Transactions of the Royal Society of Tropical Medicine and Hygiene (2008) **102**, 329—337

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevierhealth.com/journals/trst

REVIEW

Towards understanding the pathology of erythema nodosum leprosum

I.P. Kahawita*, D.N.J. Lockwood

Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

Received 12 December 2007; received in revised form 14 January 2008; accepted 14 January 2008

KEYWORDS
Leprosy;
Erythema nodosum leprosum;
Immune complexes;
Cytokines;
Cell-mediated immunity;
Pathology

Summary Erythema nodosum leprosum (ENL) is an immune-mediated complication of leprosy presenting with inflammatory skin nodules and involvement of multiple organ systems, often running a protracted course. Immune complex production and deposition as well as complement activation have long been regarded as the principal aetiology of ENL. However, new data show that cell-mediated immunity is also important. We have performed a critical analysis of studies on the pathology of ENL. Our main findings are as follows. ENL is characterised by an inflammatory infiltrate of neutrophils with vasculitis and/or panniculitis. There is deposition of immune complexes and complement together with *Mycobacterium leprae* antigens in the skin. Changes in serum levels of Igs indicate a transient, localised immune response. The major T-cell subtype in ENL is the CD4 cell, in contrast to lepromatous leprosy where CD8 cells predominate. The cytokines TNFα and IL-6 are consistently found whilst IL-4 is low or absent in ENL lesions, indicating a T_H1 type response. Keratinocyte 1a and intercellular adhesion molecule-1 (ICAM-1) have been shown to be present in the epidermis in ENL, which is evidence of a cell-mediated immune response. Co-stimulatory molecules such as B7-1 have also been studied but further work is needed to draw strong conclusions. We also highlight potential areas for future research.

1. Introduction

Erythema nodosum leprosum (ENL) is a serious, difficult to manage inflammatory complication of lepromatous (LL) or borderline lepromatous (BL) leprosy, manifesting as crops of painful, erythematous nodules with fever, malaise and inflammation elsewhere producing iritis, arthritis, neuritis and lymphadenitis. ENL may occur before, during or after treatment with multidrug therapy but in most patients ENL occurs during the first year of treatment (Becx-Bleumink and Berhe, 1992; Manandhar et al., 1999; Pocaterra et al., 2006). It often has a protracted course with episodes occurring over 7 or more years, although the majority last 12—24 months (Kumar et al., 2004; Pocaterra et al., 2006). Although the number of leprosy cases has decreased worldwide, the reac-

* Corresponding author. Tel.: +44 20 7612 7863; fax: +44 20 7637 4314.
E-mail address: indira.kahawita@gmail.com (I.P. Kahawita)

0035-9203/$ — see front matter © 2008 Royal Society of Tropical Medicine and Hygiene. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.trstmh.2008.01.004

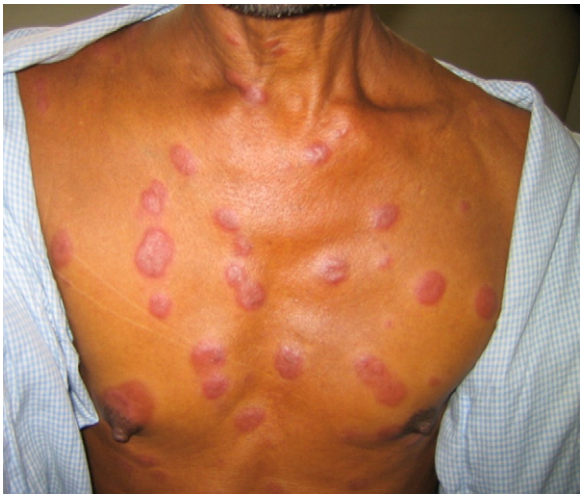

Figure 1 Skin lesions of erythema nodosum leprosum.

tions that complicate leprosy remain an important clinical problem. Patients with ENL may now present to general physicians and it is important that doctors in a wide range of specialties can recognise this entity.

Immune-mediated reactions in mycobacterial diseases are now being recognised to a wide range of mycobacteria, not just *Mycobacterium 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 (Lipman and Breen, 2006; Ustianowski et al., 2006). It is therefore useful to review the pathology of ENL since there are aspects that will be applicable to other diseases.

