Scientific Journal of
Immunology & Immunotherapy

Mini Review

Unresolved Issues in Innate Immune Response in Post Kala Azar Dermal Leishmaniasis (PKDL) - a

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Submitted: 04 October 2017; **Approved:** 09 October 2017; **Published:** 10 October 2017

Cite this article: Singh AK, Verma N, Rabi Das VN, Krishna P, Bimal S, et al. Unresolved Issues in Innate Immune Response in Post Kala Azar Dermal Leishmaniasis (PKDL). Sci J Immunol Immunother. 2017;2(1): 018-021.

Visceral Leishmaniasis (VL) which is also known as kala azar is a neglected tropical disease caused by obligate intra-macrophage protozoan *Leishmania donovani*, largely affecting individuals of low socioeconomic level [1]. Leishmaniasis is widely distributed across 88 tropical and subtropical countries; worldwide more than 350 million individuals are at risk for VL with an estimated 400,000–500,000 new case annually and 40,000–50,000 deaths per year [2,3]. About 90% of the total cases are reported in India, Bangaladesh, Sudan, Nepal, with the most cases appearing in the state of Bihar [3,4,5]. The aetiological agents of VL are grouped under *Leishmania (L.) donovani* complex that includes *L.donovani*, *L. infantum* and *L. chagasi* [6]. VL is a systemic disease that is fatal if left untreated and Post Kala-Azar Dermal Leishmaniasis (PKDL) is sequel skin manifestation of Visceral Leishmaniasis (VL). In India VL and PKDL is caused primarily by *L. donovani* and is transmitted by *phlebotomous* sand flies. It was (PKDL) first described by Brahmachari in 1922 [7]. In India approximately 5-10% of cured VL patients develop dermal lesions usually after months to years of treatment and it causes PKDL and such occurrence is more common in many countries including India, especially in Sudan where about 50-60% of cured VL develop PKDL within weeks or months [8,9].

Drugs used to control the disease are toxic and frequent resistance against these are encountered, thereby all attempts have so far failed to restrict the disease in patients residing in highly endemic areas. This is despite the fact that *Leishmania* is a severely harmful parasite globally second only next to malaria. The government of three most VL affected countries of Indian subcontinent has joined focus in the elimination of disease from the region at an earliest [10]. Such goal can be accomplished by identifying the factors in VL endemic areas especially those that influences the spread of disease in these endemic areas. Since amastigote form of *L. donovani* are present in the skin lesions and in India the transmission of leishmaniasis is considered anthroponotic, therefore it is possibly a likelihood candidate to act as reservoir for *L. donovani* and a key factor in transmission of VL in India [11]. As spread of such PKDL cases in VL endemic areas are alarming, therefore any intervention that helps to restrict and eliminate PKDL cases may be beneficial for control of VL.

PKDL is clinically characterized by the presence of hypopigmented macules, erythematous papules and/or nodules on the skin [12]. Lesions are typically manifested in form of macules (flat, nonpalpable, and hypopigmented), papules (elevated usually 0.5 cm of size), and nodules (palpable, firm, rounded and raised with bigger size around > 0.5 cm of size) [13,14]. Histo-pathologically Indian PKDL differs from African PKDL by being less granulomatous and with more plasma cells in the infiltrate. The skin biopsy from macular lesions in Indian PKDL patients demonstrate a mild to moderate infiltrate of plasma cells and lympho-histiocytes whereas the biopsy from papules usually showed follicular plugging and a dense dermal perivascular & perifollicular infiltrate in the upper half of the dermis separated from epidermis through a normal dermal collagen. In yet another manifestation shown in Indian PKDL patients as nodules, there are demonstrations of diffuse dermal infiltrate in biopsies from nodular lesions. The inflammatory cells consist of a mixture of lymphocytes, histiocytes and plasma cells [12].

