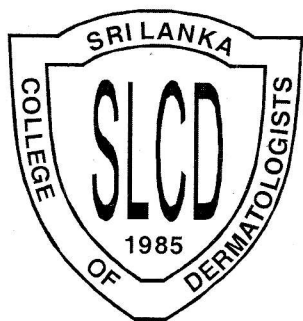




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Editorial

Towards understanding the pathology of leprosy reactions

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Introduction

Leprosy is a chronic infection of the skin and the nerves due to *Mycobacterium leprae*. Leprosy can be considered as a spectrum with two polar forms, tuberculoid and lepromatous in the ends with the subpolar borderline forms in between¹.

Leprosy reactions are immune mediated phenomena that occur before, during or after treatment with multi drug therapy (MDT). They contribute immensely to the burden of leprosy and need to be diagnosed and treated early to prevent nerve function impairment and permanent disability. There are two types of reactions: type 1 (T1R) or reversal reaction and type 2 or erythema nodosum leprosum (ENL) reaction. These distinct conditions usually occur separately but can occur in the same person simultaneously or at different times^{2,4}. It is important to recognise that both these conditions can result in permanent loss of nerve function. Nerve function impairment (NFI) is defined as any reduction in sensory or motor function. Neuritis (inflammation of the peripheral nerve trunks) may or may not be accompanied by clinically detectable NFI.

Understanding the pathogenesis is important in the diagnosis and management of leprosy reactions as disability due to leprosy is mainly due to reactions and some drugs target specific phenomena that occur during reactions. Immune mediated reactions in mycobacterial diseases are now being recognised to a wide range of mycobacteria, not just *M. leprae*. Furthermore the immune mediated reactions in mycobacterial diseases in patients with HIV and the immune reconstitution inflammatory syndrome (IRIS) illustrate the broad implications of these phenomena^{5,6}.

This article critically reviews the available literature on the pathogenesis of type 1 reactions and ENL.

Type 1 reaction (T1R)

T1R is characterised by the development of acute inflammation in skin lesions or nerves, or both⁷. Borderline forms are specifically at risk for the development of T1R⁸ but the polar forms can also give rise to T1R. Recurrences of T1R can occur thus leading to further nerve damage. Even though T1R is not a systemic illness the associated neuritis can lead to permanent disability unless treated in time. The neuritis can occur slowly over time but can also present as sudden nerve palsy.

Epidemiology and risk factors

The measured prevalence rates of T1R vary depending on whether the studies are conducted in hospital or field settings. The available figures vary from 19.8% to 30% but it is difficult to compare figures as different studies have used different denominators⁹⁻¹².

Extensive disease and having a positive slit skin smear are risk factors for T1Rs¹³. Individuals who present with WHO disability grades type 1 and 2 are significantly more likely to have severe T1Rs at diagnosis¹⁴. T1Rs are frequently seen after starting MDT or during the puerperium¹⁵.

Histopathology

Only 32–62 percent of clinically diagnosed T1Rs, are diagnosed by histopathology¹⁶. The major histopathological findings are dermal and intra-granuloma oedema, increase in giant cells and lymphocytes, and loss of normal granuloma architecture (formation of loose granulomata). A recent study involving four experienced histopathologists examining biopsies of T1R independent of each other showed that the most sensitive indicators are oedema and giant cells¹⁶. There was also a wide variation in the findings of the four pathologists indicating that histopathology is not a very useful tool in the diagnosis of T1R. There is uniform staining of the epidermis with HLA DR which can be helpful in the diagnosis¹⁶.

Immunopathology

T1Rs are delayed hypersensitivity reactions. *M. leprae* antigens have been demonstrated in the nerves and skin of patients experiencing T1Rs, localised to Schwann cells and macrophages¹⁷. Schwann cells have been shown to express Toll-like receptor 2¹⁸. *M. leprae* infection may lead to the expression of MHC II on the surface of the cells. This may give rise to antigen presentation which triggers CD4 lymphocyte killing of the infected cell which is mediated by cytokines such as tumour necrosis factor (TNF)¹⁹. Immunohistochemistry studies show greater TNF staining in the skin and nerves during T1Rs compared with non-reactional controls²⁰.

T1Rs appear to be mediated via T_H1 lymphocytes and cells from reactional lesions express the pro-inflammatory cytokines interferon gamma (IFN- γ), interleukin 12 (IL-12), IL-13, IL-6, IL-10, and the oxygen free radical producer inducible nitric oxide synthase^{21,22}. Over-expression of vascular endothelial growth factor has been shown in the dermis and epidermal dendritic cells²³. The pro-inflammatory cytokines take longer to decrease than apparent clinical cure and some skin lesions have been shown to express cytokines even 180 days after a course of steroid therapy^{21,22}.

