



# Approach of Persisters Relapse in a Smear-negative Leprosy after Second MB-MDT Completion: An Arduous Case Report

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## Abstract

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**INTRODUCTION:** Many infectious disease intervention programs, including leprosy, are cautious about the establishment of relapse and drug resistance. This case report reports on a male patient who has had two relapses and had undergone twice multibacillary multidrug therapy (MB-MDT) treatment as well.

**CASE REPORT:** A 31-year-old male, came with the main complaint of new hypopigmented patches appeared on the body since 4 months ago, which arose from his second MB-MDT treatment. He started his first MB-MDT treatment in 2019 and second MD-MDT in 2020. Slit skin smear yielded negative results and histopathological examination showed no signs of leprosy. Serological anti-PGL-1 antibody tests yielded very high IgM (3.163) and normal IgG (2) levels. PCR amplification examination showed positive, but DNA sequencing targeting *rpoB*, *folP*, and *gyrA* genes showed no mutations. He was diagnosed with persisters relapse in a borderline-lepromatous leprosy and was treated with rifampicin 600 mg/day for 2 weeks; combination of minocycline 100 mg/day, clarithromycin 500 mg/day, and clofazimine 50 mg/day for 6 months; and methylprednisolone 32 mg/day for the neuritis. No new lesions appeared during current treatment and he is also showing gradual improvement of foot drop in his left leg.

**DISCUSSION:** The fact of a very high IgM levels after 2 courses of MB-MDT indicated that there is still bacteria that continued to induce antibody formation, thus supporting the persisters bacilli hypothesis in this case. Positive results of PCR amplification conclude that there is still *Mycobacterium leprae* bacilli in skin tissues, which may be hidden in deeper tissues. We have to make a more proactive approach considering this was his 2<sup>nd</sup> times of relapse, and knowing the fact that MB-MDT was consumed religiously in the two previous treatments.

**CONCLUSION:** In an arduous case like this, proactive step must be taken. Whenever possible, the use of whole genome sequencing is strongly advised.

## Introduction

Leprosy, a chronic infectious disease caused by *Mycobacterium leprae*, continues to be a global health issue, particularly in underdeveloped countries such as Indonesia. During the year 2013, globally, 215,656 new leprosy cases were detected [1]. Leprosy primarily affects the skin and peripheral nerves. Beside those two main targets, *M. leprae* can as well affect the oral mucosa, upper respiratory tract, kidney, reticulo-endothelial system, eyes, muscles, bone and testis, and except the central nervous system [2].

Formation of relapse and drug resistance is a source of concern for many infectious disease intervention programs, particularly when chemotherapy is the primary component of the control approach [3]. This manuscript reports on a patient who has had two relapses after twice multibacillary multidrug therapy (MB-MDT). The approach taken in this case can be used as a lesson about the importance of thoroughness and proactive approach in an arduous case like this.

This case report has obtained written informed consent from the patient and was approved by the Ethics Committee of Dr. Soetomo General Academic Hospital Surabaya (0852/LOE/301.4.2.IV/2022).

## Case Report

A 31-year-old male came with main complaint of new hypopigmented patches appeared on the body. Complaints of reddened and thickened old patches were denied. He was previously diagnosed with leprosy in 2019 and underwent first MB-MDT treatment and completed 12 blisters. Slit skin smear (SSS) after first MB-MDT revealed bacterial index 2/4+ and morphological index 1%. Second MB-MDT treatment was initiated but new lesions were still appearing. While still undergoing the second MB-MDT treatment, he said new patches were still appearing on his body.

Dermatological examination revealed hypopigmented macules with diffuse borders and both earlobes showed diffuse infiltrates. Newly emerged lesions were mainly located in the right arm, abdomen, and posterior thoracic area, as shown in Figure 1. Examination of the peripheral nerves function revealed Grade 1 thickening on both ulnar nerves and decrease in motor function on the left common peroneal nerve, which causes him to experience foot drop.



Figure 1: The appearance of new skin lesions (red circle) was mostly in the form of hypopigmented macules that were scattered mainly in the upper extremities, abdomen, and posterior thorax

SSS was performed and yielded negative results. Histopathological examination (Figure 2) of new skin lesions showed shortening of the rete ridges and lymphocytes infiltration in the dermis layer. Fite-Faraco staining showed no acid-fast bacilli.

