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Clinical manifestations of leishmaniasis: A review

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ABSTRACT: Leishmaniasis is a family of infectious diseases caused by parasites of the genus *Leishmania* and transmitted through the bite of sandflies. The geographical distribution of Leishmaniasis is tied in to the abundance of sandflies, their life cycle, and the presence of the parasite reservoirs. The World Health Organization classifies Leishmaniasis as a neglected disease affecting the poorest communities around the world. This parasite is involved in pathologies that range from the cutaneous to the visceral forms, depending on the species of *Leishmania* and the host immune response. Leishmaniasis has traditionally been classified in three different clinical forms according of parasite tropism i.e. cutaneous, mucocutaneous and visceral leishmaniasis. Other clinical manifestation can also occur, including diffuse cutaneous and post-kala azar dermal leishmaniasis. Thus, present review emphasizes critically on the most recent data with regard to various clinical manifestations of leishmaniasis, prevalence of the disease, causative agents, pathogenesis and immune response.

KEYWORDS: Visceral leishmaniasis, cutaneous leishmaniasis, post kala azar dermal leishmanasis, *Leishmania.*

I.INTRODUCTION

The clinical manifestations of leishmaniasis depend on complex interactions between the virulence characteristics of the infecting *Leishmania* species and the immune response of its human host. The result is a spectrum of diseases ranging from localized skin lesions to diffuse involvement of the reticuloendothelial system [1] and thus, leishmaniasis is classified into three major types, cutaneous (CL), muco-cutaneous (MCL) and visceral leishmaniasis (VL) [2].

Cutaneous Leishmaniasis (CL)

Cutaneous leishmaniasis is endemic in more than 80 countries worldwide, and 90% of cases occur in Iran, Afghanistan, Algeria, Brazil, Pakistan, Peru, Saudi Arabia, and Syria [3,4]. *Leishmania* spp. can cause cutaneous leishmaniasis in human beings, although most infections probably remain symptomless [5]. Over 17 species of *Leishmania* cause CL [6]. Acute CL, caused by *L. major* ([5], *L. tropica, L. aethiopica* in the Old World and *L. braziliensis, L. panamensis* and *L. mexicana* in the New World are the most common cause of infection [7]. Although CL is normally localised to site of infection within dermal macrophages, metastasis to lymphatic, mucosal and bone marrow sites can occur [8]. The first sign of an infection is typically a small erythema that develops after a variable prepatent period at the site where an infected sandfly has bitten the host. The erythema develops into a papule, then a nodule that progressively ulcerates over a period of 2 weeks to 6 months to become a lesion that is characteristic of localised cutaneous leishmaniasis (LCL). Epidermal changes in CL reflect the immune response to infection, resulting in hyperplasia and epidermal thickening. Within the dermis the collagen matrix is disrupted and fibroblasts are eventually recruited during the healing process. Epidermal disruption results in discharge and eventually dries to form an encrusted border. It is this latter region where parasites are present in dermal macrophages. Resolution usually occurs following generation of the appropriate Th1 response and resulting cytokines (IFNγ, TNFα, IL-2) that confer resistance to infection with leukocyte migration resulting in necrosis and formation of healing granuloma [9]. LCL lesions vary in severity e.g., lesion size, clinical appearance [10] and time to cure. Lymphatic spread and lymph-gland involvement, which may precede lesion development, are common [11].

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Mucocutaneous Leishmaniasis (MCL)

In contrast to CL, mucocutaneous leishmaniasis is potentially life threatening and requires treatment. MCL is a known risk from *Leishmania* species of the *Viannia* subgenus, typically found in the Americas (*L. (V) braziliensis, L.(V) amazonensis, L. (V) panamensis,* and *L. (V) guyanensis)*. Clinical progression to mucosal disease is dependent on a combination of host cell-mediated immunity and parasite virulence. Although, it is usually caused by New World *Leishmania* species such as *L. panamensis* and *L. guyanensis* [12], immune compromised patients also can show MCL symptoms by other *Leishmania* species including *L. major*, *L. infantum* and *L. donovani*. MCL begins as lesions that ulcerate and become large and long-lasting that involve the human mucosal system [12] [13]. The parasite attacks the nasal (nasopharynx) or the buccal cavity and slowly degenerate the cartilagenous and soft tissues to cause disfiguration and destruction of the nasal septum, lips and larynx [12,14,15,]. Lymphadenopathy may be present and is a common finding in *L. braziliensis*-associated leishmaniasis [16].

Visceral Leishmaniasis (VL)

The protozoan parasite causing visceral leishmaniasis, a potentially fatal parasitic disease of the viscera-particularly the spleen, liver and bone marrow - due to infection by *Leishmania donovani* [13], was discovered in parallel by Sir William Leishman (Scottish army doctor) in 1900 [17] and by Charles Donovan (a professor of physiology at Madras University) in 1903 [17, 18, 19].

VL is caused by various leishmanial species in different geographical locations. 90% of global VL cases occur in six countries India, Bangladesh, Sudan, Ethiopia and Brazil [20]. It is caused by *Leishmania donovani* in the India [21], Asia and Africa (in all age groups), and by *Leishmania infantum* or *Leishmania chagasi* in the Mediterranean region, southwest and central Asia, and South America (predominantly in children). The foci of VL in India are Bihar, West Bengal, Uttar Pradesh and Jharkhand. Sporadic cases have also been reported from Gujarat (West India), Tamil Nadu and Kerala (South India) and sub-Himalayan parts of North India including Uttar Pradesh, Himachal Pradesh and Jammu and Kashmir [22]. VL is usually associated with an incubation period of 2–6 months and is characterized by fever (accompanied by chills), weakness, night sweats, anorexia, weight loss, and enlarged lymph nodes, spleen and liver. Common laboratory findings include pancytopenia and hypergammaglobulinemia [23]. Although these features are common in VL, certain variations in clinical symptoms are observed depending on the geographical location.

Post-Kala-azar Dermal Leishmaniasis (PKDL)

PKDL is a complication of visceral leishmaniasis (VL); it is characterised by macular, maculopapular, and nodular rash in a patient who has recovered from VL and who is otherwise well. The rash usually starts around the mouth from where it spreads to other parts of the body depending on severity. Most cases occur on the Indian subcontinent (India, Nepal, Bangladesh) and East Africa (Sudan, Ethiopia, Kenya), where *L. donovani* is the causative parasite. Depending on the geographical region, in *L. donovani* endemic areas 5 to 60% of patients develop a dermatosis (PKDL) during or after treatment. The skin condition has a tendency to become chronic and is characterised by macular, papular or nodular lesions in which *Leishmania* parasites may be seen. PKDL is therefore considered a reservoir for *Leishmania* parasites. The interval at which PKDL follows VL is 0–6 months in Sudan and 2–3 years in India. PKDL probably has an important role in interepidemic periods of VL, acting as a reservoir for parasites. The pathogenesis of PKDL is largely immunologically mediated and high concentrations of interleukin 10 in the peripheral blood of VL patients predict the development of PKDL. During VL, interferon γ is not produced by peripheral blood mononuclear cells (PBMC). However, after the treatment of VL, PBMC start producing interferon γ resulting in the appearance of PKDL lesions. Moreover, interferon γ producing cells cause skin inflammation as a reaction to persisting parasites in the skin [24]. This review highlights various clinical forms of leishmaniasis and their prevalence worldwide. Moreover, causative parasitic species involved and the pathogenesis caused by the same including type of the immune response generated have also been discussed.

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