Leprosy: An Overview of Pathophysiology

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Leprosy, also known as Hansen’s disease, is a chronic infectious disease caused by *Mycobacterium leprae*, a microorganism that has a predilection for the skin and nerves. The disease is clinically characterized by one or more of the three cardinal signs: hypopigmented or erythematous skin patches with definite loss of sensation, thickened peripheral nerves, and acid-fast bacilli detected on skin smears or biopsy material. *M. leprae* primarily infects Schwann cells in the peripheral nerves leading to nerve damage and the development of disabilities. Despite reduced prevalence of *M. leprae* infection in the endemic countries following implementation of multidrug therapy (MDT) program by WHO to treat leprosy, new case detection rates are still high—indicating active transmission. The susceptibility to the mycobacteria and the clinical course of the disease are attributed to the host immune response, which heralds the review of immunopathology of this complex disease.

1. Introduction

Leprosy, also known as Hansen’s disease, is a chronic infectious disease caused by *Mycobacterium leprae*, a microorganism that has a predilection for the skin and nerves. Though nonfatal, leprosy is one of the most common causes of non-traumatic peripheral neuropathy worldwide. The disease has been known to man since time immemorial. DNA taken from the shrouded remains of a man discovered in a tomb next to the old city of Jerusalem shows him to be the earliest human proven to have suffered from leprosy. The remains were dated by radiocarbon methods to 1–50 A.D. [1]. The disease probably originated in Egypt and other Middle Eastern countries as early as 2400 BCE. An apparent lack of knowledge about its treatment facilitated its spread throughout the world. *Mycobacterium leprae*, the causative agent of leprosy, was discovered by G. H. Armauer Hansen in Norway in 1873, making it the first bacterium to be identified as causing disease in humans [2, 3]. Over the past 20 years, the WHO implementation of MDT has rendered leprosy a less prevalent infection in 90% of its endemic countries with less than one case per 10,000 population. Though, it continues to be a public health problem in countries like Brazil, Congo, Madagascar, Mozambique, Nepal, and Tanzania [4].

2. *Mycobacterium leprae*

*M. leprae*, an acid-fast bacillus is a major human pathogen. In addition to humans, leprosy has been observed in nine-banded armadillo and three species of primates [5]. The bacterium can also be grown in the laboratory by injection into the footpads of mice [6]. Mycobacteria are known for their notoriously slow growth. With the doubling time of 14 days, *M. leprae* has not yet been successfully cultured in vitro [7, 8]. The genome of *M. leprae* has been sequenced in totality [9]. It presents with less than 50% coding capacity with a large number of pseudogenes. The remaining *M. leprae* genes help to define the minimal gene set necessary for in vivo survival of this mycobacterial pathogen as well as genes potentially required for infection and pathogenesis seen in leprosy.

*M. lepromatosis* is a newly identified mycobacterium which is described to cause disseminated leprosy whose significance is still not clearly understood [10, 11].

3. Genetic Determinants of Host Response

Human genetic factors influence the acquisition of leprosy and the clinical course of disease [12]. Single-nucleotide
polymerase chain reaction (SNP) association studies showed a low lym-
photokinase-α (LTA)-producing allele as a major genetic risk
factor for early onset leprosy [13]. Other SNPs to be associ-
ated with disease and/or the development of reactions in
several genes, such as vitamin D receptor (VDR), TNF-α, IL-
10, IFN-γ, HLA genes, and TLR1 are also suggested [14–17].
Linkage studies have identified polymorphic risk factors in
the promoter region shared by two genes: PARK2, coding
for an E3-ubiquitin ligase designated Parkin, and PACRG
[18]. A study also suggests that NOD2 genetic variants are
associated with susceptibility to leprosy and the develop-
ment of reactions (type I and type II) [19].

4. Transmission

Two exit routes of *M. leprae* from the human body often
described are the skin and the nasal mucosa. Lepromatous
cases show large numbers of organisms deep in the dermis,
but whether they reach the skin surface in sufficient numbers
is doubtful [20]. Although there are reports of acid-fast bac-
cilli being found in the desquamating epithelium of the
skin, there are reports that no acid-fast bacilli were found in
the epidermis, even after examining a very large number of
specimens from patients and contacts [21]. However, fairly
large numbers of *M. leprae* were found in the superficial
keratin layer of the skin of lepromatous leprosy patients, sug-
gesting that the organism could exit along with the seba-
ceous secretions [22]. The quantity of bacilli from nasal
mucosal lesions in lepromatous leprosy ranges from 10,000
to 10,000,000 [23]. Majority of lepromatous patients show
leprosy bacilli in their nasal secretions as collected through
blowing the nose [24]. Nasal secretions from lepromatous
patients could yield as much as 10 million viable organisms
per day [25].

