



Review Article

Cutaneous leishmaniasis

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ABSTRACT

Leishmaniasis is considered to be zoonotic disease, caused by a protozoan parasite of the genus *Leishmania*, and transmitted by a bite of infected female sandfly. Primary cutaneous leishmaniasis is not common disease in Nepal, however, there were cases reported from Terai region of Nepal. The patients with cutaneous leishmaniasis present with a papule or nodule at the site of inoculation, followed by formation of crusts. Differential diagnoses of cutaneous leishmaniasis include variety of skin diseases, inflammatory like impetigo, eczema, or granulomatous like sarcoidosis, lupus vulgaris, to skin tumor like basal cell carcinoma & squamous cell carcinoma. There are various procedures and laboratory techniques used to diagnose leishmaniasis. Punch skin biopsy is widely used & popular technique to diagnose cutaneous leishmaniasis. Different drugs like sodium stibogluconate, sodium antimony gluconate, Amphotericin B and Miltefosine: are used for its treatment. No vaccines are available for prevention.

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INTRODUCTION

At the turn of nineteenth century, Cunningham, Borovsky, Leishman, Donovan, Wright, Lindenberg and Vienna each independently identified the parasite that causes leishmaniasis.¹ In 1903, the term “Leishmania” was coined by Ronald Ross.² Carini identified leishmania in mucosal lesions of patients with leishmaniasis in Brazil in 1912. Bramachari described Post Kala-azar dermal leishmaniasis (PKDL) in India in 1922. Thereafter the clinical and geographical features of the human disease were supplemented by other studies.

Leishmaniasis is considered to be zoonotic disease, encountered in endemic areas in dogs, wild rodents or other mammals. It is caused by a protozoan parasite of the genus *Leishmania*, and transmitted by a bite of infected female sandfly of the genus *phlebotomus* in the old world and the genus *Lutzomyia* in the new world.³ The disease is prevalent in 98 countries and regions of the world and responsible for increasing health problems.^{4,5}

Nepal is an endemic zone for visceral leishmaniasis and *L. donovani* is endemic in south Asian countries like Nepal, India, Bangladesh and in east African countries like Ethiopia, Kenya and Sudan.⁶ So, there are series of cases of Post-Kala-azar dermal leishmaniasis (PKDL) reported from Nepal.^{7,8} Primary cutaneous leishmaniasis is not common disease in Nepal, however, there were few cases reported from Terai region of Nepal.^{9,10} Here cutaneous and muco-cutaneous leishmaniases are discussed. Visceral leishmaniasis is not included as the scope of this article.

DISCUSSION

Several leishmanial species (21 species) are responsible for leishmaniasis in humans. (Table 1).

Leishmania is clinically classified in 3 forms.

Visceral leishmaniasis

Cutaneous leishmaniasis

Muco-cutaneous leishmaniasis

Cutaneous leishmaniasis

The clinical features of cutaneous leishmaniasis tend to vary between and within regions due to different species of *Leishmania*. The patients with cutaneous leishmaniasis do not show visceral manifestation. A classical lesion starts as a papule or nodule at the site of inoculation, followed by formation of crusts (fig. 1).

Cutaneous leishmaniases are of following types.

Old world cutaneous leishmaniasis:

It is usually caused by *L. major*, *L. tropica*, and *L. aethiopica*. Cutaneous leishmaniasis caused by *L. major* is found in central Asia, Middle east, North Africa, North India and Pakistan. There are few reports from Nepal and authors have also seen cases of cutaneous leishmaniasis (fig.1). Multiple inflamed lesions are seen on the nose, lips and limbs. In our experience, common locations are nose, thigh and arms.

Cutaneous leishmaniasis caused by *L. tropica* produces painless dry ulcers of the skin on the face, feet, legs and arms. Children are usually affected and this disease is prevalent in Afghanistan, Greece, North India, Iran, Iraq, Israel, Kuwait, Lebanon, Morocco, Pakistan, Saudi Arabia, Syria, Tunisia and Turkey.²

Leishmaniasis recidivans (LR) also known as lupoid or tuberculoid leishmaniasis is also caused by *L. tropica* and characterized by slowly progressive skin lesion on the face.

