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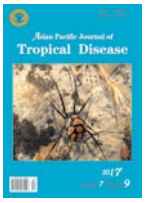

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Clinicopathological presentation of cutaneous leishmaniasis and its diagnostic algorithm

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ABSTRACT

Cutaneous leishmaniasis is transmitted by bite of *Phlebotomus* sand fly. Incidence of disease has been rising in the areas of world where there is conflict which favors disease spread. Disease is endemic in some areas of world due to conducive local environmental and geographic factors for *Phlebotomus* sand fly. In view of the constant prevalence of disease and its difficulty in diagnosis due to its complex clinicopathological presentation, an attempt is made to present various clinicopathological conditions which can mimic cutaneous leishmaniasis and to differentiate these by use of mentioned appropriate clinicopathological techniques. The purpose of this study is to guide the clinician and pathologist to make the accurate and timely diagnosis of cutaneous leishmaniasis which helps in prompt treatment and overall prevention.

1. Introduction

Cutaneous leishmaniasis is a vector-induced protozoal infection of the skin. The infected sand fly carries promastigotes to humans. The promastigotes are ingested by tissue macrophages where they transform and proliferate as amastigotes. The disease is variably distributed throughout the world and is termed as Old World and New World cutaneous leishmaniasis (Figure 1)[1-4].

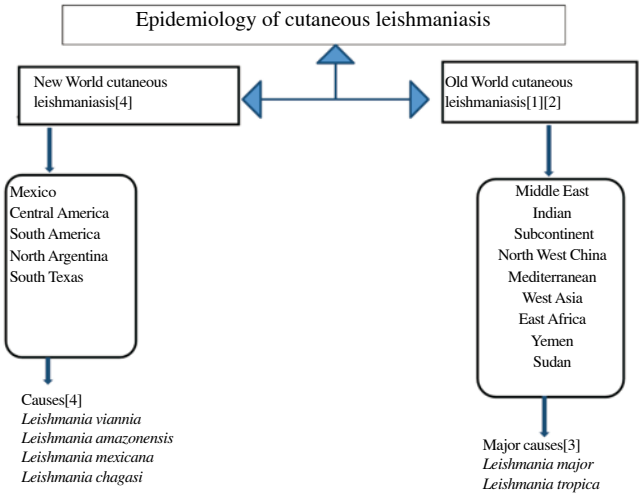

Figure 1. Epidemiology of cutaneous leishmaniasis.

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The incidence of visceral disease is increasing, often in association with HIV-1 infection in Southern Europe, where leishmaniasis is endemic. Many such patients develop unusual cutaneous manifestations. In North America and Northern Europe, the disease is seen in returning travellers, such as those conducting rural field studies, tourists and the military[5].

Leishmaniasis is endemic in 88 countries throughout Africa, Asia, Europe, and North and South America[6]. The global disease burden is 12 million, with 1.5–2 million new cases each year[7].

2. Pathogenesis of cutaneous leishmaniasis

This encompasses a range of immunological reaction varying from complete lack of immune response in diffuse cutaneous leishmaniasis to exaggerated immune response in the lupoid type[8].

3. Pathology of cutaneous leishmaniasis

The histological picture of cutaneous leishmaniasis in some endemic areas can be classified into variable presentation as in leprosy[8]. Several histological classifications have been described consisting of 4–6 categories which differs from one endemic area to another[8,9]. Ridley classification is widely followed which was later modified 10 as described in Table 1.

4. Modified Ridley's parasitic index[10]

6: More than 100 000 amastigotes per standardsection;
5: 10 001–100 000 amastigotes per standardsection;
4: 1 001–10 000 amastigotes per standard section;

3: 101–1 000 amastigotes per standard section;
2: 11–100 amastigotes per standard section;
1: 1–10 amastigotes per standard section;
0: Amastigotes not seen.

Table 1
Modified Ridley classification[10].

Group	Pathological features
Group 1	Parasitized macrophages with variable lymphocytes and plasma cells
Group 2	As above and ill formed histiocytic granulomata
Group 3	As above and epithelioid granulomata
Group 4	Epithelioid granulomatous response (with or without Langhans type multinucleated giant cells) with a few lymphocytes and plasma cells but no amastigotes
Group 5	Similar to Group 4, but without plasma cells

5. Morphology of leishmania parasite

The amastigote is about 2–5 μm small, round to oval, bodies which are present in the macrophages of infected subjects. The amastigote which is the infective form is pale, with uniform cytoplasm and has a peripheral pellicle. The nucleus is in central location, anterior to which is the kinetoplast; both of them are easily visible in routine hematoxylin-eosin staining[11].

