source, carbon dioxide laser, curettage, cautery, electrodesiccation and finally surgical excision.^{36,42,43,49} Thermotherapy using radio-frequency waves⁵⁰ and photodynamic therapy⁵¹ has given good results for LCL.

3. Intralesional therapy

Intralesional antimonials are effective treatment if used for early, uncomplicated simple sores. One to 3 ml (depending on the size of the lesion) is injected intralesionally. Success rates of up to 99.2% have been achieved using alternate day or weekly intralesional injections.^{49,52} Hypertonic sodium chloride solution has also shown a good response, when used intralesionally, for Old World cutaneous leishmaniasis. A success rate of 95% with 2% zinc sulphate and 85% with 7% sodium chloride was achieved with intralesional injections of these solutions,⁵³ while others found zinc sulphate to be less effective.⁵⁴ Other drugs

used intralesionally include bleomycin, emetine, chloroquine and amphotericin B.^{42,43}

4. Topical therapy

Many drugs have been and are being used topically with varying success rates. Paromomycin sulphate in an ointment base has been used with good results. In one study in Quetta, Pakistan, paromomycin sulphate was used topically as an 11.5% ointment. The overall efficacy was 91%.⁷ While others have shown it to be ineffective.⁵⁵ The combination of paromomycin sulphate and methyl benzethonium chloride has also been used with good success rate of up to 76%.³⁶ Other topical therapies used with varying success rates include, diminazene aceturate, 2% ketoconazole with dimethylsulfoxide and miconazole and 2% chlorpromazine with 25% methyl salicylate.⁴³ Nitric oxide-generating creams have been recently investigated as a potential topical therapy for cutaneous leishmaniasis.⁵⁶ Topical imiquimod 5% cream combined with parenteral antimony has shown a more rapid healing of lesions and improved scar quality.⁵⁷ Similarly, topically applied granulocyte-macrophage colony-stimulating factor (GM-CSF) along with parenteral antimonial therapy was more effective than treatment with antimony compounds alone.⁵⁸

5. Systemic drugs other than antimonials

Due to the side effect profile, development of resistance, parenteral route of administration and at times unavailability of antimonials, the search for other treatments has been widespread. Oral dapsone has been used extensively in India for the treatment of cutaneous leishmaniasis. Doses range from

2-4 mg/kg/day to 200 mg per day and the duration ranging from 21-45 days. Recommended dose now is 100 mg twice daily for 6 weeks (in adults). Cure rates of 80-100% have been achieved.⁵⁹ Rifampicin (600-1200 mg) alone or with INH (300 mg) has shown varying success rates in Old World cutaneous leishmaniasis.^{43,60} Varying results have been achieved with oral itraconazole given in the dose of 200 mg for 6-8 weeks.⁶¹ Other drugs that have been used to treat localized cutaneous leishmaniasis include, terbinafine,⁶² trimethoprim-sulfamethoxazole, metronidazole, ketoconazole, emetine, dihydro-emetine, levamisole,⁴³ mebendazole,⁵ amphotericin B, allopurinol,⁶³ immunotherapy such as interleukins,⁴³ oral zinc sulphate,⁶⁴ fluconazole⁶⁵ and azithromycin.⁶⁶ Treatment with orally administered drug, hexadecylphosphocholine (miltefosine) has been approved for visceral leishmaniasis. It is under clinical trial for treatment against CL and has shown promising results.⁶⁷

Vaccination

While searching for a drug, it is also important to seek a vaccine with which to strengthen the body's own defenses and prevent the disease. Vaccination trials in animal models and human beings have been performed with virulent promastigotes, attenuated or killed promastigotes and specific antigens purified from promastigotes with use of different adjuvants with varying success rates.^{5,68} Vaccination trial, using killed (autoclaved) leishmania vaccine, was also carried out in Quetta, Pakistan, during 1995-97.² A successful vaccine will be a milestone towards an effective control of leishmania

afflictions all over the world.

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