Cutaneous leishmaniasis caused by *L. aethiopica* gives rise to small cutaneous lesion on the face. Ulceration is absent.

Rarely this type of leishmaniasis may distort the nostrils and lips. Diffuse cutaneous leishmaniasis results from specific deficiency of cell-mediated immunity to leishmania antigen. It is caused by *L. aethiopica* and reported from Ethiopia and Kenya. It starts with single lesion and spreads over the face, extremities and whole body.

In Nepal, cutaneous leishmaniasis is caused by *L. tropica*⁹ and *L. major*¹¹ reported from Dharan (eastern part of Nepal). Nepalese cutaneous leishmaniasis presented with infiltrating erythematous plaque with ill-defined border and extensive crusting (fig.1). Ulceration is noted in some cases. These lesions were localized in face & neck region¹², however other sites like wrist, leg and arm are also involved.

New world cutaneous leishmaniasis:

Multiple leishmania species cause wide range of clinical features in South and Central America. A substantial proportion of infections are asymptomatic. The clinical forms are localized, disseminated, diffuse and atypical cutaneous and muco-cutaneous leishmaniasis. Localized cutaneous leishmaniasis is caused by multiple species of both the *Leishmania* and *Viannia* subgenera. Cutaneous lesions are characterized by macule at the site of inoculation, followed by papule that ulcerates. Lymphadenitis may be seen especially when it is caused by *Vianna* subgenus.

Post Kala-azar dermal leishmaniasis (PKDL):

It is caused by *L. donovani* and common in East Africa and on the Indian subcontinent, where upto 50% and 10% of patients with Kala-azar develop PKDL respectively. The lesion develops about 1 to 2 years after recovery from visceral leishmaniasis. Though visceral leishmaniasis is endemic in Nepal, the systematic epidemiological data on PKDL are still lacking.

The PKDL lesions are of 3 types:

- a. Macular & hypopigmented lesion
- b. Erythematous patch
- c. Nodules

These lesions do not ulcerate. Based on study done by Garg VK et al,⁸ Nepalese PKDL is more common in males (59%) than females (41%) and these patients presented with hypopigmented macules, papules, plaques or nodules. These lesions were of variable sizes and distributed symmetrically over face, trunk and extremities. Oral mucosa & nasal mucosa involvements were also noted.

Muco-cutaneous leishmaniasis:

Muco-cutaneous leishmaniasis is caused by *L. braziliensis* and *L. panamensis*. Most cases are reported from Bolivia,

Table 1: Leishmania found in humans¹

Subgenus	L.(Leishmania)	L.(Leishmania)	L.(Viannia)	L.(Viannia)
Old World	L. donovani L. infantum	L. major L. tropica L. killicki L. aethiopica L. infantum		
New World	L. infantum	L. infantum L. mexicana L. pifanoi L. venezuelensis L. garnhami L. amazonensis	L. braziliensis L. guyanensis L. panamensis L. shawi L. naiffi L. lainsoni L. lindenbergi L. peruviana L. colombiense	L. braziliensis L. panamensis
Principal tropism	Viscerotropic	Dermotropic	Dermotropic	Mucotropic

Brazil and Peru. There are two phases, a primary cutaneous lesion, sometimes followed by a secondary mucosal involvement. Nasal mucous membranes, pharynx, larynx and upper lip are involved. We have no experience about this type of leishmaniasis and there are no reports published in the literature from Nepal.

Leishmania and HIV infection

HIV and leishmania reinforce each other. Visceral leishmaniasis is more likely to develop in HIV-positive patients. In severely immunocompromised patients, gastrointestinal tract, peritoneum, pleura & lung may be infected. These patients show multiple, polymorphic & relapsing lesions.

Differential diagnosis of cutaneous leishmaniasis

Skin lesions of cutaneous leishmaniasis may clinically mimic variety of skin diseases, inflammatory like impetigo, eczema, or granulomatous like sarcoidosis, lupus vulgaris, to skin tumor like basal cell carcinoma & squamous cell carcinoma.