6. Clinical presentation

Cutaneous leishmaniasis can be simple or diffuse (disseminated). Different species, as well as host factors, can also affect the clinical picture, in which some species cause “wet” ulcers and others “dry” ulcers.

Inoculation occurs after a sandfly bites at an exposed part of the body (usually the legs, arms, neck, or face). Incubation occurs over weeks to months, followed by the appearance of an erythematous papule, which can change into a plaque or ulcer, which are usually painless[12] (Table 2).

7. Discussion

Cutaneous leishmaniasis exhibits wide spectrum of expression, both clinically and histopathologically. Unusual presentations have been reported around the world. Luna *et al.* has reported in 2014 from Spain a case of cutaneous leishmaniasis which presented as pyogenic granuloma[13]. Study showed that biopsy of leishmanial skin lesion can reveal non specific finding of panniculitis. It is therefore recommended that the finding of panniculitis is a clue for diagnosis of cutaneous leishmaniasis and should prompt for deeper biopsy so as not to miss the diagnosis[14].

With regards to host immune response and its association with biological behavior of disease, slower healing process is linked to poor immune response or due to infection with more pathogenic leishmania. These findings correlated with occurrence of (18.2%) caseating granulomas[15]. Velez *et al*. has reported a series of 27 cases of disseminated leishmaniasis from Colombia in 2015[16]. They observed that it has distinct clinical presentation of presence of high number of skin lesions (greater than 10 polymorphic lesions) in at least two parts of body surface with or without mucosal involvement. It is characterized by partial inhibition of specific cellular immunity against the parasite along with low production of the Th1 subset of growth factors (IL-5, IFN-γ, TNF-α, IL-10), which favor the spread of the parasite. Histological examination of the lesions can reveal the presence of a granuloma composed of lymphocytic infiltrates with very few or no parasites. The study thus inferred that etiopathogenesis, clinicopathological aspects, treatment and prognosis of disseminated leishmaniasis is different from other forms of leishmaniasis. The study concluded the good treatment response, prognosis for disseminated leishmaniasis and thereby emphasized the significance of prompt diagnosis of disseminated leishmaniasis. These findings contradicted the observations of earlier study from Brazil in 2013[16].

Koçarslan *et al.* published 54 cases of leishmaniasis in 2013 from Turkey which included Syrian refugees as well[17]. The study showed 59.3% and 40.7% affected males and females, with the face (63%) as most common site of involvement and 57.4% showed noduloulcerative lesions. Histopathological findings showed both epidermal and dermal changes. Epidermal changes are hyperkeratosis, follicular plugging whereas dermal changes include, chronic inflammatory infiltrate, leishmanial amastigote forms and non-caseating granulomas[17]. Başsorgun *et al.* in their study of 28 patients from Turkey in 2015 evaluated the epidermal and dermal changes that would predict the histopathological diagnosis of cutaneous leishmaniasis and found that epidermal thinning/thickening, and orthokeratosis were early stage indicators, while exocytosis, hyperparakeratosis, and epidermal thinning were indicative of late stage disease[18]. Highly unlikely forms of presentation usually show a marked acanthosis or even wide areas of necrosis that can mimic other conditions such as squamous cell carcinoma, deep fungal infection or secondary syphilis, granulomatous lesions (sarcoidal and elastolytic) and simulating lupoid rosacea or granuloma annulare[19,20].

Table 2
The clinical presentation and outcome of the different type of disease in New World and Old World.

Disease type	Clinical presentation			Outcome		
Localized, cutaneous disease	New World type	Old World type		New World		Old World
	Solitary nodule	Multiple lesions		Progress to mucocutaneous disease		Heal by scar in few months
Diffuse, cutaneous disease	Primary lesion progress to involve face, ears, buttocks, extremities resemble lepromatous leprosy			Disfigurement, recurrence		
Leishmaniasis recidivans	New ulcers/papules form at site of old scar and proceed to psoriasiform lesion			Resistance to treatment		
Post-kala-azar dermal leishmaniasis	India	Africa	Sudan	India	Africa	Sudan
	Hypopigmented erythematous macules on face trunk, progress to plaques nodules	Erythematous, papular rash on the face, buttocks, and extremities	Measles like facial rash, spread to other areas	Need intensive treatment	Resolve spontaneously	Heal, relapse

Non specific pathologies which can coexist with cutaneous leishmaniasis include inflammatory diseases (panniculitis, subacute spongiotic dermatitis, lichen planus) or infectious/granulomatous conditions (tuberculosis-like lesions, sarcoidosis, pityriasis lichenoides, indeterminate leprosy), and neoplastic lesions (mycosis, anaplastic T-cell lymphoma). The role of PCR technique in these cases is appreciated to rule out the above mentioned findings and to arrive at proper diagnosis[21]. Visceral leishmaniasis is more common in patients coinfected with HIV which can manifest with cutaneous disease as papulonodular lesions. These papulonodular lesions should be differentiated from HIV related conditions like multiple dermatofibromas or Kaposi sarcomas due to the incidental presence of the parasite in lesions such as Kaposi sarcomas, bacillary angiomatosis, herpes zoster and simplex. In this context, cutaneous detection of leishmania is common in HIV-infected individuals with visceral disease[22,23].

