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TUBERCULOID CUTANEOUS LEISHMANIASIS: PATHOGENESIS, CLINICAL FEATURES, DIAGNOSIS AND MODERN TREATMENT APPROACHES

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ABSTRACT

Tuberculoid cutaneous leishmaniasis is a chronic granulomatous form of cutaneous leishmaniasis characterized by persistent skin lesions, low parasite burden, and strong cell-mediated immune response. The disease usually develops after healing of primary cutaneous leishmaniasis and clinically resembles cutaneous tuberculosis, sarcoidosis, lupus vulgaris, and other granulomatous dermatoses. Tuberculoid leishmaniasis remains an important public health problem in endemic regions of Asia, the Middle East, Africa, and Latin America. Delayed diagnosis and inappropriate treatment may lead to chronic inflammation, scarring, cosmetic deformities, and psychological consequences. This article reviews the epidemiology, etiology, immunopathogenesis, clinical manifestations, diagnostic approaches, differential diagnosis, complications, and modern therapeutic strategies of tuberculoid cutaneous leishmaniasis. Special attention is given to advances in molecular diagnostics, histopathological findings, and current pharmacological management.

Keywords: tuberculoid leishmaniasis, cutaneous leishmaniasis, Leishmania tropica, granulomatous inflammation, dermatology, tropical diseases, parasitic skin infections.

INTRODUCTION

Leishmaniasis is a vector-borne parasitic disease caused by protozoa of the genus *Leishmania*. The disease is transmitted by infected female phlebotomine sandflies and is considered one of the major neglected tropical diseases worldwide. According to the World Health Organization, more than one billion people live in endemic regions and are at risk of infection. Cutaneous leishmaniasis is the most common clinical form of the disease and accounts for more than one million new cases annually worldwide.

Cutaneous leishmaniasis presents with a broad clinical spectrum depending on the infecting species, host immune response, geographical location, and genetic susceptibility. Clinical manifestations range from self-healing ulcers to chronic diffuse or mucocutaneous forms. Tuberculoid cutaneous leishmaniasis represents one of the chronic atypical variants characterized by granulomatous inflammation and scarcity of detectable parasites.

Tuberculoid leishmaniasis is particularly important because of its diagnostic complexity. The lesions often mimic tuberculosis, lupus vulgaris, sarcoidosis, discoid lupus erythematosus, fungal infections, and other chronic dermatoses. Consequently, patients frequently receive delayed or incorrect treatment.

The disease commonly develops months or years after primary cutaneous lesions have healed. It usually appears around old scars and is associated with persistent immune activation against residual parasitic antigens. Although the parasite load is extremely low, the inflammatory response remains active for prolonged periods, resulting in chronic skin destruction and scar formation.

The clinical significance of tuberculoid leishmaniasis extends beyond dermatology. Chronic facial lesions may cause cosmetic disfigurement, social stigmatization, depression, anxiety, and reduced quality of life. Therefore, early diagnosis and adequate treatment are essential to prevent long-term complications.

Historical background

Leishmaniasis has been recognized for centuries in endemic tropical and subtropical regions. Ancient descriptions resembling cutaneous leishmaniasis were documented in Middle Eastern and Central Asian medical literature. The causative organism was first identified in the early twentieth century by William Leishman and Charles Donovan.

The tuberculoid form of cutaneous leishmaniasis was later described as a chronic granulomatous reaction occurring in patients with strong cellular immunity. Researchers observed that these patients demonstrated fewer parasites in tissue sections but more pronounced inflammatory infiltrates.

Historically, tuberculoid leishmaniasis was often confused with cutaneous tuberculosis because of similar clinical and histopathological findings. Advances in histopathology, immunology, and molecular biology have improved understanding of the disease and enabled more accurate diagnosis.

Epidemiology

Leishmaniasis is endemic in more than 90 countries across Asia, Africa, the Middle East, southern Europe, and Latin America. The Eastern Mediterranean region accounts for the majority of cutaneous leishmaniasis cases worldwide.

Tuberculoid cutaneous leishmaniasis is most frequently reported in:

Afghanistan ,Iran ,Syria ,Pakistan ,India ,Uzbekistan ,Turkmenistan

Saudi Arabia ,Brazil

The disease is commonly associated with *Leishmania tropica*, although *Leishmania major* and other species may occasionally produce similar manifestations.

Several epidemiological factors contribute to disease transmission:

poverty; malnutrition; migration; war and displacement; climate change;

urbanization; poor sanitation; increased vector exposure.