Uzun et al¹³ reported a patient with an uncommon cutaneous leishmaniasis lesion that clinically resembled allergic

contact dermatitis. Unusual clinical forms of cutaneous leishmaniasis have been reported including the palmoplantar form, chancriform lesion at the glans penis and penile shaft, zosteriform lesions at the trunk, erysipeloid form at the upper lip and adjacent cheek, annular form at the penile shaft and acute paronychia forms at the nail folds and fingers. Akman et al¹⁴ have observed cutaneous leishmaniasis cases that mimicked erysipelas, rosacea, hydroa vacciniforme, eczema, leg ulcer, sarcoidosis, discoid lupus erythematosus, leprosy, drug eruption, lupus vulgaris, basal cell carcinoma and squamous cell carcinoma. Akcali C et al¹⁵ and Oetken T et al¹⁶ also reported cases of cutaneous leishmaniasis that mimicked squamous cell carcinoma clinically. Table 2 shows the list of differential diagnoses of cutaneous leishmaniasis based on clinical ground.

It has been suggested that cutaneous leishmaniasis may be a “great imitator” in the regions where cutaneous leishmaniasis is endemic.

Laboratory diagnosis

There are various procedures and laboratory techniques used to diagnose leishmaniasis.

Slit skin smear test: The affected area of the skin is cleaned

Table 2: Clinical differential diagnoses of Cutaneous Leishmaniasis¹⁵

Erysipelas	Wegener's granulomatosis	Sarcoidosis	Keloid
Kerion	Tuberculosis cutis	Rosacea	Jessner's lymphocytic infiltrate
Impetigo	Syphilitic gummata	Swimming pool granuloma	Lupus vulgaris
Furuncle	Yaws	Foreign body granuloma	Basal cell carcinoma
Ecthyma	Pyogenic granuloma	Granuloma faciale	Keratoacanthoma
Wart	Blastomycosis	Eczema	Squamous cell carcinoma
Insect bite	Histoplasmosis	Hydroa vacciniforme	Lymphocytoma cutis
Orf	Paracoccidiomycosis	Leg ulcer	Leukaemia
Psoriasis	Sporotrichosis	Discoid lupus erythematosus	Lymphoma
Molluscum contagiosum	Chromoblastomycosis	Drug eruption	Cutaneous metastases



Figure 1: Clinical picture of cutaneous leishmaniasis. Erythematous plaque with crusting over nose.

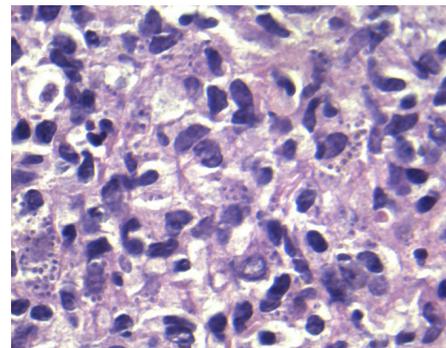


Figure 2: Skin biopsy, showing numerous intracellular amastigotes of *Leishmania* species. (HE stain, X1000).

and squeezed firmly between the index finger & thumb to give 3-4 mm incision of 3 mm depth. Then slit smear is made for Giemsa staining and demonstration of leishmania species.

Touch imprint test: This technique is suitable for ulcerative lesion and imprints are prepared directly from ulcer after cleaning it. Then Giemsa staining is performed to examine leishmania.

Skin punch biopsy: This is most widely used technique to diagnose cutaneous leishmaniasis in Nepal.

H&E section reveals granulomatous infiltrate in the dermis. In some cases, the entire dermis is diffusely infiltrated by lymphocytes & histiocytes with ill-formed granulomas, while discrete granulomas may be encountered in other cases. In our experience, amastigotes of leishmania are found in the upper dermis within the cytoplasm of macrophages (fig.2). The overlying epidermis is usually hyperplastic. Differential diagnoses include other granulomatous disease of the skin like lupus vulgaris, sarcoidosis, fungal infection, leprosy etc. However presence of amastigotes rules out most of these diseases. The spores of *Histoplasma capsulatum* may mimic amastigotes of leishmania. PAS stain is used to differentiate them as spores of *Histoplasma* are PAS positive and amastigotes of leishmania are PAS negative. Immunohistochemistry can be used for confirmation of the diagnosis.

