Case Report

Treatment of multibacillary leprosy following the development of dapsone hypersensitivity syndrome

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Abstract

Background: World Health Organization (WHO) multi-drug therapy (MDT) is the current standard treatment for leprosy. A wide range of frequency of adverse effects caused by MDT has been reported. Dapsone hypersensitivity syndrome (DHS) is a serious adverse effect caused by dapsone. Prompt withdrawal of dapsone is important aspect in the management of DHS. Alternative regimens are needed to treat leprosy patient with DHS.

Case Illustration: A 37-year-old man with multibacillary (MB) leprosy developed DHS in 39 days after the initiation of WHO MDT. Dapsone was withdrawn and methylprednisolone of 75 mg/day was prescribed. Twelve days after admission the patient showed clinical and laboratory improvement and was discharged. Treatment for multibacillary leprosy was continued with rifampicin and clofazimine with standard dosage. The bacterial index (BI) and morphological index (MI) showed +1 and 0 respectively in one month after the completion of 12 pulses of modified MB-MDT.

Discussion: In the event of severe dapsone toxicity like DHS, WHO recommends that no modification to MDT is required other than immediately stopping dapsone in the case of those receiving MB-MDT. Multiple doses of rifampicin, ofloxacin and minocycline (ROM) therapy can be used as another alternative in leprosy patient with severe adverse effect while taking dapsone.

Conclusion: Combination of rifampicin and clofazimine may be effective in treating MB leprosy with dapsone toxicity.

Keywords: dapsone, dapsone hypersensitivity syndrome, leprosy, WHO MDT

Background

Although the World Health Organization (WHO) has noted that the frequency of adverse reactions caused by multidrug therapy (MDT) is very low, a wide range of frequent adverse reactions caused by MDT has been reported in different studies.1 A study of 187 patients treated with MDT by Goulart et al. in Minas Gerais reported that 71 (37.9%) patients had adverse effects.2 A study of 194 patients treated with MDT by Deps et al. in Brazil reported that 88 (45%) patients had adverse effects to at least one MDT component.3 A study of 176 patients treated with MDT by Singh et al. in India reported that 79 (44.9%) patients had adverse effects due to one or more components of MDT. When such reactions occur, the standard regimen should be adjusted so that treatments can be continued.1

WHO stated that alternative treatments could be given to patients who do not tolerate MDT due to adverse reactions or contraindications. However, first, it is essential to make sure that the adverse reactions noticed are due to the anti-leprosy drugs.3

Dapsone hypersensitivity syndrome (DHS) is an idiosyncratic adverse effect caused by dapsone. It is a type of drug-induced hypersensitivity syndrome with a triad of eruptions, fever, and organ involvement (including liver, kidney, hematological system, and others). It usually develops within two to eight weeks after the administration of dapsone, which supports the
other name “fifth-week dapsone dermatitis”. The main treatment for DHS is the immediate discontinuation of the drug followed by initiation of oral or parenteral glucocorticoids (1 mg/kg/day), depending on the severity. This case report aimed to highlight the alternative treatments that can be given to patients with MB leprosy who do not tolerate dapsone.

Case Illustration

A 37-year-old man who was on MB-MDT for 39 days, presented with an erythematous rash associated with high-grade fever, jaundice, malaise, nausea, and vomiting for three days before admission to our emergency department. He also presented with multiple erythematous plaques without itching on his face, trunk, and limbs for one year.

Two months before admission, he consulted his physician in Pangkalpinang hospital with complaints of fever, arthralgia, and plaques that had become more erythematous. A slit skin smear from his earlobes and a plaque on his trunk in Pangkalpinang hospital revealed acid-fast bacilli (AFB) but did not report the bacterial index (BI) and morphological index (MI). He was treated with rifampicin, ofloxacin, and minocycline (ROM) therapy (single-dose) and methylprednisolone 2 x 16 mg. Two weeks after treatment, the clinical signs and symptoms showed improvement and then continued to MDT-MB. Thirty-nine days after treatment with MB-MDT, he had a high-grade fever, malaise, nausea, vomiting, jaundice, and generalized erythematous rash.

On physical examination, the patient was jaundiced, his temperature was 39.5°C, and his conjunctiva appeared pale. There was no palpable lymphadenopathy or evidence of thyroid enlargement. His bilateral ulnar nerves were thickened without tenderness. The abdominal examination revealed a slightly tender, enlarged liver 2 cm below the costal margin. His skin evaluation revealed a generalized, maculopapular, erythematous rash with multiple erythematous plaques on his face, trunk, and limbs (Figure 1). Some lesions had a punched-out appearance.

The laboratory test performed during admission showed anemia (Hb 10.1 gr/dl) and an increased liver function test (total bilirubin 10.8 mg/dl, direct bilirubin 8.47 mg/dl, indirect bilirubin 2.33 mg/dl, AST 215 U/L, ALT 447 U/L, and alkaline phosphatase 187 U/L). The serology test for the hepatitis B virus was negative. A diagnosis of DHS was established based on the patient’s medical history, clinical findings, and laboratory tests. Dapsone was withdrawn and methylprednisolone 75 mg/day, curcumin 20 mg tid, paracetamol 500 mg, and N-acetylcysteine 200 mg tid was prescribed. Treatment for MB leprosy was continued with clofazimine 50 mg daily. Rifampicin in the third blister pack would be given if the liver function test was normal. Twelve days after admission, the patient showed clinical and laboratory improvement (Hb 11.4 g/dl, total bilirubin 2.6 mg/dl, direct bilirubin 1.49 mg/dl, indirect bilirubin 1.11 mg/dl, AST 33 U/L, ALT 51 U/L, and alkaline phosphatase 78 U/L) and was discharged.

