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CASE STUDY

# Multibasillary Leprae Lepromatous Leprosy Type Relaps with Erythema Nodosum Leprosum Reaction: Establishing the Diagnosis

**Nurrachmat Mulianto[1], Putri Oktriana[1], Ferry Arrochman[1], Brian Wasita[2], Ambar Mudigdo[2], Ria Margiana[3*]**

1. *Department of Dermatology and Venerology, Faculty of Medicine, Sebelas Maret University, Dr. Moewardi General Hospital, Surakarta, Indonesia.*
2. *Department of Pathology Anatomy, Faculty of Medicine, Sebelas Maret University, DR. Moewardi General Hospital, Surakarta, Indonesia.*
3. *Department of Anatomy, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.*

***Corresponding Author: Ria Margiana, email: margianaria@gmail.com**

## Abstract

Introduction: Leprosy or Morbus Hansen is a disease caused by infection with Mycobacterium Leprae with manifestations in the skin and peripheral nerves that can cause neuropathy or disability. The case of relapse in leprosy is a condition in which patients who have successfully completed the MDT (multi drug therapy) program with complete and appropriate but there are new symptoms of the disease either during the monitoring period or after. ENL reactions can occur at any time, namely before, during and after MDT therapy. Case: A woman aged 43 years comes to Dermatology and Venereology Clinic with complaints of red bumps accompanied by pain in the face and extremities. On physical examination fromt the facial, superior and inferior limbs appear multiple erythematous nodules with partial hyper pigmented, multiple, indistinct boundaries. Investigation in the form of an AFB test indicates the presence of IB + 3 and IM 0% which previously earned IB +1 IM 2.09%. Histopathological examination revealed an ENL reaction with a red acid-resistant bacillus. The patient is diagnosed with leprosy MB type LL RFT1, 5 years relapsed with ENL. Discussion: Relapse or recurrence in leprosy can occur due to a variety of factors, one of which is due to the presence of persistent leprosy bacilli, Becx-Bleumink criteria can be used as a reference for diagnosing relapse that includes clinical features, BTA examination and histopathological features.

**Keywords**: *Erythema nodosum leprosum, Leprosy, Relapse.*

## Introduction

Leprosy is a disease caused by *Mycobacterium Leprae* infection which manifests on the skin and peripheral nerves that can cause neuropathy or disability [1]. The prevalence of leprosy is higher in males than females, which is 2:1. Based on 2015 data from the World Health Organization (WHO), there were 211,973 new cases per 100,000 people worldwide and 1,093 cases were recorded in Southeast Asia.

The number of new cases of leprosy found in Indonesia in 2017 was 10,477 cases in 100,000 people, with the most recorded cases in Java, and other endemic areas such as Sulawesi, West Nusa Tenggara and Papua [2, 3].

Leprosy is classified as paucibacillary leprosy (PB) and multi-bacillary leprosy (MB). PB leprosy (paucibacillary) has a clinical description of 1 to 5 lesions without the discovery of *M. leprae* bacilli in acid-fast bacillus (AFB) examination, whereas MB leprosy has a clinical description of more than 5 lesions, and there are many *M. leprae* bacilli found on AFB smear examination [1]. Ridley-Jopling has classified leprosy into several types, namely tuberculoid

(TT), borderline tuberculoid (BT), mid-borderline tuberculoid (BB), borderline lepromatous (BL), and lepromatous leprosy (LL) [4, 5].

Relapsing case of leprosy according to WHO is a condition where a patient who has completed the MDT program (multi drug therapy) completely (complete of therapy) experiences new signs and symptoms of the disease both during the monitoring period or afterwards. Relapse criteria for multi-bacillary leprosy (MB) is characterized by an increase in the number of *M. Leprae* with an increase in the bacterial index (BI) +2 or more on the examination of skin smear and histopathology accompanied by clinical deterioration [5, 6]. In the course of the disease, someone with leprosy can experience a condition called a reaction that can occur at any time, that is, before, during, or after treatment.

Leprosy reactions are distinguished according to the underlying hypersensitivity reactions, namely type 1 leprosy reaction or reversal reaction and type 2 leprosy reaction or erythema nodusum leprosum (ENL) [7, 8].This paper discusses a case report regarding the diagnosis of MB leprosy relapse with ENL reaction. This paper aimed to increase the knowledge on the diagnosis of MB leprosy relapse with ENL reaction, which is known as a rare case, so that appropriate therapeutic management can be provided.