Mechanism of nerve damage

The exact mechanism of nerve damage has not been explained. It has been shown that Schwann cell receptors targeted by *M. leprae* may play a role in demyelination²⁴. Infected Schwann cells process and present antigens to MHC II restricted CD4+ T cells. The activated T cells may then kill the Schwann cells²⁵.

Silent neuropathy

Van Brakel and Khawas proposed the term "Silent Neuropathy" (SN) to describe the phenomenon of nerve function impairment occurring in the absence of symptoms. It is therefore only detected if physicians perform a careful examination of the peripheral nervous system. In Nepal 13% of patients developed SN. The majority of SN was present at diagnosis or developed during the first year of MDT²⁶. The treatment of SN is the same as for T1R.

Type 1 reaction and HIV

With the advent of HIV in epidemic proportions in countries endemic for leprosy it was expected that there will be an increase in the incidence of leprosy similar to that seen in tuberculosis. So far there is no evidence of such a phenomenon.

Since highly active anti retroviral therapy (HAART) became widely available a new entity called immune reconstitution inflammatory phenomenon (IRIS) has been described. IRIS is characterised by the sudden worsening of previously existing infective conditions (eg. tuberculosis) in a patient whose CD4+ count recovers dramatically from a previously very low value, due to recent HAART. There are several reports of T1R presenting as IRIS within 6 months of starting HAART in patients with co-existing leprosy and HIV^{5,6}. Even though Sri Lanka has a very low incidence of both leprosy and HIV it is necessary for dermatologists to be aware of this entity as HAART is now available free of charge in Sri Lanka.

Erythema nodosum leprosum (ENL) reaction

ENL usually complicates lepromatous and borderline lepromatous leprosy. The majority of patients with ENL go on to develop several episodes over many years, as multiple acute episodes or chronic ENL^{13,27}. Less than 10% of patients in a large cohort in India had only a single episode of ENL while 62.5% had chronic ENL²⁷.

The hallmark feature of ENL is the appearance of painful, erythematous crops of nodules. There is usually systemic upset with fever, malaise and prostration. Peripheral oedema and transient proteinuria can also occur. Iritis and episcleritis can occur and may be sight threatening. Other features such as pain, photophobia and lacrimation may be absent⁷. Orchitis, lymphadenopathy, organomegaly, joint involvement, dactylitis, and bone tenderness, especially over the tibia, are well recognised features of ENL. Neuritis, in the form of painful enlarged nerves and nerve function impairment, may occur as part of ENL. The neuritis may be less dramatic than in T1R but it is important to recognise nerve involvement early to prevent permanent loss of function.

Epidemiology and risk factors

There is wide geographic variation in the prevalence of ENL reactions. In Brazil 37% of new BL and LL cases experience ENL¹². In Asia reported figures vary between 19-26% of BL and LL cases in Nepal, India, and Thailand^{12,14,27,28}.

ENL reactions occur most commonly during the first year of MDT²⁷⁻²⁹. One third of patients with ENL have the diagnosis of leprosy made at the same time as their reaction^{28, 29}.

Lepromatous leprosy (LL) and a bacillary index (BI) greater than 4+ have been shown to be risk factors for ENL^{27,28}. Pregnancy, lactation, puberty, intercurrent infection, vaccination, and psychological stress have been considered to precipitate ENL⁷ but these associations have not been confirmed in prospective studies.

Histopathology

The inflammatory infiltrate in ENL is situated in the dermis and the subcutis. The constituent cells vary with the timing of the skin biopsy. In acute lesions where skin biopsy is performed within 72 hours of occurrence, the predominant cell type is the neutrophil. Eosinophils, and mast cells may also be present³⁰. Skin biopsies performed later show fewer neutrophils and increasing numbers of lymphocytes, plasma cells and histiocytes, representing a chronic inflammatory

infiltrate. The other histological features reported in ENL are oedema of the dermis, and subcutis, vasculitis and panniculitis³⁰.

Changes due to leprosy will also be evident. The infiltrate due to LL may contain histiocytes with fatty change and foamy cells arranged diffusely. In biopsies from patients with BL leprosy the granuloma may contain histiocytes and lymphocytes¹. In both cases large numbers of acid fast bacilli, usually granular in appearance, will be found. It has been shown that in skin biopsies from ENL lesions the bacilli become granular more rapidly compared to non reactional lesions with comparable bacillary index (BI)³¹.