Serologic anti-PGL-1 antibody test showed very high IgM and normal IgG levels, namely 3.163 (normal range: <630 U/mL) and 2 (normal range: <605 U/mL), respectively. PCR amplification showed positive results (Figure 3). DNA sequencing targeting *rpoB*, *folP*, and *gyrA* genes to see if there were any mutations that induce resistance to rifampin, dapsone, and ofloxacin, respectively, showed no mutations in those genes (Figure 4).

A diagnosis of persisters relapse was confirmed. He was then initiated to receive rifampicin 600 mg/day for 2 weeks; minocycline 100 mg/day, clarithromycin

500 mg/day, and clofazimine 50 mg/day for 6 months; and methylprednisolone 32 mg/day for the neuropathy. Methyl-prednisolone was carefully tapered over 12 weeks, as recommended by WHO. After 2 months of treatment, he came back with satisfactory results. No new lesions appeared during current treatment and he is also showing gradual improvement of foot drop in his left leg.

## Discussion

Relapse in leprosy is a challenging situation for clinicians and requires special attention. Estimates of relapse rates varied significantly among locations. This is most likely owing to differences in the criteria of relapse, the range of skin smear positive in MB cases, the proportions of previously dapsone-treated and untreated patients, and the length of follow-up. After completion of MDT, the probability of relapse is actually very low, both for PB and MB patients [4]. Because we have been living in the era of MDT since 1981, we can ignore the monotherapy being the risk factor. Likewise, risk factor for inadequate and irregular therapy can be excluded, since this patient has an excellent track record of compliance previous MB-MDT.

We decided to consider diagnosis of relapse in leprosy even though it did not completely fulfill the WHO relapse criteria. Decision to diagnose a relapse case requires in-depth analysis and discussion, based primarily on the findings that new lesions were still appearing and that the IgM anti-PGL-1 antibody level was still very high despite 2 courses of MB-MDT. Chance of reinfection can be ruled out as there were no families or people around who suffer or were undergoing leprosy treatment; therefore, the strongest possibility left is a relapse due to persisters bacilli.

The possibility of a late reversal reaction in this patient can be ruled out, considering that the skin lesions that arise were all hypopigmented macules, where there was no increased erythema, swelling, tenderness in the old lesions. This patient also did

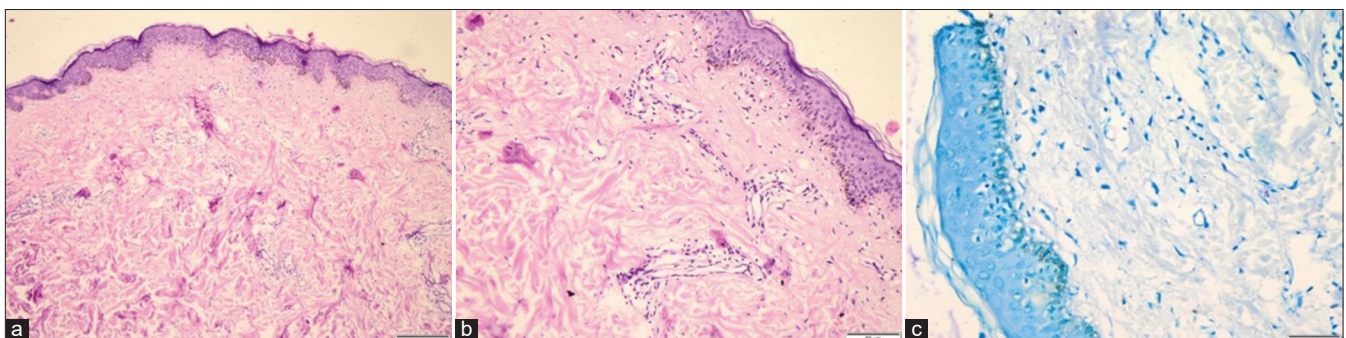


Figure 2: Histopathological examination of the new skin lesions. (a) Shortening of rete ridges (H&E staining, 100 × magnification); (b) Lymphocytes infiltration of dermis (H&E staining, 200 × magnification) and; (c) No acid-fast bacilli found on Fite-Faraco staining (400 × magnification)

