Drug resistance to rifampicin in a case of steroid-dependent erythema nodosum leprosum and the therapeutic implications of resistance and reactions in leprosy

Dear Editor,

A 30-year-old male, who was a treated case of lepromatous leprosy (LL), presented with recurrent severe episodes of erythema nodosum leprosum (ENL) for 5 months, 15 months after completing a 2-year course of multibacillary multidrug therapy (MBMDT). He had a baseline bacillary index (BI) of 6+ and suffered multiple episodes of ENL during his initial treatment course as well, necessitating multiple courses of prednisolone (1 mg/kg/day). A slit skin smear (SSS) done at the end of 12 months MDT revealed a BI of 3+. The current ENL episode was associated with neuritis (involving bilateral ulnar nerves and posterior tibial nerves) with an ENLIST (Erythema Nodsum Leprosum International Study) ENL severity score of 10 (includes 10 items [pain, fever, number, inflammation, and extent of ENL lesion, peripheral edema, bone pain, lymphadenopathy, neuritis, joint pain] each having a score ranging from 0–3). The skin biopsy was consistent with ENL and the fite stain showing fragmented bacilli (BI: 3–4+). No trigger factor could be found on investigation, and drug sensitivity testing was undertaken for mutations in rpoB, folP, and gyrA genes and revealed a mutation in rpoB at codon 456 (Ser456Leu) (Fig. 1).

As the patient was self-medicating with prednisolone 20 mg intermittently for 5 months with minimal response, he was switched to methylprednisolone 32 mg daily along with methotrexate 7.5 mg once a week. Consequent to the resistance report, second-line alternate anti-leprosy therapy (ALT) comprising of minocycline 100 mg/day, clofazimine 50 mg/day, and ofloxacin 400 mg/day was initiated following which the dose of steroid could be gradually tapered to 8 mg/day over a period of the next 2 months, while methotrexate was increased to 10 mg/week. Notably, the patient had unilateral neuritis which did not respond adequately, hence methotrexate was stopped, and he was initiated on thalidomide 50 mg daily along with methylprednisolone 8 mg alternate day, a dose on which he is now well controlled. He has now completed 5 months of ALT.

The focus of resistance surveillance studies so far has been on relapsed cases, with the complete exclusion of reactions in the study group which contrasts with the rising reports of resistance associated with reactions—both ENL and type 1 reaction (T1R) (Table 1).

Most cases of chronic ENL do not consistently respond to steroids or the immunosuppressive drugs administered. Walker et al. noted that ENL is “chronic” in the majority of patients (70.7%), which necessitates prolonged doses of steroids, thus leading to steroid dependence and side effects. Thus, an attempt must be made to look for triggers for ENL which can help to modulate the treatment without prolonged steroid administration. The various triggers reported include intercurrent infection, injury, surgery, physical/mental stress, immunizations, a strongly positive Mantoux test, pregnancy and parturition, potassium iodide and antileprosy drugs, and possibly drug resistance. Common infections causing Type 2 reaction include oral infections, urinary tract infections, sinus infections, respiratory tract infections, hepatitis B and C, malaria, and filariasis.

The average MI in patients of ENL ranges from 0.7 to 25 (mean MI of 8.5) with a decreasing severity of ENL associated with a lower mean MI. Thus, a high bacterial load and
Table 1 Summary of existing reports of resistance with mutations in rpoB gene in leprosy reactions and their treatment outcomes

