ARTICLE

Are leprosy reactions autoinflammatory diseases?

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ABSTRACT

There are two types of leprosy reactions: reversal reactions or type 1 and erythema nodosum leprosum or type 2. Deformity and disability associated with leprosy are frequently the result of uncontrolled or untreated reactions. Although there is current availability of glucocorticoids as the mainstay of therapy, much needs to be learned about the etiology, risk factors, and pathogenesis of leprosy reactions. There is some evidence that leprosy reactions may represent, particularly, erythema nodosum leprosum autoinflammatory disease due to the aberrant activation of the innate immune system. The role for herpesviruses influencing autophagy in macrophages needs to be evaluated in the pathogenesis of leprosy reactions.

Key words: autoinflammatory, erythema nodosum leprosum, reactions, leprosy.

INTRODUCTION

Since the pioneer publication on a new classification of the immunological diseases by McGonagle and McDermott in 2006,[1] a substantial number of diseases are currently considered in the category of autoinflammatory diseases.[2] This group of diseases manifest with seemingly unprovoked periodic or relapsing episodes of tissue-damaging inflammation. Different from autoimmune diseases, autoinflammatory disorders are not characterized by high-titer of autoantibodies or antigen-specific T cells of classical autoimmunity.[1,2] Instead, self-directed inflammation led by innate immune cells (macrophages and polymorphonuclear cells) results in recurrent and often long-term sequelae in different target organs. Many of these diseases are the result of the interaction of environmental factors with polymorphisms of genes involved in the innate immune response to tissue damage or by external pathogens. Six different categories of auto-inflammatory diseases have been proposed including IL-1 activation disorders, NF-κβ activation syndromes, protein misfolding disorders, complement regulatory diseases, disturbances in cytokine signaling, and macrophage activation syndromes.[1] Through one of the above pathogenic mechanisms, disease results in a dysregulated inflammatory response leading to end organ damage. As a result of this new nosologic rubric, diseases such as hereditary angioedema, gout and crystalline arthropathies, Behcet's disease, Still's disease and many others have been grouped under the autoinflammatory disease banner.[2]

Leprosy and Leprosy Reactions

Leprosy is a chronic bacterial infectious disease caused by infection due to *Mycobacterium leprae* that affects mainly peripheral nerves and skin and sometimes the respiratory mucosa. It may present with a broad spectrum of bacteriological, immunological, and clinical features.[3,4] Additionally, during the course of *M. leprae* infection, many patients develop the sudden onset of acute inflammatory complications affecting the skin and nerves and other organs. These resemble autoimmune diseases, often requiring long-term anti-inflammatory therapy. These episodes, termed 'leprosy reactions', can occur prior to treatment, during treatment, of after treatment completion. Deformity and disability associated with leprosy are frequently the result of uncontrolled or untreated reactions.[4,5] There are two types of leprosy reactions: reversal reactions or type 1 and erythema nodosum leprosum (ENL) or type 2.[5]

Although there have been some attempts to use other immunosuppressive or immunomodulatory drugs, corticosteroids remain the standard of care for the acute symptoms of severe reactions with daily regimens tapered over a 3–6 month course.[4,5] The need for long-term corticosteroid

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use to control leprosy reactions is widely known among practitioners caring for patients with leprosy and is widely reported in the literature.[4] In fact, many patients require repeated treatment for multiple acute episodes or long-term corticosteroid use, particularly with type 2 reactions.[6] The clinical course in many patients resembles that of patients with episodes of relapsing inflammation of autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus. To demonstrate this clinical phenomenon, from January 2004 to July 2010 we provided care for 21 patients with a leprosy diagnosis. Of these patients, 11 were classified as lepromatous leprosy (borderline lepromatous or polar lepromatous) according to the Ridley-Joplin staging and all were treated with regimens consistent of daily rifampin, dapsone and clofazimine according to the recommendations of the National Hansen's Disease Program in the U.S. Duration of treatment ranged from 2 to 3 years in this group of patients. We follow our patients with improvement of clinical symptoms and performance of skin smears and skin biopsies. Among this group of patients, 9/11 (81%) developed type 2 reactions requiring long-term corticosteroid treatment. In only 2/9 patients, we were able to taper off steroids. The remaining patients (7/9) continue to receive prednisone at dosages varying from 5 mg to 20 mg daily due to recurrence of inflammation. This clinical dilemma generates frustration for the patient and the providers, particularly due to the occurrence of sometimes disabling side effects from the long-term use of corticosteroids such as diabetes mellitus, cataracts, osteoporosis, and others.

There is a need to rethink and apply modern approaches to address the substantial impact caused by leprosy reactions. The use of multidrug therapy (MDT) is crucial but has not proven to be the panacea as evidenced by the significant sequelae associated with dysfunction of the peripheral nerves inflicted by leprosy reactions.