Immunopathology

It has long been accepted that ENL is an immune complex mediated phenomenon but recent evidence points at the importance of cell mediated immunity in the pathogenesis of ENL. The exact mechanism of pathogenesis of ENL is not known.

Role of immune complexes

It has been shown that immune complexes and complement are present in the skin in 59% biopsies³². *M. leprae* antigen, IgG, IgM, complement C3, C1q and C3d have been shown to be present in same sites, both intra-cellularly within polymorphs (PMN), and extra-cellularly in the inflammatory exudates³³. It is widely accepted that ENL is due to the deposition of immune complexes locally in the skin.

Antibodies to phenolic glycolipid 1 (PGL-1), a cell wall component of *M. leprae*, have been shown to be present in increasing amounts across the spectrum of leprosy from TT to LL³⁴. These antibodies do not play a protective role against *M. leprae* infection but may have an important role in the pathogenesis of reactions. The level of anti PGL IgM in serum of patients with ENL is significantly lower than that in sera of patients with LL and comparable BI but no ENL^{34,35}. Antibodies in the serum being used up in immune complexes is a possible explanation for this phenomenon.

Role of cell mediated immunity

There is evidence of increased T cell activity in ENL compared to LL without reaction. Patients with lepromatous leprosy without reaction have a CD4+: CD8+ ratio of about 1:2 with a predominance of T suppressor cells^{36,37}. In patients with lepromatous leprosy with ENL this ratio is reversed with a CD4+: CD8+ of 2:1^{36,38-40}.

The role of B cells in ENL has not been studied in great detail. There is only one study where an increase in the absolute numbers of B lymphocytes had been shown in ENL⁴¹. There is renewed interest in the role played by B cells in autoimmune disorders like rheumatoid arthritis and SLE^{42,43}. In addition to the well known action of being the precursors for antigen secreting plasma cells, B cells have now been shown to act as antigen presenting cells, and to play an important role in the initiation, and regulation of T and B cell responses^{42,44}. Whether B cells play an important role in ENL is an area for future research.

Cytokines in ENL

There is evidence of both T_H1- and T_H2-type involvement in ENL in skin lesions and serum⁴⁵⁻⁴⁹. TNF α and IL-6 were shown to be present in almost all reactional lesions by many authors⁴⁵⁻⁴⁸. Peripheral blood mononuclear cells (PBMC) from patients with ENL show the highest release of TNF α compared with inactive ENL, RR and LL lesions⁵⁰. Sreenivasan et al (1998) found a T_H1-like cytokine pattern in 64% of ENL sera and 85% of RR sera with basal expression of IFN γ , which was mirrored in the skin lesions. This was further confirmed by Moraes et al who detected IFN in 84% of ENL and all RR lesions. The other cytokines found in varying amounts in ENL lesions are IL-12, IL-10 and IL12p⁴⁰. IL-4 was found to be absent or present in low amounts in ENL Lesions^{45,46,49}. This is strong evidence that ENL is associated with a T_H1-type reaction, as the major cytokines expressed in a T_H2-type response are IL-4, IL-5 and IL10.

Changes in the epidermis

The thickness of the nucleated epidermis is increased in ENL², with increased numbers of Langerhans cells in the epidermis in both ENL and RR lesions^{36,40,51,52}. ENL lesions show a strong but patchy keratinocyte 1a expression^{51,52}. Keratinocyte 1a expression in the human epidermis is a sign of delayed type hypersensitivity reaction or cell-mediated immune responses. In addition, the epidermis in ENL has been demonstrated to strongly express ICAM-1 on keratinocytes and LFA-1 on epidermal lymphocytes compared with RR and non-reactional LL lesions⁵³. ICAM-1 and LFA-1 act as co-stimulatory molecules to enhance the cell-mediated immune response. The changes observed in the epidermis in ENL suggest that the epidermis plays an immunological role in the pathogenesis of ENL.

Conclusions

Reactions in leprosy are complex immunological phenomena which are probably triggered by the

release of *M. leprae* antigens. T1R is a delayed type hypersensitivity reaction with TH1 cytokines being involved in the pathogenesis.

The pathogenesis of ENL reaction is complex with both immune complexes and cell mediated immunity playing important roles. There are many gaps in the knowledge about how ENL reactions occur. Future research should look into the pathogenesis of both types of leprosy reactions in greater detail to explain the mystery behind these interesting immunological phenomena.

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