<table>
<thead>
<tr>
<th>Author et al.2</th>
<th>Diagnosis</th>
<th>Initial treatment</th>
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<th>Management after resistance testing</th>
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<tr>
<td>Sinha et al.2</td>
<td>BT to BL with Type 1 downgrading reaction</td>
<td>Started MBMDT and oral prednisolone 40 mg once daily</td>
<td>rpoB gene mutation: Ser456Leu</td>
<td>Second line ALTc</td>
<td>Drug resistance and viable bacilli could be a possible cause of downgrading T1R</td>
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<tr>
<td>Arora P et al.4</td>
<td>LL with recurrent ENL</td>
<td>Prednisolone 1 mg/kg of body weight along with clofazimine 100 mg followed by flare on tapering steroids</td>
<td>rpoB gene mutation: Ser456Leu</td>
<td>Second line ALTc</td>
<td>Patient with repeated reactions refractory to conventional therapy should be tested for resistance</td>
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<td>Sardana et al.3</td>
<td>Late ENL (EM-like) LL leprosy treated with MBMDT x 2 year</td>
<td>Prednisolone 60 mg/day Patient continued to develop 6–7 new ENL lesions every day initially</td>
<td>rpoB gene mutation: Ser437Gln</td>
<td>Rapid control of ENL and fast tapering of steroids</td>
<td>Chronic, atypical, and severe reactions are an emergent indication for resistance testing</td>
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<tr>
<td>Sardana et al.5</td>
<td>Late reversal reaction (LL treated with MBMDT 12m)</td>
<td>Prednisolone 40 mg with a gradual tapering of the dose over 4 weeks</td>
<td>rpoB gene mutation: Thr433Ile</td>
<td>Second line ALTc</td>
<td>Monotherapy with steroids in late reactions should be preceded by resistance testing</td>
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<td>Our case</td>
<td>LL with recurrent ENL during and after MBMDT</td>
<td>Prednisolone 0.5 mg/kg/day during MDT T, methylprednisolone, methotrexate after RFT for late ENL</td>
<td>Rifampicin resistance detected after RFT</td>
<td>Second line ALTc</td>
<td>Underlying resistance can be a cause of recurrent ENL</td>
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bNew MB case with BI >2, late, atypical and chronic reactions refractory to treatment.
cMinocycline 100 mg/day, clofazimine 50 mg/day, and ofloxacin 400 mg/day for 6 months (intensive phase), and ofloxacin 400 mg/day and clofazimine 50 mg/day for the next 18 months (maintenance phase).

consequent antigenic load can lead to ENL, and recurrences occur till the antigen is cleared. This is supported by the higher reported incidence of ENL in the pre-MDT era (50% of LL and 25% of borderline leprosy [BL]) than after widespread MBMDT coverage (28% in LL and 7.5% in BL cases). Although clofazimine has been presumed to be the reason for this, the disappointingly low efficacy of the drug in preventing ENL as reported in a recent trial does not support this view. Thus MBMDT which facilitates rapid bacterial clearance, compared to dapsone monotherapy, is largely instrumental in lowering the risk of ENL. Notably viable bacilli can trigger T1R (both downgrading and upgrading reactions) apart from ENL. Thus, if rifampicin resistance is suspected in leprosy reactions, administration of an alternate leprosy regimen can achieve a faster reduction in bacterial load and early smear negativity, thus controlling reactions and enabling rapid tapering/stopping of steroid, consequently avoiding steroid side effects (Table 1). Continuation of MBMDT in such cases with steroids and immunosuppressive agents (ISA) (which is the norm in severe reactions) would lead to a compromised host immune response, and the live resistant bacilli can potentially multiply and spread to the community. Pertinently we have observed that changing the treatment regimen does not always lead to dramatic resolution of reactions as both ofloxacin and minocycline kill 99.99% of bacilli only after 28–56 days.

While our case adds to the select reports of rpoB gene mutation as a possible trigger factor in reactions (ENL, and T1R downgrading and upgrading) (Table 1), a prospective case-control study comparing the prevalence of resistance in reactive versus non-reactional leprosy patients is the need of the hour to confirm this association.

Acknowledgments

This work is part of an ongoing project on the study of resistance genes in leprosy reactions using PCR to target rpoB, folP1, and gyrA in collaboration with the Stanley Browne Laboratory, New Delhi, India.
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