Late Leprosy Reaction Presenting as Erythema Multiforme-Like Erythema Nodosum Leprosum with Underlying Rifampicin Resistance and its Potential Implications

Kabir Sardana1, Anita Kulhari2, Sinu Rose Mathachan2, Ananta Khurana2, Prekshi Bansal2, Arvind Ahuja3, Mallika Lavania3, Madhvi Ahuja3

1Department of Dermatology and STDs, Dr. RML Hospital and PGIMER, Departments of 2Dermatology and STDs and 3Pathology, Dr. RML Hospital and ABVIMS, New Delhi, India

Abstract

Erythema multiforme (EM)-like erythema nodosum leprosum (ENL) is a rare atypical presentation, and its late appearance after the completion of multidrug therapy (MDT) is unusual. We describe the case of a lepromatous leprosy patient who after the completion of MDT presented to us with late EM-like ENL and was found to be resistant to rifampicin. We discuss the implications of this finding and the potential role of resistant bacilli in causing reactions with atypical presentations.

Keywords: Erythema multiforme like, erythema nodosum leprosum, leprosy, multibacillary, multidrug therapy, real-time PCR, resistance, steroids

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Introduction

While Type 2 reactions have been reported routinely during multidrug therapy (MDT), late leprosy reactions, especially late Type 2 reactions (erythema nodosum leprosum [ENL]), are uncommon. In fact, the published literature on reactionary states in multibacillary (MB) patients consequent to the completion of MDT are uncommon.1 The few studies on this topic have found that the majority of cases are of Type 1 reaction.2-4 While various theories have been propounded for the occurrence of ENL, it is pertinent to note that it generally occurs during the rapid killing of bacilli from effective chemotherapy, and like other antigen-antibody complex diseases, it occurs particularly in a state of antigen excess.5-8 Our patient presented to us with atypical “erythema multiforme (EM)-like” ENL 1 year after the completion of MDT, and based on two previous cases,9,10 we evaluated the patient for resistance. We detail our observations and the implications of our findings in the prevalent treatment of ENL.

Case Report

A 40-year-old male, a known case of lepromatous leprosy treated with MB-MDT for 2 years, presented to us after an asymptomatic period of 1 year with the acute eruption of crops of multiple painful evanescent red-raised targetoid lesions associated with fever, myalgias, and conjunctival congestion. The lesions appeared initially on the upper limbs and progressed to lower limbs, trunk, back, face, and ears. While smaller lesions coalesced to form larger ones, few subsided on their own leaving behind pigmentation. Subsequently, vesicles started developing over the newly appearing lesions on the upper limb and back. There was no history of recent illness, trauma, surgery, or drug intake. Cutaneous examination revealed multiple tender erythematous plaques with well-defined raised outer margins and central dusky hue giving a targetoid appearance, present over the neck, trunk, all four limbs, and buttocks [Figure 1].

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Address for correspondence: Dr. Anita Kulhari,
Department of Dermatology and STDs, Dr. RML Hospital and ABVIMS,
New Delhi-110001, India.
E-mail: anitakulhari2008@gmail.com

ORCID:
Anita Kulhari: https://orcid.org/0000-0001-6229-7194

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Few plaques on the left flank showed vesiculation. Bilateral radial, ulnar, radial cutaneous, and lateral popliteal nerves were enlarged, firm, and nontender. Bilateral posterior tibial nerves were enlarged and firm with Grade 2 tenderness. Deep tendon reflexes were normal.

On investigation, slit-skin smear from the left ear, left eyebrow, and a plaque showed bacteriological index (BI) of 1+, 0, and 1+, respectively, with presence of granular bacilli. Skin biopsy taken from an early lesion showed an unremarkable epidermis with pandermal perivascular, periadnexal, periappendageal, and perineural lymphohistiocytic infiltrate, with many foam cells, extending to superficial subcutis with vessel walls showing neutrophilic infiltration suggestive of vasculitis [Figures 2 and 3]. Fite stain was negative. Based on the clinical appearance, systemic symptoms, and classical histopathological picture, a diagnosis of EM-like ENL was made. Treatment was initiated with prednisolone 60 mg/day. While the existing lesions began to heal with decreasing erythema, edema, and tenderness, the patient continued to develop 6–7 new evanescent painful papules and nodules every day initially. Gradually, over the course of his hospital stay, however, the lesions subsided. He was discharged on prednisolone 40 mg with clofazimine 50 mg daily.[7] The resistance testing revealed a mutation in the rpoB gene with a change in amino acid threonine to isoleucine at codon position 433 (Thr433Ile) and 441 (Asp441Tyr) indicating rifampicin resistance [Figure 4]. A viability-based assay targeting the 16S rRNA gene region using real-time Polymerase chain reaction (PCR) showed amplification after 33 cycles possibly due to the low BI (BI = 0.66+).

**Discussion**

ENL is a Type 3 hypersensitivity reaction caused by antigen-antibody complex deposition and can have rare atypical presentations. Conventional teaching has been that a high BI is a risk factor for the development of ENL which strongly suggests that the process is antigen driven. In most cases, no definite cause can be found, and the reaction is believed to be seen when the bacilli are granular and thus is a consequence of antigenic excess due to the bacillary load.[8] Late reactions have been reported after 2 years of MDT, with reversal reactions occurring in 1%–9% of patients and ENL
in 3% of patients, which is generally mild.\cite{9-11} In our case, the ENL was atypical with an “EM-like” morphology. In our case, the patient had a low BI, and no trigger factor could be elicited. Thus, based on a previous case of chronic ENL,\cite{6} who tested positive for rifampicin resistance gene mutation, we replicated this test in our case and discovered rifampicin resistance [Figure 2].

What is alarming is that in an era where reactions, neuritis, and disability are the primary concerns, the reduction of the duration of regimen of MDT to 1 year has been suggested by the World Health Organization (WHO), but there are instances where reactions can occur after this fixed duration therapy. A more pertinent issue is that the treatment of reactions is primarily corticosteroids with occasional use of adjuvant immunosuppressive drugs. We feel that cases of chronic and persistent severe reactions are an emergent indication for resistance testing,\cite{5,6} as this can enable a logical intervention of second-line drugs, instead of steroids, which can predispose to both reactivation of the disease, spread of resistant strains, and relapses. Herein, we may emphasize that in our case due to the low concentration of cDNA, the threshold cycle (Ct) value was 33 cycles which is due to the low bacterial load (BI of 0.77), and this corresponds to an approximate 515 copies of *Mycobacterium leprae* specific repetitive element gene and 62fg *M. leprae* DNA.\cite{12}

The patient was subsequently administered second-line therapy as proposed by the WHO,\cite{13} our case, in conjunction with previous reports,\cite{5,6} suggests that resistance can explain some cases of reactions and can also explain the lack of control of chronic ENL cases with conventional treatments. To arrive at a firm conclusion of this hypothesis, a larger study from leprosy endemic countries is needed to highlight the role of resistance as a potential cause for leprosy reactions.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**