ENL is classically seen as an immune complex-mediated phenomenon but recent data suggest that cell-mediated immune responses play an important role. Understanding the pathogenesis will promote further research into the development of better, safer and more effective treatment.

We have critically reviewed the current data on the pathology of ENL and also highlight where further research is needed.

The search strategy used was a PubMed search with the terms 'leprosy', 'ENL', 'histopathology', 'immunohistochemistry', 'immune complexes', 'cytokines', 'B lymphocytes', 'MMP' and 'risk factors' in varying combinations. Only English language articles were selected. Some cross-references from articles retrieved from the PubMed search were also used. All searches were complete to the end of September 2007.

2. Erythema nodosum leprosum (type 2 reactions)

ENL (or type 2 leprosy reactions) is an immune-mediated phenomenon occurring in patients with LL or BL leprosy. The reaction causes acute inflammation in any organ or tissue invaded by the leprosy bacillus (Pfaltzgraff and Ramu, 1994).

The skin lesions present as erythematous, tender papules or nodules that may be superficial or deep seated (Figure 1). The lesions differ clinically from erythema nodosum by their evanescent nature, large number of lesions and widespread distribution beyond the lower legs (Pfaltzgraff and Ramu, 1994). In severe reactions, skin lesions may become vesicular, bullous or necrotic (Jopling and McDougall, 1988).

Table 1 Clinical features of erythema nodosum leprosum

- Painful, tender, erythematous skin nodules appearing in crops
- Generalised illness with fever and malaise
- Neuritis, less severe than type 1 reactions
- Iritis, episcleritis or conjunctivitis
- Orchitis
- Tender, generalised lymphadenopathy
- Arthritis or arthralgia
- Bone pain and tenderness, especially tibial tenderness
- Dactylitis
- Oedema of the extremities
- Transient proteinuria
- Exacerbation of upper respiratory symptoms

ENL reaction usually produces a generalised illness with high fever, systemic upset, oedema of the face, hands and feet, and proteinuria (Table 1). Other manifestations include iritis, episcleritis, arthritis, arthralgia, dactylitis, lymphadenopathy, organomegaly and orchitis (Figure 2) (Pfaltzgraff and Ramu, 1994). Neuritis may be part of ENL but is often milder than that seen in type 1 reactions.

There are no good quality contemporary studies on the effect of ENL on the liver (Cook and Corachan, 1982; Kumar et al., 1987). The only significant abnormality in renal function found in patients with ENL compared with LL patients without ENL is impaired creatinine clearance (Bajaj et al., 1981).

The majority of patients with ENL experience multiple acute episodes or chronic ENL lasting more than 6 months (Pocaterra et al., 2006). ENL can have a protracted course lasting several years (Kumar et al., 2004). It is usually diagnosed clinically but a skin biopsy can be helpful. Corticosteroids are the mainstay of treatment (Girdhar et al., 2002; WHO, 1998) but many other alternatives are used (Burte et al., 1983; Helmy et al., 1971; Moreira et al., 1998; Sales et al., 2007; Villahermosa et al., 2005). Thalidomide

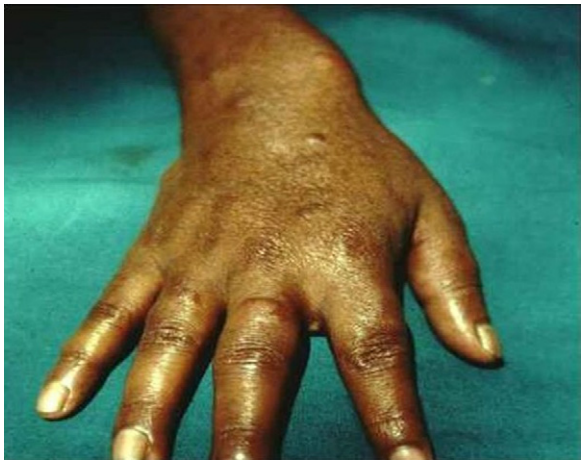

Figure 2 Hand showing dactylitis and nodules.