Suspected resistance of MDT-MB in multibacillary leprosy of Hansen’s disease: Two case reports

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Abstract
Resistance to multidrug therapy (MDT) is one of the complications in the treatment of Hansen’s disease/Morbus Hansen (MH). There are two types of resistancy, which are primary and secondary. MDT-multibacillary (MB) resistance must be suspected when no clinical improvement and the acid-fast bacilli (AFB) index is not reduced after 12 months of therapy. A 28-year-old woman with paresthesia on her face, arms and legs since 2.5 years ago, accompanied by thickening of the right posterior tibial nerve. The AFB examination showed a bacteriological index (BI) of 15/6 and morphological index (MI) of 0.50%. The second case, a 42-year-old man came with paresthetic lesions on his face, chest, back, both arms and legs since 2 years ago, accompanied by thickening of ulnar and lateral peroneal nerve. The BI was 12/5 and the MI was 0.40%. Both patients were diagnosed with borderline lepromatous type of MH and received MDT-MB for 12 months. Diagnosis of suspected resistance was established because no clinical improvement or any significant decrease of AFB index after completing the MDT treatment. The patients had secondary resistance after polymerase chain reaction evaluation showed that they were still rifampicin-sensitive. There was clinical improvement and significant decrease in FAB index after the patients continued the MDT-MB treatment with 600 mg additional rifampicin. The diagnosis of bacterial resistance should be made based on clinical evaluation before completion of treatment. Based on the two case reports, the resistance suspected may be secondary. Treatment using additional regimen can be initiated once the resistance has been proven.

Keywords: Hansen’s disease, MDT resistance, clinical improvement, acid fast bacilli index

Abstrak

Kata kunci: Morbus Hansen, resistensi MDT, perbaikan klinis, indeks basil tahan asam
Introduction

Hansen’s disease or morbus Hansen (MH) is a chronic infection caused by Mycobacterium leprae (M. leprae) attacking peripheral nerve, skin, oral mucosa, upper respiratory tract, kidney, reticuloendothelial system, eyes, muscles, bone and testis, except the central nervous system.\textsuperscript{1,2} The disease may lead to disabilities, particularly on eyes, hands and feet; therefore, early detection and prompt treatment are essential.\textsuperscript{3}

MH is still a health problem in developing countries, including Indonesia. In 2012, the incidence of leprosy in Indonesia was 23,169 cases, ranked third worldwide after India and Brazil.\textsuperscript{4} However, the Global Leprosy Statistics reported that the number of leprosy cases is decreasing in approximately 20 countries worldwide.\textsuperscript{4,5}

MH treatment currently refers to WHO multidrug therapy (MDT) regimen.\textsuperscript{3} The standard treatment for MH is determined by the WHO Expert Committee (2012), in which paucibacillary cases (PB) receive MDT-PB as many as 6 doses, which should be completed in 6 months; while the multibacillary (MB) cases are treated with MDT-MB as many as 12 doses completed in 12 months.\textsuperscript{6} The treatment of MH uses a predetermined dose and interval without considering clinical manifestation. The treatment is ceased based on the recommended treatment duration.\textsuperscript{7,8}

The principle in evaluating the effectiveness of MH treatment is by counting the incidence of relapse. Relapse is a recurrent MH case in patients who have completed their treatment without any evidence of re-infection. The low relapse incidence indicates successful treatment of MDT regimen. WHO recommends a periodic surveillance after the patients have completed their treatment regimens.\textsuperscript{7}

Resistance is one of complications in treatment of MH. There are primary and secondary resistances. Primary resistance is caused by infection of resistant microorganisms since the beginning of the onset; while secondary resistance occurs due to irregular or monotherapy treatment.

Presently, no standard clinical diagnostic criteria have been developed for MH resistance. The evaluation of microorganism resistance in MH is very difficult and it can only be done by inoculation into mice foot pad or DNA sequencing and microarray.\textsuperscript{8,5} Suspected resistance is assumed when there is no clinical improvement and there is no reduction of the acid-fast bacilli (AFB) index after receiving or completing MDT-MB for leprosy. The polymerase chain reaction (PCR) showed that there were active microorganisms in both patients of our case report. Treatment using additional regimen can be initiated once the resistance has been proven.

In 2012, Siskawati conducted a study in Jakarta on the resistance and its association with the compliance of taking medicine in patients with MH. The study found that there was a relatively high incidence of resistance (28.6%) in patients with MH who had poor compliance. The study also found silent mutation in the microorganisms associated with resistance against rifampicin.\textsuperscript{10}

The treatment of rifampicin resistance according to WHO guidelines includes 50 mg of clofazimine and two additional medications, i.e. 400 mg ofloxacin and 100 mg minocycline daily or 500 mg clarithromycin for the first 6 months course, which is followed with 50 mg clofazimine and 400 mg ofloxacin or 100 mg minocycline daily until the 18\textsuperscript{th} month. While for dapson resistance, WHO does not recommend modified treatment for MB patients.\textsuperscript{8}

Resistance can occur due to persistent M. leprae microorganism. The microorganism can unexpectedly become active again, but still sensitive to rifampicin. Based on that rationale, in addition to the above mentioned regimens, some experts still use additional rifampicin to treat the suspected secondary resistance. Using the modification, it is expected that the additional dose of rifampicin can eliminate persistent microorganism in the MDT-MB treatment.\textsuperscript{9}

Resistance in MH cases is strongly associated with the incidence of relapse. Relapse is defined by WHO (1988) as a patient who successfully completes an adequate course of MDT treatment, but subsequently develops new signs and symptoms of leprosy, either during the surveillance period (2 years for PB and 5 years for MB leprosy) or thereafter.\textsuperscript{7,11,12}

Inappropriate MH treatment regimens is one of the major causes of resistance, either primary or secondary.\textsuperscript{7} Clinicians should be careful in establishing diagnosis and providing treatment for MH, particularly for the cases of relapse or resistance.
Cases

The first case is about a 28-year-old woman with a paresthetic lesion on her face, both arms and legs since 2.5 years ago before treatment (Figure 1, 2). The lesions were accompanied with thickening of right posterior tibial nerve. The AFB examination prior to the treatment showed a bacteriological index (BI) of 15/6 and morphological index (MI) of 0.50%. The results of AFB examination after the patient completed the treatment regimen were BI of 17/6 and MI of 0%.