Sandflies are most active from dusk to dawn. Transmission occurs through bites of infected female sandflies. Reservoir hosts vary depending on species and geographical region. Humans may serve as reservoirs in anthroponotic transmission cycles, particularly in *L. tropica* endemic regions.

Etiology

Tuberculoid cutaneous leishmaniasis is caused by intracellular protozoan parasites belonging to the genus *Leishmania*. The main etiological agents include:

Leishmania tropica ,*Leishmania major* ,rarely *Leishmania infantum*

The parasite exists in two major forms:

1. Promastigote form in sandflies.
2. Amastigote form within human macrophages.

Following inoculation into human skin during a sandfly bite, promastigotes are phagocytosed by macrophages and transform into intracellular amastigotes. These multiply within phagolysosomes and spread locally.

The clinical outcome depends largely on the host immune response rather than parasite burden alone.

Immunopathogenesis

The pathogenesis of tuberculoid leishmaniasis is strongly related to cell-mediated immunity. Patients typically exhibit vigorous T-helper 1 (Th1) immune responses characterized by increased production of:

interferon-gamma,interleukin-2,tumor necrosis factor-alpha.

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These cytokines activate macrophages and promote granuloma formation. Because of the strong immune response, parasite numbers become extremely low and difficult to identify microscopically.

Granulomatous inflammation develops around residual parasitic antigens and may persist long after the primary lesion has healed. Histologically, lesions contain:

epithelioid histiocytes, multinucleated giant cells, lymphocytes,

fibroblasts,macrophages.

The immunological pattern resembles tuberculosis, explaining the term “tuberculoid” leishmaniasis.

Host genetic factors also influence susceptibility and disease severity. Malnutrition, immunosuppression, HIV infection, and chronic systemic diseases may alter clinical presentation and treatment outcomes.

Life cycle of leishmania

The life cycle of *Leishmania* involves both sandflies and mammalian hosts.

1. Infected female sandflies inject promastigotes during blood feeding.
2. Promastigotes enter macrophages.
3. Transformation into amastigotes occurs inside phagolysosomes.
4. Amastigotes multiply intracellularly.
5. Sandflies ingest infected macrophages during subsequent blood meals.
6. Parasites transform again into promastigotes within the sandfly gut.

This cycle maintains endemic transmission in human and animal populations.

Clinical manifestations

Tuberculoid cutaneous leishmaniasis usually develops gradually and follows chronic progression. Lesions commonly appear near scars of previously healed cutaneous leishmaniasis.

Common sites

Face,cheeks,nose,forehead,ears,upper extremities.

Primary clinical features

erythematous papules, infiltrated plaques, reddish-brown nodules,scaling,crusting,

chronic ulceration,

scar formation.

Lesions are often painless and slowly progressive. The surface may become rough and verrucous. Borders are usually elevated and irregular.

In chronic disease, lesions may persist for years. Some patients develop multiple satellite papules around old scars.

Diascopy occasionally reveals “apple jelly” nodules similar to lupus vulgaris.

Histopathology

Histopathological examination is essential in diagnosis.

Typical findings include:

tuberculoid granulomas,epithelioid cell infiltration,Langhans giant cells,lymphocytic infiltrates,dermal fibrosis,epidermal hyperplasia.

Necrosis is generally absent or minimal.

Parasites are scarce and frequently undetectable using routine microscopy. Therefore, special stains, immunohistochemistry, and molecular methods are often required.

Diagnostic methods

Diagnosis of tuberculoid cutaneous leishmaniasis may be challenging because parasite load is very low.

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Clinical evaluation

Diagnosis begins with:detailed travel history,residence in endemic areas,

chronic skin lesions.

history of previous cutaneous leishmaniasis.

Chronic non-healing lesions in endemic areas should raise suspicion for leishmaniasis.

Microscopy

Giemsa-stained smears may reveal amastigotes. However, sensitivity is low in tuberculoid forms because of sparse parasites.

Histopathology

Skin biopsy demonstrates granulomatous inflammation compatible with tuberculoid reaction.

Culture

Parasites may be cultured using specialized media, although sensitivity is variable.

Polymerase Chain Reaction (PCR)

PCR is considered one of the most sensitive diagnostic methods for chronic lesions and low parasite burdens. Molecular techniques enable species identification and guide therapy.

Montenegro Skin Test

The leishmanin skin test may show positive delayed hypersensitivity reactions reflecting cellular immunity.

Dermoscopy

Dermoscopy may reveal:yellow tears,white starburst patterns,

vascular structures,hyperkeratosis.