The entry route of *M. leprae* into the human body is also
not definitively known. The skin and the upper respiratory
tract are most likely; however, recent research increasingly
favours the respiratory route [26, 27].

5. Incubation Period

Measuring the incubation period in leprosy is diffi-
cult because of the lack of adequate immunological tools
and slow onset of the disease. The minimum incubation period
reported is as short as a few weeks and this is based on the
very occasional occurrence of leprosy among young infants
[28]. The maximum incubation period reported is as long
as 30 years, or even as observed among war veterans known
to have been exposed for short periods in endemic areas but
otherwise living in nonendemic areas. It is generally agreed
that the average incubation period is between three and ten
years [29].

6. Risk Factors

Those living in endemic areas with poor conditions such
as inadequate bedding, contaminated water, and insufficient
diet, or other diseases that compromise immune function are
at highest risk for acquiring *M. leprae* infection. There has
been concern that coinfection with HIV might exacerbate
the pathogenesis of leprosy lesions and/or lead to increased
susceptibility to leprosy as it is seen with tuberculosis. How-
ever, HIV infection has not been reported to increase sus-
sceptibility to leprosy, impact on immune response to *M.
leprae*, or to have a significant effect on the pathogenesis of
neural or skin lesions to date [30, 31]. On the contrary, ini-
tiation of antiretroviral treatment has been reported to be
associated with activation of subclinical *M. leprae* infection
and exacerbation of existing leprosy lesions (type I reaction)
likely as part of immune reconstitution inflammatory syn-
drome [32–34].

7. Interaction of *M. leprae* with
Schwann Cells and Macrophages

Schwann cells (SCs) are a major target for infection by *M.
leprae* leading to injury of the nerve, demyelination, and con-
sequent disability. Binding of *M. leprae* to SCs induces demy-
elination and loss of axonal conductance [35]. It has been
shown that *M. leprae* can invade SCs by a specific laminin-
binding protein of 21 kDa in addition to PGL-1 [36, 37].
PGL-1, a major unique glycoconjugate on the *M. leprae*
surface, binds laminin-2, which explains the predilection of
the bacterium for peripheral nerves [37]. The identification
of the *M. leprae*-targeted SC receptor, dystroglycan (DG), sug-
gests a role for this molecule in early nerve degeneration [38].
*Mycobacterium leprae*-induced demyelination is a result of
direct bacterial ligation to neuregulin receptor, ErbB2 and
Erb1/2 activation, and subsequent MAP kinase signaling and
proliferation [39].

Macrophages are one of the most abundant host cells
to come in contact with mycobacteria. Phagocytosis of *M.
leprae* by monocyte-derived macrophages can be mediated
by complement receptors CR1 (CD35), CR3 (CD11b/CD18),
and CR4 (CD11c/CD18) and is regulated by protein kinase
[40, 41]. Nonresponsiveness towards *M. leprae* seems to cor-
relate with a Th2 cytokine profile.

8. Disease Classification

Leprosy is classified within two poles of the disease with transi-
tion between the clinical forms [42]. Clinical, histopatho-
logical, and immunological criteria identify five forms of
leprosy: tuberculoid polar leprosy (TT), borderline tubercu-
loid (BT), midborderline (BB), borderline lepromatous (BL),
and lepromatous polar leprosy (LL). Patients were divided
into two groups for therapeutic purposes: paucibacillary (TT,
BT) and multibacillary (midborderline (BB), BL, LL) [43]. It
was recommended later that the classification is to be based
on the number of skin lesions, less than or equal to five
for paucibacillary (PB) and greater than five for the multi-
bacillary (MB) form.

9. Clinical Features (Table 1)

9.1. Indeterminate Leprosy. Indeterminate (I) is a prelude to
the determinate forms of leprosy [44, 45]. It is characterized
by an ill-defined, bizarre hypopigmented macule(s) with
9.2. Polyneuritic Leprosy. Manifesting with only neural signs without any evidence of skin lesions, polyneuritic leprosy mostly well recognized in the Indian subcontinent. The affected nerves are thickened, tender, or both. Localized involvement of the nerves may form nerve abscesses [46].