Figure 1. Clinical Features of Dapsone Hypersensitivity Syndrome after Taking Multibacillary-Multidrug Therapy for 39 Days with Jaundice and Generalized Maculopapular Erythematous Rash with Multiple Erythematous Plaques.
His methylprednisolone dose was tapered down, and treatment for MB leprosy was continued with rifampicin and clofazimine at the standard dosage. Signs of a reversal reaction or erythema nodosum leprosum were not detected during modified MB-MDT. His skin examination revealed multiple hyperpigmented patches on his face, trunk, and limbs after being released from treatment (Figure 2). One month after release from treatment, a slit skin smear from his ear lobes, and a patch on his trunk revealed AFB of BI+ and MI 0. Long-term follow-up is needed in this patient to detect relapse in the future.

Discussion

WHO has initiated the leprosy elimination program to reduce prevalence of leprosy to less than one case per 10,000 population. Some important components of this elimination program are knowledge and information about diagnosis, prompt diagnosis, and effective treatment.6 Since its introduction, MDT has been an essential tool in leprosy elimination. MDT regimens have been very useful in the treatment and control of leprosy.6 However, patients with severe adverse reactions while taking MDT need an alternative regimen. A study by Goulart et al. in Minas Gerais reported that 39.4% of patients who had adverse effects due to MDT received an alternative regimen.2 A study by Singh et al. in India reported that 5.1% of patients who had adverse effects due to MDT received an alternative regimen.1

The three drugs comprising MDT all have recognized adverse effects. Dapsone is associated with severe adverse effects, such as DHS, dermatitis, hepatitis, agranulocytosis, and severe hemolysis.8 A study by Deps et al. in Brazil reported that 85 (43.8%) patients had adverse effects to dapsone. Discontinuation of dapsone was performed in 46 (54.1%) patients.3 A study by Singh et al. in India reported that 73 (41.5%) patients had adverse effects to dapsone. Dapsone was discontinued in six (8.2%) patients.1 The exact incidence of DHS is unclear because of the lack of a global monitoring system for DHS. A study by Tian et al. in China showed that the total incidence of DHS was about 0.85%–1.23%. The mortality rate was 11.1% among DHS patients.4 A study by Pandey et al. among patients started MDT between 1990 and 2006, 2% developed DHS, and 0.25% died due to DHS.9 A study by Singh et al. in India reported that 1% of patients developed DHS.1

In the event of severe dapsone toxicity, like DHS, WHO recommends that no modification of MDT is required other than immediate discontinuation of dapsone in the case of those receiving MB-MDT. Individuals being treated for paucibacillary (PB) leprosy should have the dapsone discontinued and have clofazimine as substitute with standard dosage used in MB-MDT regimen for six months.10 Based on this recommendation, we continued the treatment of MB leprosy with rifampicin and clofazimine with the standard dosage for this patient. Slit skin smear in one month after the completion of 12 pulses of modified MB-MDT (without dapsone) showed BI of +1 without robust staining of AFB (MI was 0).
A retrospective study by Sapkota et al. showed no relapse cases in 67 patients who completed a modified regimen of MDT due to adverse event attributed to dapsone. Thirty patients who received rifampicin and clofazimine showed a steady decline in the mean BI.\(^6\) Over 99.9% of live bacilli are killed from the action of rifampicin. Changes in MI are rapid, and it falls to zero within five weeks following treatment with rifampicin containing MDT. MI shows the percentage of solid stained bacilli which indicate alive bacilli. It is a more sensitive parameter of therapeutic failure, non-compliance, drug resistance, or relapse.\(^1\)

In 1997, a combination of rifampicin (600 mg), ofloxacin (400 mg), and minocycline (100 mg)—ROM therapy—was approved for single-lesion PB leprosy. In the late 1990s, there have been many studies related to the use of ROM therapy, and some of these have also included multilesional PB leprosy and even MB leprosy.\(^6\) A study by Ura et al. compared conventional MB-MDT with monthly doses of ROM administered for two years in patients with MB leprosy. This study showed that both treatments were equally efficacious.\(^12\) A study by Villahermosa et al. compared 24 monthly doses of ROM with two years of MB-MDT in patients with MB leprosy. This study showed similar improvements in the lesions, bacterial index, and histology in both groups.\(^13\) Therefore, monthly doses of ROM administered for two years can be used as an alternative treatment in patients with MB leprosy who do not tolerate dapsone.

The limitation of our case was the lack of BI and MI before treatment. Therefore, we could not compare the BI and MI before and after treatment with rifampicin and clofazimine. The BI and MI showed +1 and 0, respectively, one month after the completion of 12 pulses of modified MB-MDT. Based on this report, we concluded that the combination of rifampicin and clofazimine might be effective for MB leprosy. Long-term follow-up is needed to detect relapse in the future.

**Conclusion**

We reported the development of DHS during treatment with MDT in patients with MB leprosy. The prompt withdrawal of dapsone was needed in this patient. An alternative treatment with rifampicin and clofazimine showed clinical and laboratory improvement.

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