## Case

A 43-year-old woman from Sragen, who works as a farm labour, came to the Dermatology and Venerology Clinic of Dr. Moewardi General Hospital with complaints of painful lumps on the face as well as both arms and legs for 2 weeks before the patient went to the hospital. Complaints accompanied by joint and muscle pains and fever. The patient had been examined by a dermatologist at Sragen General Hospital and had received 4 kinds of medication, namely compounded medication (the patient did not know the ingredients), methylprednisolone tablets at a dose of 20 mg/day, nerve vitamin tablets twice a day and topical medication. At that time, AFB examination of the two ear lobes had also been carried out, resulting in the bacterial index (BI) +1 and morphological index (MI) 2.09%.

One week later, the patient went back to the doctor for check-up and there was no improvement, so the patient was referred to Dr. Moewardi General Hospital and AFB examination was done once again. From past medical history, the patient had a history of leprosy in 2016. At that time complaints consisted of thickened patches on the face and some of her body; by a dermatologist she was diagnosed with leprosy and received MDT for 12 months.

The patient claimed to take medication regularly and finished leprosy treatment 1.5 years ago and was declared free of leprosy with the result of AFB examination, conducted at a *puskesmas* (community health centre), at BI +1 and MI 0%. There has been no history of family and people surrounding the patient experiencing similar disease.

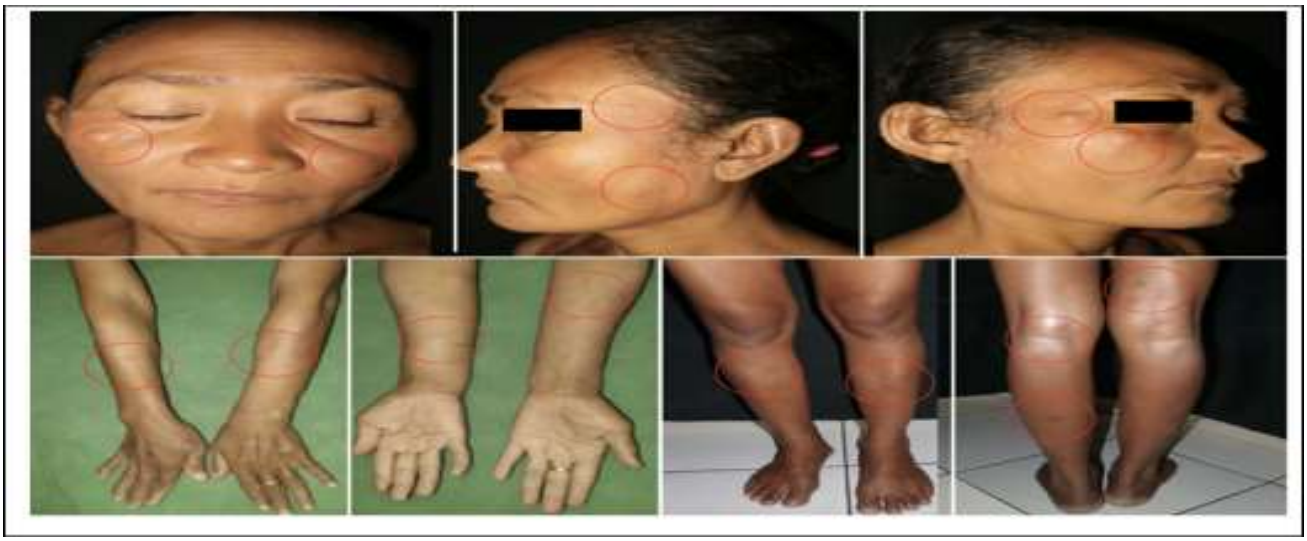

**Figure 1: The status of dermatovenereology status in the facial region or *regio facialis* (right and left cheeks), multiple erythematous nodules with multiple hyperpigmentation patches appear. In the superior and inferior extremity regions, the hyperpigmentation patches are accompanied by the presence of xerotic skin**

In the physical examination, blood pressure 120/80 mmHg, pulse 80x per minute, breathing count 20x per minute, body temperature 36°C, pain scale 2, body weight 45 kg and height 155 cm were obtained. Dermatological status in the facial region was not madarosis, on the right and left cheeks multiple erythematous nodules with multiple hyperpigmentation patches had appeared, on the inferior and superior extremity regions multiple hyperpigmentation patches with xerosis cutis had become visible. There has been no shortening of the fingers or toes (Figure 1). The result of nerve thickening examination was within normal limit; the expression of pain was found in the palpation of the left ulnar nerve and left posterior tibial nerve. In the sensory examination using palpation on both palms and both feet, there was no abnormality. The result of the examination of muscle strength of both eyes, superior and inferior extremity muscles was good. Based on the anamnesis and physical examination of the patient, a differential diagnosis of relapse in multi-bacillary leprosy with ENL reaction and multi-bacillary leprosy with RFT for 1.5 years of with ENL was obtained. In the AFB examination (acid-fast bacilli) conducted at Dr. Moewardi, samples taken from both ear lobes and nodule lesions in the right arm showed bacterial index (BI) +3 and morphological index (MI) 0%.