9.3. Histoid Leprosy. Histoid leprosy is relatively uncommon, distinct clinical, and bacteriologic and histopathologic expression of multibacillary leprosy [47]. It may occur as a primary manifestation of the disease or in consequence to secondary drug resistance to dapsone following irregular monotherapy. It manifests as numerous cutaneous nodules and plaques primarily over the back, buttocks, face, and bony prominences.

10. Histopathological Reactions

Histopathologically, skin lesions from tuberculoid patients are characterized by inflammatory infiltrate containing well-formed granulomas with differentiated macrophages, epithelioid and giant cells, and a predominance of CD4+ T cells at the lesion site, with low or absent bacteria. Patients show a vigorous-specific immune response to M. leprae with a Th1 profile, IFN-γ production, and a positive skin test (lepromin or Mitsuda reaction).

Lepromatous patients present with several skin lesions with a preponderance of CD8+ T cells in situ, absence of granuloma formation, high bacterial load, and a flattened epidermis [48]. The number of bacilli from a newly diagnosed lepromatous patient can reach 10^12 bacteria per gram of tissue. Patients with LL leprosy have a CD4:CD8 ratio of approximately 1:2 with a predominant Th2 type response and high titers of anti-M. leprae antibodies. Cell-mediated immunity against M. leprae is either modest or absent, characterized by negative skin test and diminished lymphocyte proliferation [49, 50].

11. Leprosy Reactions

Leprosy reactions are the acute episodes of clinical inflammation occurring during the chronic course of disease. They pose a challenging problem because they increase morbidity due to nerve damage even after the completion of treatment. They are classified as type I (reversal reaction; RR) or type II (erythema nodosum leprosum; ENL) reactions. Type I reaction occurs in borderline patients (BT, midborderline and BL) whereas ENL only occurs in BL and LL forms. Reactions are interpreted as a shift in patients’ immunologic status. Chemotherapy, pregnancy, concurrent infections, and emotional and physical stress have been identified as predisposing conditions to reactions [51]. Both types of reactions have been found to cause neuritis, representing the primary cause of irreversible deformities.

Type I reaction is characterized by edema and erythema of existing skin lesions, the formation of new skin lesions, neuritis, additional sensory and motor loss, and edema of the hands, feet, and face, but systemic symptoms are uncommon. The presence of an inflammatory infiltrate with a predominance of CD4+ T cells, differentiated macrophages and thickened epidermis have been observed in RR. Type II reaction is characterized by the appearance of tender, erythematous, subcutaneous nodules located on apparently normal skin, and is frequently accompanied by systemic symptoms, such as fever, malaise, enlarged lymph nodes, anorexia, weight loss, arthralgia, and edema. Additional organs including the testes, joints, eyes, and nerves may also be affected. There may be significant leukocytosis that typically recedes after the reactional state. Presence of high levels of proinflammatory cytokines such as TNF-α, IL-6, and IL-1β in the sera of ENL patients suggests that these pleiotropic inflammatory cytokines may be at least partially responsible for the clinical manifestations of a type II reaction [52, 53].

12. Immunology of Leprosy Reactions

Type I reaction is a naturally occurring delayed-type hypersensitivity response to M. leprae. Clinically, it is characterized
by “upgrading” of the clinical picture towards the tuberculous pole, including a reduction in bacillary load. Immunologically, it is characterized by the development of strong skin test reactivity as well as lymphocyte responsiveness and a predominant Th1 response [54, 55]. RR episodes have been associated with the infiltration of IFN-γ and TNF-secreting CD4+ lymphocytes in skin lesions and nerves, resulting in edema and painful inflammation [56, 57]. Immunologic markers like CXCL10 are described as a potential tool for discriminating RR [58]. A significant increase in FoxP3 may augment the immune response towards the elimination of the pathogen and/or mediate the pathologic manifestations of the disease. TNF-α can be induced following stimulation of cells with total, or components of M. leprae, namely, lipoarabinomannan (the mycobacteria “lipopolysaccharide”-like component) a potent TNF inducer [66]. In addition, mycolyl-arabinogalactan-peptidoglycan complex of Mycobacterium species, the protein-peptidoglycan complex, and muramyl dipeptide all elicit significant TNF-α release [66].

References

Interdisciplinary Perspectives on Infectious Diseases