The underlying pathology in patients with VL pre-disposing to PKDL is often attributed to parasite-specific cellular immunity. Both VL and PKDL have an immunological basis of cure but the precise immunological mechanisms responsible for different clinical manifestation at the level of cellular immunity are relatively less defined. Marginal to massive infiltration of mononuclear cells are seen in skin histopathology of PKDL lesion depending upon type of lesions. Hypo-pigmented patches demonstrates small lymphocytes with scanty parasites in the dermis which reverts at the nodular stage with high accumulation of CD4+ and CD8+ cell types, primarily of CD8+ phenotypes in the granuloma of nodular type. This all shows predominance of CD8+ cells in leishmanoid lesion [15]. This was shown through up regulated IL10 production by CD8+ T cells in Indian PKDL patients and some other studies has also provided evidence for the role of IL-10 producing TGF-β in immunopathogenicity which can regulate the Interferon-gamma (IFN-γ) dominant protective Th1 response in patients both in Peripheral Blood Mononuclear Cells (PBMC) and in dermal lesions of PKDL patients [16-20]. Additionally, there are reports on a mixed T cell response in PKDL patients as patients were shown with upregulated production of both IL-10 and TNF-α [16,18]. IL-10 irrespective of its cellular sources often considered as hallmark for PKDL and for this, IgG3 and IgG1were observed as surrogate marker and due to this, both are considered conspicuous feature in PKDL patients with high expression (IL-10, IgG1 and IgG3)[16]. Apart from CD8+ T cells which produce high granzyme B, expression of CD4+ T cells also remains high in PBMCs of PKDL patients. Amongst CD4+ T cells, Th17 cell lineage of CD4+ T cells were recently discussed with role during pathogenicity by inducing TNF-α and nitric oxide production in tissue lesion of PKDL patients [21].

Cellular immune response though extensively worked out many of the crucial aspects on innate immune response remain unresolved during PKDL infection. The role of macrophage (Mφ) in anti-leishmanial defence against VL and PKDL is well established [22]. Comparatively Polymorphonuclear leukocyte (PMNs or neutrophils) and their involvement during immune response is least worked out, even though they are the effector cells of innate immunity with an ability to initiate acute inflammatory reactions [23]. During these reactions PMNs normally destroy invading pathogens [24]. Neutrophil's (PMNs), can utilize several strategies to counter *Leishmania donovani* (*L.donovani*) by phagocytosis, generation of reactive oxygen metabolites or through release of Neutrophil Extracellular Trap (NET) [25]. Reports are available and they suggest survival of *Leishmania infantum* inside NET by a mechanism mediated by parasite specific nuclease 3'-nucleotidase/nucleases [25]. Among other major functions, inflammatory PMN's should also participate in the recruitment and activation of natural killer cells and T-helper type 1 cell and thereby regulate the development of the protective immune response against intracellular pathogens [26-29]. These cells need to be classically and clinically explored because of their involvement in recruitment of macrophages (Mφ), the preferred host for leishmania [23]. Although, reports on lower recruitment of $CD1a^{+}$ Langerhans cells are available, the similar information on Mφ and PMN's is relatively scarce to reach at actual cause for the lesser availability of potent innate cells during severity of disease at the inflammation site in PKDL patients [30]. A thorough understanding of the role of Mϕ and PMN's during leishmania infection in skin is worth pursuing. This will be particularly important to know the mechanism of recruitment of these innate cells in terms of rolling,

diapedesis and inflammatory responses induced by these cells against leishmania parasite in the skin. As Known, leukocytes rolling are mediated through cross-linking of L-selectin (CD62L) with its ligand on endothelium and it plays a crucial role in leukocyte trafficking [31,32]. The activation events then slowly appear with shedding of L-selectin (CD62L) with an up-regulated integrin CD11b expression to help immune cells to bind ICAM-1 and ICAM-2 that finally leads to mediate adhesion and migration following support through inflammatory mediators such as IL-1, TNF-α and many chemokines such as MIP1α, CXCL8/IL8 etc [31,32]. TNF-alpha is considered a potent inducer of MMP9. It has been reported that the ratio of Matrix Metalloproteinase (MMP 9) and tissue inhibitors of Matrix Metalloproteinase 1 (TIMP 1) are found higher in PKDL [33]. MMPs are produced by T cells eosinophils, neutrophils and particularly by activated macrophages [34]. Therefore it is likely that release of these inflammatory mediators in PKDL may have relation with functioning of these innate immune cells and may have ultimate impact on outcome of disease.

Although literatures indicates some role of innate immune cell during pathogenesis of PKDL but relatively less explored in context to leukocyte trafficking, chemokine- cytokine interaction and signal transduction from circulatory site to PKDL lesion.

ACKNOWLEDGMENTS

The authors acknowledge Rajendra Memorial Research Institute of Medical Sciences, Indian Council of Medical Research, Patna 800 007, India for providing fellowship support to one of the investigators (Ashish Kumar Singh) in this study.

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