Crosstalk and Continuum: Understanding the VL-PKDL Disease Axis in Leishmaniasis

Medhavi Sudarshan[1*] and Sumit Sharan[2]

[1]Assistant Professor, JNL College Khagaul, Patliputra University, Patna

[2]Department of Community Medicine, Katihar Medical College, Katihar

* Corresponding Author, Assistant Professor, JNL College Khagaul, Patliputra University, Patna

Abstract

Sequential signs of Leishmania donovani infection include visceral leishmaniasis (VL) and post-kala-azar dermal leishmaniasis (PKDL), which demonstrate the parasite's ability to persist, modulate the immune system, and dermal reactivation. The mechanistic and immunological interactions between VL and PKDL are reviewed in this article, with particular attention paid to the implications for public health, host immune reprogramming, and parasite persistence. Controlling transmission and creating focused treatment interventions require an understanding of this continuum.

Introduction

Leishmania, a protozoan parasite that causes Leishmaniasis, belongs to category of neglected tropical disease, is spread to humans through the bites of female phelobotomine sand flies. Leishmaniasis is prevalent in over 90 countries worldwide, with the majority of cases occurring in tropical and subtropical climates. Among its clinical manifestations (cutaneous, mucocutaneous, and visceral), visceral leishmaniasis (VL), often known as kala-azar, is the most serious and possibly deadly if not treated. VL damages internal organs, mainly the spleen, liver, and bone marrow, causing systemic inflammation, immunosuppression, and high morbidity and mortality [1]. *Leishmania donovani*, which grows inside host macrophages, is the main cause of VL in East Africa and the Indian subcontinent. Although national elimination programs have made significant strides in controlling VL in recent years, a new set of difficulties has emerged with the emergence of Post-Kala-azar Dermal Leishmaniasis (PKDL), a cutaneous condition that affects a subset of patients after treatment. Months to years after VL has been clinically cured, PKDL can show up as macular, papular, or nodular skin lesions, especially on the face and upper body [2]. Importantly, PKDL patients are silent carriers of the disease because they have live parasites in their dermal tissues even when they don't have systemic symptoms. This makes it more difficult to eradicate VL in endemic areas, particularly since PKDL cases frequently go unreported or untreated because of stigma, ignorance, and inadequate surveillance systems [3]. In terms of immunology, VL and PKDL are linked by a similar but changing immune environment. While PKDL frequently displays a mixed cytokine profile, indicating an attempt at immune recovery, VL is distinguished by profound immunosuppression and the dominance of regulatory cytokines such as IL-10 [4]. Rather than representing a binary of disease states, these variations represent a continuum. In order to develop integrated control strategies, it is essential to comprehend the immunopathological transition from VL to PKDL as well as the roles played by genetic and environmental factors.

Pathogenesis of Visceral Leishmaniasis (VL)

When infected sandflies transfer *Leishmania donovani* parasites into the dermis, VL starts. Macrophages phagocytose the parasites, which then develop into intracellular amastigotes and multiply inside phagolysosomes. According to Singh and Sundar (2015), the main sites of dissemination include the spleen, liver, and bone marrow, where infected macrophages proliferate . Systemic immunological suppression is a characteristic of VL. There is an upregulation of regulatory cytokines like TGF-β and IL-10 and a downregulation of key Th1 cytokines like

IFN-γ and IL-12, which are in charge of nitric oxide generation and macrophage activation. This immunological failure allows parasites to replicate unrestrained [5]. Bone marrow suppression causes pancytopenia, the liver swells from mononuclear infiltration, and the spleen has hyperplasia. Patients usually associated with symptoms of protracted fever, weight loss, hepatosplenomegaly, and anemia. Without therapy, the fatality rate exceeds 90%. Even after treatment, residual parasites may remain in immune-privileged locations, providing the framework for future PKDL growth.

Development of Post-Kala-azar Dermal Leishmaniasis (PKDL)

Up to 60% of treated VL patients in Sudan and 5–10% of cases in India had PKDL. Mostly seen on the face, upper limbs, and trunk, it presents as cutaneous lesions that might be hypopigmented macules, papules, or nodules [2]. Geographical location, patient immunity, and parasite strain all affect the clinical presentation. IFN-γ and TNF-α are upregulated in PKDL, a paradoxical condition of immunological reactivation, although IL-10 and IL-4 still prevent total parasite removal. Prolonged, non-healing cutaneous lesions are caused by the juxtaposition of regulatory and pro-inflammatory cytokines. Furthermore, T regulatory cells (Tregs) suppress effector responses by infiltrating cutaneous wounds [6]. Although the precise mechanism causing PKDL is still unknown, it is believed to involve host immunogenetic predisposition, potential drug-induced immune modulation, and incomplete parasite clearance after treatment. The infection cycle may be strengthened by the possibility of transmission back to sandflies due to the parasites' persistence in skin macrophages.