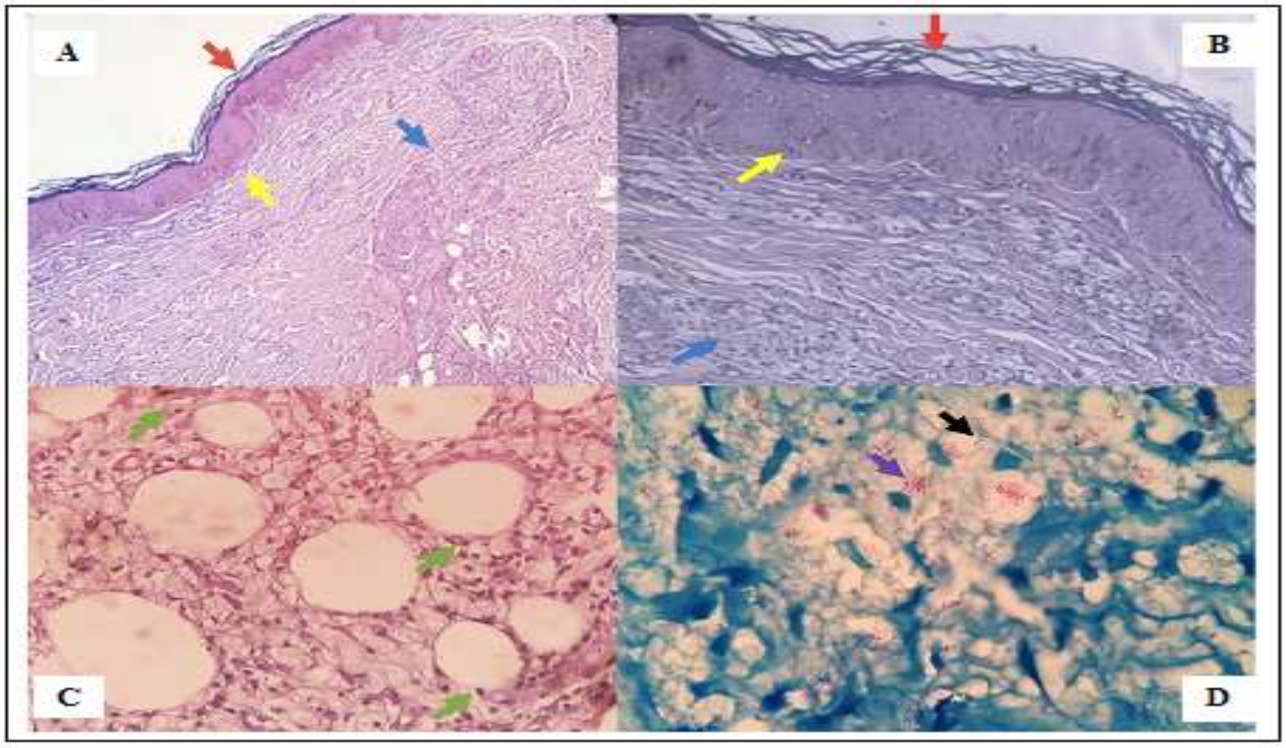


**Figure 2: A. (HE staining, weak magnification), B. (Strong magnification) Basket weave-type hyperkeratosis (red arrows) and horizontal rete-ridges (yellow arrows) can be seen in the epidermis, granulomas to the lower part of the fat can be found in the dermis (blue arrows) C. (Stronger magnification) Panniculitis can be seen in the dermis (green arrows). D. (FF staining, very strong magnification) acid-fast bacilli in the form of intact rods can be seen (black arrow 1) and some are partially intact in the form of fragments and granules (purple arrow) in the dermis**

In the histopathological examination with hematoxylin-eosin (HE) staining on weak magnification, basket weave-type hyperkeratosis and horizontal rete-ridges were found in the epidermis, granulomas could be seen in the dermis, the tubercle foci reached to the lower part of the fat with foamy macrophage cells, and there appeared to be an infiltration of inflammatory cells around the fat tissues (panniculitis) (Figure 2). In fite-faraco (FF) staining, some of the acid-fast bacilli were in the form of intact rods and the rest were partially intact (fragments and granules). The result of calculation per visual field was bacterial index (BI) +4. Based on the results of the anamnesis, physical examination and histopathological examination, the patient was diagnosed with multi-bacillary leprosy type LL relapse with RFT of 1.5 years with erythema nodosum leprosum. In this patient, the treatment for the ENL reaction was prednisone tablet 40 mg/day for 2 weeks, paracetamol tablet 500

 

mg/8 hours, MDT (multi drug therapy) of MB type MH with caplet rifampicin regimen 600 mg/month, clofazimin tablet 300 mg/month and the following day 50 mg/24 hours, and dapsone tablets 100 mg/24 hours.