Differential diagnosis for leishmaniasis of skin can range from infectious/inflammatory conditions (deep fungal infection, tropical pyoderma, pyogenic granuloma, psoriasis, atypical mycobacteriosis, cutaneous diphtheria, rhinoscleroma) to metastasis of skin and skin ulcers due to trauma and stasis[12].

The diagnosis[24] is made by combination of clinical findings (supported by epidemiological information) and diagnostic laboratory methods. Numerous laboratory methods have been described with a huge variation in diagnostic test accuracy, including visualization of parasite directly (microscopy, histopathology and parasite culture) and or with serological and molecular indirect diagnostic testing. The type and use of the diagnostic test depends on the available facilities and financial resources of the laboratory diagnostic facility and not on test accuracy of laboratory even though the test in question might have higher sensitivity/specificity.

The gold standard of diagnosis for leishmaniasis is the demonstration of parasite due to specific and reliable nature of test. This is typically undertaken by material collected from suspicious lesions and subjected to histopathologic examination of fixed tissue or parasite *in vitro* culture. Microscopical identification of amastigotes in Giemsa-stained lesion smears of biopsies, scrapings, or impression smears facilitates the diagnosis. The highest diagnostic yield is obtained by material collected from the ulcer margin. Studies have shown the superiority of aspiration cytology technique when compared to commonly used scraping smears in the detection of amastigotes and microgranuloma, along with better slide background, and good patient comfort[25]. Literature reveals the rapidity, simplicity and higher sensitivity (85.3%) of press imprint cytology smear technique over histopathology (44%) for the diagnosis of cutaneous leishmaniasis[26].

Highly sensitive, easier to use, culture methods have been possible by newly developed mini- and micro-culture technologies even when the parasite burden is low, along with the advantage of being less costly because of the smaller volume of culture medium required compared to routine tube culture method of Novy-MacNeal-Nicolle medium. A drawback of micro-culture is that this technique does not allow for further species determination[27].

Tests (indirect fluorescent antibody, ELISA, Western blot, lateral flow assay, and direct agglutination test) to detect antibody against leishmania is not successful because of inadequate humoral immunity induced by the parasite and the resultant low sensitivity indicating their incomplete role[28,29].

The disease is characterized by good cell mediated immunity which can be measured by leishmania intradermal skin test (LST) or Montenegro skin test. This test is used in diagnosis of cutaneous leishmaniasis (*e.g.* in epidemiologic surveys and vaccine studies) because of its simple use and because of its high sensitivity (86.4% up to 100%). Delayed-type hypersensitivity skin reactions to LST $\geqslant$ 5 mm are considered positive and < 5 mm are considered negative. Correlation between the test result and outcome of disease is proven by the fact that patients with negative LST and diagnostic confirmation by other tests are more prone to relapse or treatment failure[30,31].

Identification of exact species/strain is possible only by special studies such as PCR along with restriction fragment length polymorphism/sequencing which will facilitate patient management. PCR technique is rapid, sensitive and specific but not easily available[32,33].

70%–75% of estimated incidence of global cutaneous leishmaniasis are seen in Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica and Peru[34] (Table 3).

Table 3

Estimated global cutaneous leishmaniasis.

Country	Annual incidence	Year of incidence
Afghanistan	32 145	2010
Algeria	2 254	2008
Brazil	21 147	2010
Iran	21 211	2010
Syria	42 165	2010
Colombia	14 654	2010
Ethiopia	50 000	2011
North Sudan	6 062	2011
Peru	8 232	2010
Costa Rica	1 143	2010

8. Conclusion

In view of diverse clinical and pathological presentation of cutaneous leishmaniasis which might contribute to difficulty in diagnosis, the physician and histopathologist should be aware of the various clinicopathological manifestations of this disease and also should consider all the differential diagnostic conditions. This will enable them to make an accurate diagnosis by use of appropriate laboratory methods and thereby help the clinician to treat and control the condition effectively.

Conflict of interest statement

We declare that we have no conflict of interest.

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