Immunological Crosstalk Between VL and PKDL

The immunological crosstalk between VL and PKDL represents a fine balance between recovery and relapse. The immunological transition from VL to PKDL reflects a complex interplay of regulatory and effector immune mechanisms that fail to fully eliminate the parasite and instead establish a dermal reservoir. A partial immune rebound, insufficient to restore protective Th1 dominance, creates a permissive niche in the skin that favors chronic infection. Understanding these dynamics is essential for designing immunotherapeutic strategies and vaccines that prevent PKDL development in VL-treated individuals. During active VL, the host immune response is profoundly suppressed. The transition from visceral leishmaniasis (VL) to post-kala-azar dermal leishmaniasis (PKDL) is orchestrated by complex immune remodeling following treatment [7]. During active VL, pro-inflammatory Th1 responses are significantly suppressed, while immunosuppressive cytokines such as IL-10 and TGF-β dominate the immune environment [8]. This immunosuppressive cytokine milieu inhibits effective parasite clearance and promotes disease progression. Following antileishmanial therapy, Th1 activity begins to recover; however, in patients who develop PKDL, this recovery remains incomplete or dysregulated, resulting in a heterogeneous cytokine profile in dermal tissues [9]. During active VL, the host immune response is profoundly suppressed. Th1-type responses, including interferon-gamma (IFN-γ) and interleukin-12 (IL-12), which are essential for macrophage activation and parasite clearance, are significantly downregulated. Concurrently, anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) dominate the cytokine milieu [8]. IL-10, secreted by multiple immune cell types including regulatory T cells (Tregs), inhibits antigen presentation, suppresses IFN-γ production, and directly impairs leishmanicidal activity of macrophages [10]. Two pivotal immune players involved in this transition are memory T cells and regulatory T cells (Tregs). Tregs facilitate immune tolerance and allow parasite persistence by actively suppressing Th1-type effector responses through IL-10 and TGF-β production [11]. Meanwhile, memory T cells formed during VL can home to skin tissue, where residual *Leishmania* antigens reactivate them, leading to chronic low-grade inflammation that

fails to eliminate the parasite [9]. Another determinant of disease outcome is macrophage polarization. VL induces a shift toward alternatively activated (M2) macrophages, which support parasite survival through anti-inflammatory functions [10]. In PKDL, incomplete repolarization toward the pro-inflammatory M1 phenotype limits leishmanicidal activity, facilitating the persistence of parasites in dermal niches [7]. Altogether, these factors converge to form a dermal immunological niche defined by persistent inflammation, immune evasion, and relapse risk.

Parasite Persistence and Adaptation

The remarkable phenotypic plasticity of *Leishmania donovani* allows it to persist in a variety of host microenvironments. Through strategies including downregulating antigen presentation, altering host signaling pathways, and generating stress response proteins, the parasite in VL evade immune detection [12]. In PKDL, parasites can avoid effector mechanisms in a less inflammatory environment found in the dermal environment. Research indicates that *Leishmania* experiences transcriptional and metabolic changes that improve its survival in dermal macrophages, such as adapting to nutrient-poor environments and exhibiting resistance to oxidative stress. A subpopulation of parasites also survives due to immune changes brought on by treatment and insufficient drug penetration in skin tissues. Long after the visceral infection has subsided, these parasites may still be the cause of PKDL lesions.

Genetic and Epigenetic Influences

A key component of the VL-PKDL continuum is host genetic susceptibility. Changes in immune responses and a higher risk of developing PKDL have been associated with polymorphisms in cytokine genes such as TNFA, IFNG, and IL10 [13]. The development of the disease is also influenced by genetic variation in the genes for heat shock protein and solute carrier. Immune regulatory gene expression is modulated by epigenetic regulation, which includes DNA methylation and histone acetylation. Impaired parasite clearance may result from the epigenetic silencing of important cytokine pathways. Epigenetic plasticity is demonstrated by *Leishmania*, which modifies gene expression to withstand immunological and drug pressure. Genetic predispositions are exacerbated by environmental factors that further modify immune responses, such as co-infections, inadequate housing, and malnutrition.

Therapeutic Interventions and Immune Reprogramming

Miltefosine, paromomycin, and amphotericin B (liposomal and deoxycholate) are common treatments for VL [14, 15]. These treatments work well to eradicate visceral infections, but because of their limited penetration and changed pharmacodynamics, they have varying degrees of effectiveness against dermal reservoirs [16]. Paradoxically, immunological reconstitution after treatment may trigger PKDL, particularly when paired with insufficient drug exposure in skin tissues [5]. In order to guarantee total parasite eradication, prolonged and combination therapies are currently being considered. New approaches include host-directed treatments, such as checkpoint inhibitors, IL-10 neutralization, and therapeutic vaccines that boost Th1 responses [17]. However, because of the possibility of aggravating tissue damage, these methods need to be carefully considered [8].

PKDL and Public Health Impact

PKDL acts as a reservoir for the *Leishmania* parasite, allowing it to thrive in human populations. Skin lesions of PKDL person can aid in the transmission of this disease to other humans by sandflies [18, 19]. This causes the persistence of disease in the widespread disease prone regions. Although the number of VL cases decreases, sandflies that feed on PKDL lesions can still transmit the parasite to other humans [20]. Integral control strategies

are required to overcome the undermining of elimination programs by this concealed reservoir [2]. Because of the absence of symptoms, variable presentation, and social stigma, surveillance systems frequently fail to detect PKDL. Why? The identification and treatment of PKDL cases necessitate active case detection, dermatological training, and community education [21]. In addition, vector control must be maintained in regions where the PKDL load is established [22].

Strategies for Integrated Control

A successful VL-PKDL control strategy involves long-term follow-up for VL patients, rapid diagnostic methods for PKDL identification, drug formulations that penetrate skin, monitoring cytokine biomarkers like IFN-γ and IL-10, and combating social stigma. Current vaccination campaigns target both PKDL and VL, but a combination of medical, social, and vector control strategies is necessary for success [23, 24]. Both VL and PKDL are the targets of current vaccination campaigns, and several of the candidates have shown promise in preclinical animals. [25, 26]. Implementing medical, social, and vector control strategies in concert will be necessary for success [27].

Conclusion

The continuum from VL to PKDL is influenced by immune regulation, therapeutic gaps, and parasite resilience. It is necessary to implement integrated control strategies that recognise PKDL as a crucial element in *Leishmania* transmission due to the pathological and immunological interactions among these disease forms. The development of improved diagnostic techniques, more effective treatments, and a deeper comprehension of host-parasite interactions will be critical to the global effort to eradicate leishmaniasis.

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