Reversal reaction and Mitsuda conversion in polar lepromatous leprosy: a case report

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Summary A 22-year-old male polar lepromatous leprosy patient who became Mitsuda positive after 36 months of multidrug therapy (MDT) is reported. Lepromatous leprosy (LL) is a state of specific immunosuppression and is invariably irreversible. The finding of Mitsuda positivity in histopathologically proven polar lepromatous leprosy is extremely uncommon, and conversion of lepromin status following MDT has not so far been reported. This case report confirms the observations made by Waters et al.1 regarding lepromin conversion in lepromatous patients.

Case report

A 22-year-old male patient attended the hospital in 2000 with complaints of multiple nodular lesions all over the body for the past year and loss of sensation over both feet for the past 6 months. On examination, he had multiple, soft, papulonodular lesions symmetrically distributed all over his body. The face looked shiny and had minimal madarosis. There were nodular lesions over both the ear helices as well as the chin (Figure 1). The skin in between the nodules was thickened. Loss of sweating was present almost all over the body except for the axillae, where compensatory hyperhidrosis was clearly evident. Soles were dry and fissured. Bilateral radial and lateral popliteal nerves were thickened and non-tender.

Skin smears done from routine sites found an average bacterial index (BI) of 5.25 + and a morphological index (MI) of 1.25%. Skin biopsy done from the left buttock revealed an atrophic epidermis with flattened rete ridges. A clear zone was present separating the granuloma from the epidermis. In the dermis, granuloma composed of macrophages and histiocytes replaced most of the dermis, with a granuloma fraction of 70% (Figure 2). Acid-fast stained sections showed bacilli to a load of 5 + . Lepromin test done with 0.1 ml of lepromin (H) was negative at 21 days clinically and a biopsy taken from the lepromin test site showed only a small focal collection of foamy macrophages along with lymphocytes occupying 30% of the dermis. Acid-fast stained sections showed bacilli in macrophages confirming a negative lepromin reaction.

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Following all the clinico-immunopathological evaluations, the patient was classified as a case of polar lepromatous leprosy. He received treatment in the form of rifampicin 600 mg once a month, clofazimine 300 mg once a month and 100 mg daily along with dapsone 100 mg daily (MDT) for 36 months. At the time of release from treatment, the patient had diffuse involvement of the face with a thick, shiny infiltrated skin. Nodules over his face were

Figure 1. Photograph showing a lepromatous leprosy patient with diffuse infiltration of the face, ear lobes and chin with few papulonodular lesions on the chin.

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Figure 2. Photomicrograph to show a sheet of macrophages in the dermis separated from the flattened atrophic epidermis by a clear zone, a typical feature of lepromatous leprosy. (H&E × 600).
decreased in size and number and the ear lobules were wrinkled. Bilateral ulnar and lateral popliteal nerves were enlarged and his BI remained at 4+.

A year later, the patient revisited the hospital with multiple papuloplaque lesions over the trunk and limbs of 6 months duration. On examination, he had multiple, hypopigmented, infiltrated plaques over the trunk and limbs varying in size from 3 × 3 cm to 5 × 4 cm. The surface was smooth. Margins were ill to well defined. Multiple papulonodular lesions were present over the ear margins. Bilateral ulnar and lateral popliteal nerves were enlarged. There was sensory loss confined to the distal extremities. Visible deformities were not present. Clofazimine-induced pigmentary changes were obvious in both the legs as well as the lateral aspect of the arms. Skin smear done from routine sites showed an average BI of 1+. Skin biopsy taken from the hypopigmented lesion on upper back showed focal granulomas composed of numerous epithelioid cells, scattered Langhan’s giant cells and lymphocytes around adnexal structures destroying most of them (Figure 3). There was significant tissue oedema and fibrosis. Acid-fast stained sections showed no bacilli. Features were suggestive of borderline tuberculoid leprosy with type I reaction. Lepromin test done again with 0.1 ml lepromin (H) and read after 3 weeks showed an induration of 4 mm. Biopsy of the test site showed dermal granulomas composed of epithelioid cells, few poorly formed Langhan’s giant cells and perivascular and periannexal lymphocytic infiltrate (Figure 4). The features were consistent with a positive lepromin reaction. The dermal nerves showed significant intra and perineural lymphocytic infiltration. The lymphocytic response was moderate to good with a granuloma fraction of 40%. Acid-fast stained sections showed bacilli within the granulomas.

Discussion

In lepromatous leprosy, there is specific immunosuppression, which once attained, is normally irreversible. This is proven by (a) persistent lepromin negativity, (b) non-responsiveness of
lymphoproliferative assays against *Mycobacterium leprae* and (c) the persistence of negative skin test responses to *M. leprae* soluble cytoplasmic antigens. The Mitsuda test,\(^3\) which measures the specific immune response against intradermally injected lepromin, has a high prognostic value for susceptibility or resistance to infection by *M. leprae*. The general consensus regarding polar lepromatous patients classified according to the Ridley–Jopling scale\(^4\) is that they start as Mitsuda negative and remain Mitsuda negative life-long. The rare claims of lepromin conversions on attainment of clinical inactivity in the pre-sulphone era almost certainly refers to borderline cases and reflects the lack of precision in classification at that time.\(^5\) Waters *et al.*\(^2\) observed lepromin negativity in LL patients whom they followed up for 10–12 years after anti-leprosy therapy with dapsone. The same authors in a later report\(^1\) found an increase in the intensity of lepromin reaction in 50% of their lepromatous leprosy patients after 22 years of follow-up. Hasting and Job\(^6\) experimented with transfer factor in polar lepromatous patients who had clinico-histopathological evidence of reversal reactions, suggesting a partial restoration of the immunologic deficit in these patients.

It is possible that there are two groups of LL patients. In one group, lepromin remains negative, as they are anergic to the antigen of *M. leprae* from their inception. They belong to the primary LL group and genetic predisposition may play a role in their pathogenesis. It is reported that the *NRAMP1* gene plays a regulatory role in the development of acquired antimycobacterial immune responses as determined by in vivo Mitsuda test reaction in a group of Vietnamese patients.\(^7\) The other group is the secondary LL patients, who initially belong to the borderline group and during the course of the disease downgrade to LL leprosy. Such patients, following anti-leprosy therapy, may revert to borderline spectrum and give a positive lepromin response.

The patient under report may belong to the secondary LL group and became Mitsuda positive within 4 years of starting multidrug treatment. Compared with the observations of Waters *et al.*,\(^1\) lepromin conversion took place rather fast in this patient (4 years versus 22 years).

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**Figure 4.** Photomicrograph from the lepromin test site showing dense collections of lymphocytes with focal areas of epithelioid cell collection indicating a positive lepromin reaction (H&E × 300).
Another interesting observation is the reversal reaction that occurred in the patient, resulting in significant reduction in BI from $4^{+}$ to $1^{+}$ in 1 year and presence of granuloma composed of epithelioid cells and giant cells. The possible partial immunorestorative function of MDT itself in such patients should be considered, though large-scale studies are indicated to prove it beyond any reasonable doubt.

References