In the second case, a 42-year-old man came with paresthesia lesion on his face, chest, back, both arms and legs since 2 years before having treatment (Figure 3, 4). The lesions were accompanied with thickening of ulnar nerve and bilateral lateral peroneal nerve. The AFB examination prior to treatment showed that the BI was 12/5 and the MI was 0.40%; while after completing the therapy regimen, the BI was 15/6 and the MI was 0.16%. Unfortunately, both patients did not have AFB examination in the middle of regimen course. Both patients were diagnosed with borderline lepromatous (BL) type of MH and received MDT-MB for 12 months.

There was no clinical improvement or any significant decrease of AFB index following the treatment in both patients, particularly for the male patient who still had positive MI; therefore, a diagnosis of suspected resistance was established. Both patients said that they took the medication regularly and MDT had been completed in 12 months and both denied any error in taking their medicine or having another contact with leprosy patients during treatment.
The patients continued MDT-MB treatment with additional 600 mg rifampicin in every two weeks at the beginning of the month for 15 months in the first patient and for 18 months in the second patient. Both patients had leprosy reaction, but the reaction could be managed by oral steroid treatment.

Additional treatment was stopped when there was clinical improvement and better results of AFB examination, particularly for the MI. On the follow-up after the completion of treatment, there was a clinical improvement and the AFB index was reduced significantly. PCR was performed to establish the diagnosis and positive results for M. leprae were found for both patients. Moreover, subsequent DNA sequencing examination was performed and the result showed that both patients were still sensitive to rifampicin. However, the DNA sequencing test on dapsone resistance still could not be performed due to some problems.

Discussion

The first and most common case of resistance is dapsone resistance (1953) due to monotherapy. Rifampicin resistance was reported for the first time in 1976 and in most cases, it was caused by irregular treatment and monotherapy. Clofazimine resistance has been rarely reported despite the drug has been used for more than four decades. Ofloxacin is an alternative regimen used in some countries as no treatment guideline has been developed in those countries. In Japan, the determination of MDT as MH treatment guideline has just been started since 2000 and there were two ofloxacin resistance cases reported in 2000 and 2003, which were due to DNA mutation.9

A 28-year-old female patient and a 42-year-old male patient with a diagnosis of BL type MH and suspected resistance did not show any clinical improvement and lower bacteriological index after completing 12 regimens of MDT-MB treatment. The diagnosis of MH was made based on history taking, physical examination, and laboratory workup. Bacteriological examination performed prior to the MDT-MB treatment showed high rate of BI and MI.

There are some factors that can affect the development of resistance. One of those factors is irregular MDT treatment,7,10 which was denied by both patients. Reactivation of lesions may also be caused by re-infection.

The diagnosis of resistance should be established within 6 months after the patient has received treatment. The patient can be evaluated based on clinical manifestations and AFB test. The AFB test for patients with suspected resistance should be done periodically every 3 months by considering the clinical situation of the patient.9

In both patients, we found high BI at the beginning of the test. After completing 12-month regimen of treatment, the patients did not experience any significant clinical improvement and there was increased BI on their MH lesions. Clinical improvement on the skin lesions of the patients was found after prolonged MDT treatment and additional rifampicin treatment of 600 mg/day for the first 2 weeks. The additional rifampicin was aimed to eliminate persistent microorganism that may possibly occur.9

In both patients, we did not perform AFB test in the middle of treatment course. In addition to the clinical manifestation, the results of AFB test should also be a reference of possible drug resistance that occurs in the patients. The AFB test should be repeated on the same skin lesion for simple evaluation.

In the cases with rifampicin resistance, WHO suggests giving an alternative regimen using additional ofloxacin and minocycline; while for cases with dapsone resistance, WHO does not suggest any modification. To have a confirmed diagnosis of drug resistance, we need to perform an inoculation into mice feet, DNA sequencing or microarray test. The results of DNA sequencing showed that both patients were still sensitive to rifampicin; however, the possibility of dapsone resistance still could not be excluded.7-10

The diagnosis of suspected resistance should be made clinically before the treatment has been completed so that the alternative treatment can be administered immediately.10 If there is no clinical improvement during or after the MDT course, then drug resistance can be suspected. The suspected resistance should be evaluated when there is no significant clinical or bacteriological improvement during the MDT regimen course.9,11 Based on the two case reports, the suspected resistance was secondary resistance which occurred after MDT had been completed. Modification of treatment could be considered when the diagnosis of suspected resistance had been established before it was confirmed with DNA sequencing.9

Rifampicin is a main drug in MDT-MB treatment as it has the strongest bacteriolytic effect. Before
giving the additional regimen, it is better to perform PCR and DNA sequencing in order to identify the microorganism sensitivity to rifampicin. There is no standard guideline for the additional therapy regimen; therefore, the regimen can be stopped when there is a significant improvement, either clinical or bacteriological, and we need to perform periodic clinical examination and AFB test every 3 months.9,10

References
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