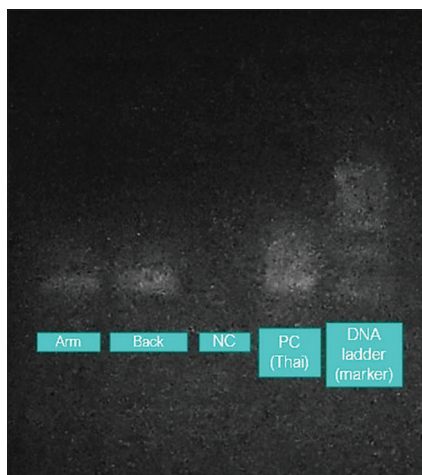


Figure 3: PCR amplification of *M. leprae* yielded positive results from both arm and back specimens

not have acute painful neuritis, as in the patient with a reversal reaction.

Very high IgM antibody found in this case is a sign of a reservoir of bacilli residing in the body. Antibodies generated from T-independent pathway of humoral immune response induced by non-protein antigens (polysaccharides and other multivalent antigens) are low-affinity and have short-lived plasma cells [5]. The fact that there were high IgM levels even after 2 courses of MB-MDT indicated that there is still bacteria continued to induce antibody formation, thus supporting the persists bacilli hypothesis in this case.

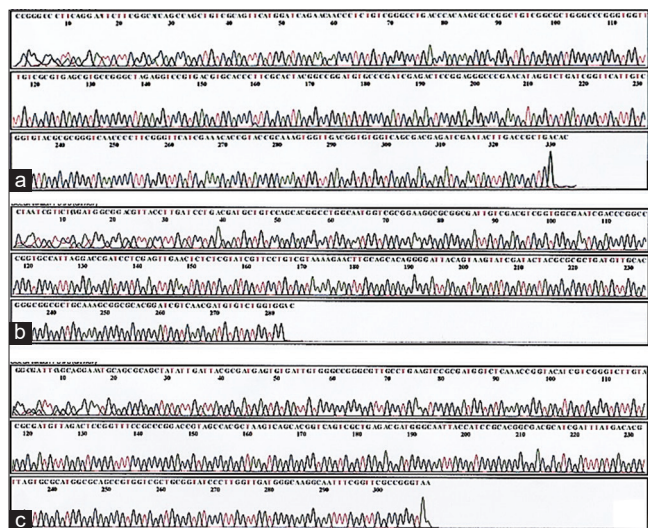


Figure 4: DNA sequencing of the (a) *rpoB*; (b) *folP*; and (c) *gyrA* genes showed no mutations in those genes

The use of PCR and DNA sequencing has a crucial role to determine whether drug resistance occurs in this patient [6]. Molecular techniques serve as a potent tool for the quick diagnosis of drug-resistant *M. leprae* and give critical information on future chemotherapeutic approaches for leprosy control. Positive results of both specimens (right arm and back) on PCR amplification, conclude that there is *M. leprae* bacilli which may be hidden in deeper tissues, make it hard to be detected by superficial SSS.

Meanwhile, no mutations in *folP*, *rpoB*, and *gyrA* genes, indicating that there is no drug resistance. However, it should be noted that the sequencing performed was not a whole genome DNA sequencing. What we use (as recommended by the WHO) is a direct sequencing of PCR products using the Maxam-Gilbert method, which only covers 300 bp of the whole genome. In fact, *M. leprae* bacilli has 3.268.203 bp, thus the possibility of drug resistance is still cannot be completely ruled out [3].

Until now, there has been no fixed guideline for second relapse as seen in this case. We have to make a more proactive approach considering this was his 2<sup>nd</sup> times of relapse, and knowing the fact that MB-MDT was consumed religiously in previous treatments. We decided to initiate second-line therapy and the administration of rifampicin for 2 weeks is intended to provide a strong bactericidal effect, targeting persistent bacteria found in deeper locations. Administration of corticosteroid was not intended to suppress reversal reaction, but as a prevention of disability [7], [8].

## Conclusion

A complete and holistic examination is needed in cases of relapse in leprosy, as it is a very challenging condition for clinicians, seeing that the actual incidence is actually low. In an arduous case like this, we must take a proactive step by giving second-line therapy, considering that giving a third MB-MDT is not a wise choice. Whenever possible, the use of whole genome sequencing is strongly advised, to really prove the presence or absence of drug resistance.

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