Fine needle aspiration cytology (FNAC): We have no experience about FNAC diagnosis of leishmaniasis. However, nodular and indurated lesions are subjected to fine needle aspiration and cytological examination may reveal amastigotes of leishmania. There are several case reports emphasizing the role of FNAC in diagnosis of cutaneous leishmaniasis.¹⁷⁻¹⁹ Cytology smears reveal granuloma with intracellular as well as extracellular amastigotes of leishmania. The following system of grading of parasites used for splenic punctures²⁰ can be used for cytology smears if required. Authors have used this grading system to assess parasitic load in punch biopsy sections.

The average amastigote density is graded as follows.

6+: >100 parasites per field (viewed with a 10x eyepieces and 100x oil-immersion lens)

5+: 10-100 parasites per field

4+: 1-10 parasites per field

3+: 1-10 parasites per 10 fields

2+: 1-10 parasites per 100 fields

1+: 1-10 parasites per 1000 fields

0: 0 parasites per 1000 fields

Culture: Skin biopsy specimen can be subjected for culture in following media:²¹

a. Modified Nicole-Novy-McNeal (NNN) medium

b. Modified NNN medium plus RPMI 1640 medium and 10% heat inactivated fetal bovine serum (HIFBS)

c. Modified NNN medium plus medium 199 and 10% HIFBS

d. RPMI 1640 medium plus 30% HIFBS

e. Schneider's *Drosophila* medium plus various concentration of HIFBS.

PCR for characterization of causative organisms: DNA extracted from cultured organisms can be used for PCR to identify the species of leishmania.

TREATMENT

Following antileishmanial drugs are used for the treatment of cutaneous leishmaniasis.

Pentavalent antimonials:

Intralesional infiltration of 1-5 ml (100 mg/ml) sodium stibogluconate (SSG) can be given to patients with cutaneous leishmaniasis on alternate days for three days once a month and this results in complete healing by the end of second month in most cases.²¹ A larger dose and > 3 schedules were needed for multiple and larger lesions. Sharma et al used intramuscular SSG (800 mg/day) in addition to intralesional SSG in multiple lesions.²¹ The alternative drug is meglumine antimoniate, which is considered to be first line choice of drugs in Ecuador.³ In Nepal, PKDL patients are treated with an intramuscular injection of sodium antimony gluconate (20 mg/Kg/day) for a period ranging from 30 to 72 days.⁸ There are issues of drug resistance and in Nepal, SSG resistant cases of visceral leishmaniasis were documented.^{22,23} So far, this issue was not reported from Nepal in cutaneous leishmaniasis.

Amphotericin B:

Inj. Amphotericin B in a dose of 25 mg in 5% dextrose can be administered intravenously 6 hourly with a total dose of 1980 mg. One of our patients received this therapy with dramatic improvement and no recurrence is noted till now.

Miltefosine:

Miltefosine is prescribed in a dose of 50 mg thrice a day for 28 days. One of our patients received Miltefosine with dramatic improvement and no recurrence till now.

Control of leishmaniasis

There are no organized efforts to control cutaneous leishmaniasis in Nepal. The disease is prevalent in Terai region of Nepal and there are cases from hilly region of Nepal as well. The patients from hilly region have travel history to India or Terai region of Nepal. The true burden of this disease in Nepal is not known. In neighboring countries like India, Bangladesh & Srilanka it represents a major health problem as in Nepal with case burden as high as 21 cases per 10,000 populations.²⁴⁻²⁶ There were attempts to control leishmaniasis in Indian subcontinent²⁴ and collective efforts in future can bring positive results.

Prophylactic vaccines

There is no vaccine for general use against leishmaniasis. However, intradermal inoculation of live virulent *L. major* promastigotes from a fresh culture has been used intermittently for many years to protect against *L. major* infection.¹

CONCLUSION

Case reports and case series published in the literature indicate that the cutaneous leishmaniasis is a disease

prevalent in Nepal, though its true burden is not known. Dermatologists should be aware of this disease and it should be kept as one of the differential diagnoses while suspecting granulomatous or malignant disease of the skin. Pathologists should search for amastigotes of leishmania when vague or discrete granulomas are present in skin biopsies.

Conflict of Interest: None

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