Differential diagnosis

Tuberculoid leishmaniasis must be differentiated from several granulomatous and infectious diseases:

cutaneous tuberculosis,lupus vulgaris,sarcoidosis,leprosy,discoid lupus erythematosus,deep fungal infections,syphilis,chronic eczema,psoriasis

cutaneous lymphoma.

Differential diagnosis is especially important in endemic regions where tuberculosis and fungal infections are common.

Complications

Untreated or chronic disease may lead to:

permanent scarring,facial deformity,secondary bacterial infection,pigmentary abnormalities.

psychological distress

anxiety and depression,social isolation.

Facial involvement may significantly affect self-esteem and social interactions.

Treatment

Treatment depends on:

lesion size,lesion location,species identification,immune status, duration of disease.

risk of mucosal spread.

Modern treatment approaches include systemic and local therapies.

Pentavalent Antimonials

Traditional first-line drugs include:

sodium stibogluconate;

meglumine antimoniate.

These agents inhibit parasite metabolism and remain widely used in endemic regions.

However, adverse effects may include:

Hepatotoxicity,cardiotoxicity,pancreatitis,arthralgia.

nephrotoxicity.

Amphotericin B

Liposomal amphotericin B is highly effective and often used in resistant or severe cases.

Advantages:

high efficacy;

lower toxicity in liposomal formulations.

Disadvantages:

expensive;

requires intravenous administration.

Miltefosine

Miltefosine is the first effective oral antileishmanial drug.

Benefits:

oral administration;

good efficacy.

Limitations:

gastrointestinal side effects;

teratogenicity;

emerging resistance.

Azole Antifungals

Fluconazole and ketoconazole may show partial efficacy in selected cases.

Local Therapies

Local treatments include:

Cryotherapy,thermotherapy,intralesional antimonials,topical paromomycin,laser therapy.

These approaches are useful for limited lesions.

Immunotherapy

Research continues into:

interferon-gamma therapy,therapeutic vaccines,immunomodulators.

Combination therapy may improve outcomes in chronic disease.

Drug resistance

Drug resistance is an emerging global problem in leishmaniasis management. Resistance to antimonials has been increasingly reported in South Asia and other endemic areas.

Mechanisms include:altered parasite metabolism,drug efflux pumps,genetic mutations,host immune factors.

Development of novel therapies remains a priority in tropical medicine.

Prevention

Preventive strategies focus on reducing sandfly exposure and controlling reservoirs.

Personal protective measures

insect repellents,long-sleeved clothing,bed nets,avoiding outdoor exposure at night.

Environmental control

vector control programs,waste management,housing improvements,insecticide spraying.

Currently, no universally effective vaccine exists.

Public health importance

Leishmaniasis represents a major neglected tropical disease with substantial social and economic impact. Chronic skin lesions contribute to:

Disability,stigmatization,reduced productivity,psychological morbidity.

Conflict zones, refugee camps, and impoverished communities are particularly vulnerable.

International health organizations continue to emphasize:

early detection,vector control,access to medications,improved surveillance systems.

Recent advances

Recent developments in leishmaniasis research include:

molecular diagnostics,genomic studies,targeted immunotherapy,nanoparticle drug delivery systems,vaccine research.

artificial intelligence-assisted diagnostics.

PCR-based diagnostics have significantly improved sensitivity in chronic granulomatous lesions.

Novel biomarkers are being investigated for monitoring treatment response and predicting relapse.

Prognosis

The prognosis of tuberculoid cutaneous leishmaniasis is generally favorable with timely treatment. However, chronic lesions may persist for years and leave permanent scars.

Early intervention improves cosmetic outcomes and reduces complications.

Relapses may occur in:

immunocompromised patients;

inadequately treated cases;

patients with persistent immune dysregulation.

CONCLUSION

Tuberculoid cutaneous leishmaniasis is a chronic granulomatous variant of cutaneous leishmaniasis characterized by low parasite burden and strong cell-mediated immune response. The disease remains a significant diagnostic and therapeutic challenge because of its resemblance to tuberculosis and other granulomatous dermatoses.

Accurate diagnosis requires integration of clinical, histopathological, and molecular findings. PCR and advanced laboratory methods have improved detection in chronic lesions where parasites are scarce.

Modern treatment strategies include pentavalent antimonials, amphotericin B, miltefosine, local therapies, and emerging immunomodulatory approaches. Early diagnosis and appropriate therapy are essential to prevent chronic scarring and psychosocial complications.

Future research should focus on vaccine development, novel therapeutic agents, and improved public health interventions to reduce the global burden of leishmaniasis.

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