Are Leprosy Reactions Autoinflammatory Diseases?

In the last few decades, there have been substantial improvements in the outlook of patients with leprosy after the advent of MDT and with the use of anti-inflammatory therapies.[4] As a result, the worldwide prevalence of the diseases has significantly decreased. Yet, leprosy continues to be a poorly understood illness and often the statistics do not capture the remaining disability and dysfunction even after completing MDT.

Therefore, the availability of MDT providing microbiological cure is insufficient to prevent nerve damage and sequelae associated with leprosy reactions. The killing of *M. leprae* with the use of MDT does not reverse existing nerve damage. Reactions occurring after completion of MDT may produce further nerve degeneration. The precise mechanisms leading to severe nerve damage during reactions remain to be fully elucidated. For decades, scientists have focused on attributing a cell-mediated T-cell response to type 1 reactions and, in the case of type 2 reactions, to the production and deposition of immune complexes. Data supporting this wide array of immune phenomena are available[3,4] but clearly do not provide a comprehensive picture that translates into management of existing cases.

We believe that an innovative approach should be undertaken to improve our understanding of leprosy reactions. Indeed, there is some recent evidence to suggest that leprosy reactions, particularly type 2 reactions, may fit into the immunopathogenic framework that underlines the autoinflammatory diseases. Searching for better diagnostic and therapeutic tools from this renewed approach may offer the opportunity to attract scientific attention and funding resources to solve the unanswered issues of the clinical conundrum surrounding leprosy reactions.

We suggest that infection with *Mycobacterium leprae* elicits, in some individuals, in addition to the underlying skin and nerves damage caused by *M. leprae* invading the endoneurium and Schwann cells, further recurrent activation of the innate immune system leading to further nerve and skin injury. Overwhelming and dysregulated activation of macrophages and neutrophils may result from the release of endogenous cellular contents from skin or nerve damage as a result of the presence of the bacteria in this tissue. Alternatively, persistent activation of the innate immune system by mycobacterium components (viable bacilli or nonviable bacilli in macrophages) eliciting and sustaining an exuberant inflammatory response triggered by pattern-associated molecular patterns (PAMPs).[2] In this manner, molecular interactions secondary to damage-associated molecular patterns (DAMPs) or PAMPs are recognized by pattern recognition receptors located in the cell membrane of neutrophils such as the toll-like receptors.[2] Recruitment of neutrophils to the skin and nerve can result in tissue injury by chronic deposition of immune complexes in tissues produced by the release of toxic oxygen intermediates and proteases. In patients with

type 2 reactions (ENL), polymorphonuclear cells are the signature cell identified causing the crops of new inflammatory skin lesions.[7]

Genetic variability may play a role in susceptibility to infection, clinical manifestations, and possibly to a risk of leprosy reactions. This genetic variability may lead to abnormal sensing of bacteria or to any of the pathogenic mechanisms involved in the classification of autoinflammatory diseases. According to a recent genomewide association study, there is evidence that susceptibility and clinical phenotype of leprosy derive from genetic variants of the innate immune system.[8] These findings support a two-step model for the development of leprosy in which successful infection of *M. leprae* is first established in genetically predisposed persons followed by clinical manifestation of disease influenced by the same or other host and environmental factors. Several of the proteins encoded by the genes identified in this study[8] are involved in microbial sensing and in the early innate immune inflammatory responses, specifically intracellular signaling pathways that prompt the activation of the transcriptional regulator nuclear factor (NF-κβ). This, in turn, stimulates the transcription of genes encoding the pro-inflammatory cytokines that ultimately leads to the activation of the acquired immune system.[7,9,10] Further research efforts are needed to link genetic variation among genes associated with the innate immune response and the risk of leprosy reactions.

Despite some achievements in the control of leprosy during the last few decades, it remains a public health and clinical challenge in many settings including the U.S.[4] Thus, we will continue in the future to deal with this infectious disease and the immunological disorders elicited by it. We urgently need a better understanding of this ancient disease with the use of modern technologies and application of innovative approaches. The term "leprosy reactions" need to be revisited based on existing scientific evidence and the need for further understanding of these largely unexplained immune phenomena.

Human infection caused by *M. leprae* provides a unique opportunity to link genetic and environmental factors involved in the innate and adaptive immune responses to an infectious pathogen leading to persistent immune activation, even when the bacterium is killed by antimicrobials. Considering leprosy reactions as immunological diseases under the auto-inflammatory banner is a good starting point that will likely provide future scientific and financial attention. We believe that this paradigm shift will eventually provide us with a better armamentarium of preventive and management strategies against leprosy reactions. At this point in time, leprosy (and leprosy reactions) needs not to continue to be a neglected infectious disease.

Competing interests: None to declare.

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