INTRODUCTION

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* that primarily affects the skin and the peripheral nerves. The World Health Organization (WHO) recommended chemotheraphy for leprosy, the multidrug therapy (MDT) for both pauci- and multi-bacillary (PB and MB) disease, is well tolerated and well accepted. It has greatly helped in controlling the disease. Three standard first-line drugs – rifampicin, clofazimine, and dapsone – are used in the multidrug regimes.[1] However, not all patients can be treated with these regimens and alternate therapies are required occasionally. One such condition is hepatitis, which precludes the use of rifampicin and dapsone. The WHO has recommended an alternative therapy with clarithromycin, ofloxacin, and clofazimine as a hepatosafe regimen.[2] Herewith, we present an unusual alternative for treating a leprosy case with hepatitis.

CASE REPORT

An 18-year-old male student from Mumbai presented with hypopigmented, hypoesthetic patches on the face and back since 11 years, with a worsening right partial claw hand since 2 years [Figures 1 and 2]. The patient consulted a private practitioner, who diagnosed him as a case of leprosy in reaction, and started him on MB-MDT along with tapering doses of prednisolone (from 60 mg). However, within 2 weeks of starting treatment, the patient experienced diarrhea and vomiting with yellowish discoloration of eyes. He was then diagnosed as a case of drug-induced hepatitis. The MB-MDT and prednisolone were stopped. This was 2 months prior to presentation and the patient had taken no treatment since then.

Clinical examination findings were consistent with the diagnosis of borderline tuberculoid Hansen’s Disease in Type 1 reaction. All the routine investigations were within normal limits. The slit skin smear was negative and histopathology of the skin lesion revealed epithelioid cell granulomas with few Langhans’ giant cells with dermal edema, thus confirming the diagnosis of borderline tuberculoid Hansen’s in Type 1 reaction.

The patient was restarted on MB-MDT along with gradually tapering doses of prednisolone (from 40 mg). Liver function test (LFT) was done on the 2nd day and 10th day considering past history of drug-induced hepatitis, and his transaminases, especially alanine transferase (serum
glutamic pyruvic transaminase) was found to be raised more than 2.5 times the upper limit of normal [Table 1]. The patient was then diagnosed as a case of dapsone-induced hepatitis and the patient was advised to continue monthly rifampicin and daily clofazimine with prednisolone in tapering doses. The patient was followed up after 30 days with severe nausea and frank icterus and was admitted under a physician’s care. He was then diagnosed as a case of chronic active hepatitis, either drug-induced or autoimmune and was investigated for the same. The transaminases were raised [Table 1]. The viral hepatitis markers were negative. Antinuclear antibodies, anti-Smith antibodies, and anti-liver kidney microsomal Type 1 antibodies done to rule out autoimmune hepatitis were negative. Liver biopsy was done to estimate the copper content, which was within normal limits ruling out Wilson’s disease. The patient was shifted onto a hepatosafe alternative regimen of daily clofazimine 50 mg with clarithromycin 500 mg and ofloxacin 400 mg, as is recommended by the WHO and Indian Association of Leprologists.

This regimen was continued for 2 months with regular monitoring of LFT, which remained persistently deranged [Table 2]. It was then decided to start a monthly regimen which would allow the liver time to recover. Hence finally, monthly rifampicin, ofloxacin, and minocycline (ROM [rifampicin 600 mg + ofloxacin 400 mg + minocycline 100 mg]) pulse regime, which has already been recommended by the WHO for leprosy,[3] was started. Surprisingly, the patient’s raised LFTs steadily normalized after that [Tables 2 and 3]. The patient completed 24 monthly ROM pulses uneventfully and has shown definite clinical improvement without any further liver function alterations. The monthly ROM was stopped after 24 pulses. Slit skin smear and skin biopsy were done after stopping the ROM therapy. Slit skin smear was negative whereas skin biopsy revealed epidermal thinning with focal loss of rete ridges, periadnexal, and perivascular sparse lymphocytic infiltrate with few epithelioid cells.

| Table 1: Depicting the rise in Liver function tests on starting MBMDT |
|-----------------|---|---|---|---|
| Date            | Bil | SGOT | SGPT | Treatment                                      |
| January 30, 2013| 0.4 | 28   | 35   | Tapering doses of prednisolone from 40 mg, MBMDT |
| 2nd day         | 0.6 | 31   | 47   | Tapering doses of prednisolone from 40 mg, MBMDT |
| 10th day        | 0.9 | 102  | 660  | Dapsone stopped, daily clofazimine and monthly rifampicin continued along with prednisolone |
| After 1 month   | 0.6 | 340  | 532  | Clofazimine and rifampicin stopped Prednisolone continued |

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, MBMDT: Multibacillary multi-drug therapy

| Table 2: Depicting the decrease in Liver function tests on starting ROM therapy |
|-----------------|---|---|---|---|
| Date            | Bil | SGOT | SGPT | Treatment                                      |
| 3 months after stopping rifampicin and clofazimine | 0.4 | 84   | 225  | Daily clarithromycin + ofloxacin + clofazimine started Prednisolone continued |
| 2 months after clarithromycin + ofloxacin + clofazimine | 0.4 | 232  | 427  | Clarithromycin + ofloxacin + clofazimine stopped Prednisolone continued |
| 1 month after stopping clarithromycin + ofloxacin + clofazimine | 190 | 440  |      | Monthly ROM pulses started                      |
| 7 months after starting Monthly ROM pulses | 0.4 | 35   | 38   | Monthly ROM pulses continued                    |

ROM: Rifampin, ofloxacin, and minocycline, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase
in the dermis and with no evidence of granuloma with a negative Fite stain.

DISCUSSION

The first-line drugs used in the multidrug treatment regimens of leprosy include rifampicin, clofazimine, and dapsone. The standard adult treatment regimen for MB leprosy (MB-MDT) is rifampicin (600 mg once a month), clofazimine (300 mg monthly and 50 mg daily), and dapsone (100 mg daily) for a total duration of 12 months. PB-MDT includes rifampicin (600 mg once a month) and dapsone (100 mg daily) for a total duration of 6 months.[2]

Of these drugs, rifampicin and dapsone are hepatotoxic. As per the WHO recommendations in the hepatosafe regimen, rifampicin can be substituted with daily ofloxacin and minocycline or clarithromycin if patients develop intolerance, intercurrent diseases such as chronic hepatitis, or are infected with rifampicin-resistant M. leprae. The duration of treatment with this regime is 24 months with the initial intensive phase of 6 months consisting of daily clofazimine, ofloxacin, and minocycline or clarithromycin. The 18-month maintenance consists of daily clofazimine and ofloxacin or minocycline.

In patients intolerant to dapsone, as per the WHO recommendations, no further modification of the regimen apart from withholding dapsone is required for patients with MB leprosy. In case of PB leprosy, however, clofazimine – in the dosage used in the standard MB-MDT – is to be substituted for dapsone, in the 6-month treatment regimen.[2]

In our patient, we had stopped dapsone initially and then rifampicin in view of hepatotoxicity and started the WHO-recommended hepatosafe regimen. However, our patient’s increased LFTs showed persistent derangement. Although clarithromycin, ofloxacin, and clofazimine can cause hepatotoxicity, this is not as common. Clarithromycin is eliminated by renal and nonrenal mechanisms. It is metabolized in the liver to several metabolites, the active 14-hydroxy metabolite being most significant. The elimination half-lives are 3–7 h for clarithromycin and 5–9 h for 14-hydroxyclarithromycin. Metabolism is saturable with longer half-lives observed after larger doses.[4] Clofazimine is highly lipophilic and concentrates in lipid-rich tissues, especially reticuloendothelial tissues including liver. The drug is metabolized in the liver and has a half-life of approximately 70 days. Clofazimine-induced hepatotoxicity is very rare.[5] Ofloxacin is predominantly metabolized in kidney.[6] Hence, two drugs of this regimen, i.e. clarithromycin and clofazimine, are metabolized, partially or completely, in the liver. These drugs have a longer half-life and hence, it is possible that daily intake of these medications resulted in persistent hepatitis. In contrast, rifampicin and minocycline of the ROM regime are significantly metabolized in the liver and are also the common causes of drug-induced hepatotoxicity. However, rifampicin induces its own metabolism and shortens its half-life to 2–3 h.[7] Minocycline has a half-life of 11–22 h and its half-life is not prolonged in patients with hepatic failure.[3,6] It is possible that due to monthly administration and comparatively shorter half-lives of these molecules, the resultant metabolism did not worsen the hepatitis, allowing the hepatocytes time to recover and hence resulting in the normalization of transaminase levels in our patient over time.

Through this case, we would like to put forth that even the hepatosafe regimen of clofazimine, clarithromycin, and ofloxacin may exacerbate hepatitis. In such cases, one can consider once-monthly rifampicin, ofloxacin, and minocycline. Further trials would be necessary to validate the place of monthly rifampicin, ofloxacin, and minocycline as a hepatosafe alternative.

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Conflicts of interest
There are no conflicts of interest.

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