## Discussion

Leprosy, also known as Morbus Hansen or Hansen's Diseasse (HD) is a chronic infectious disease caused by *Mycobacterium leprae (M. Leprae)*, which is obligate intracellular acid-fast bacteria, mainly infecting the Schwann cells, manifesting in the skin [9]. The introduction of multidrug therapy (MDT) and the application of anti-inflammatory therapies have led to significant improvements in the long-term health outcomes for people diagnosed with Hansen's disease (HD) [10]. Even though the global prevalence of leprosy has substantially declined, the condition is still incorrectly understood, and the statistics do not often include the dysfunction and disability that remain after the completion of the MDT [11, 12].

Studies show that a 1991 World Health Assembly resolution for elimination of leprosy was attained by the year 2000 at the global level [10]. It reduced the HD prevalence to one case of the disease in a population of 10, 0000 people [13]. However, it has argued that this objective is still far from being achieved in many parts where leprosy is endemic. This is true, considering that the incidences of the illness have not shown a significant decrease over the last decade.

Among millions of patients who have received multidrug therapy, many still experience long-term complications of HD, including deformity and social stigma, as well as temporary and permanent disability. In 2011, more than 219, 075 cases of leprosy were reported indicating the persistent transmission of the illness despite its prevalence and overall decline [13].

Under the present treatment scheme of the World Health Organization (WHO), many patients complete HT treatment in less than one year. Therefore, the worldwide prevalence of this disease is often below the incidence. In 2012, an upward of 181,941 cases of HD was reported, with Brazil and India dominating the cases [10].

As noted, HD emerges from infection with *Mycobacterium leprae*, an intracellular acid-fast bacillus. Estimates show that 95% of the world's population is vulnerable to leprosy, although variation among population groups associated with genetic factors and bacillus exposure exists [13]. The traditional interaction model of an infectious agent such as pathogen, host, and environment seems to be a unique one in the case of HD. There is a little variability of pathogen and virulence to illustrate the various clinical forms, with the potential exception of the newly discovered species *Mycobacterium lepromatosis* in HD patients who had diffuse leprosy of Lucio and Latapi [11].

Nonetheless, the studies indicate that most of the clinical phenotypes could be as a result of genetic variability determined by different biological pathways modulated by *M. leprae*. They could also be due to the reprogramming of adult Schwan cells as well as the interactions of innate and adaptive immunity. Based on these clinical phenotypes, some populations have increased prevalence rates than others. For instance, individuals living in the Western Pacific, particularly Micronesia, have high cases of HD in the world.

Among the vulnerable populations, there are different ways in which the immune systems of individuals respond to bacilli in the body [12]. These reactions give the physicians the impression that HD presents itself uniquely in every individual's body. This presentation shows that there are different classifications of leprosy [10, 11, 12].

The classifications of HD should be identified by clinical prognosis to determine the potentially infectious cases [10]. In the course of the disease, a reaction as an immune response to the *M. Leprae* bacilli can occur. Erythema nodosum leprosum (ENL) or type 2 reaction is one form of reaction as a humoral immune mechanism, an increase in TNFα concentration in the circulation forms a complex from the result of antigen-antibody reaction that involves the activation of the complement system.

This reaction is found in patients over the age of 30 years and is associated with low socioeconomic level such as farmers and labours [14, 15].

 

In this case, the patient was 43 years old and worked as a farmer which is a high prevalence group for ENL.

The reaction of erythema nodosum leprosum (ENL) leprosy is characterized by fever, arthralgia, myalgia, anorexia and painful nodules. Purplish red nodules are scattered diversely on the body but are more common on the face and the extensor part of the extremity [16]. In this case, based on the anamnesis of the patient, her main complaint was in the form of painful reddish lumps accompanied by fever for 2 weeks before going to the hospital.

There are other complaints in the form of arthralgia and myalgia. In the physical examination of the dermatological status, multiple erythematous nodules were found with the accompaniment of pressure pain. These findings are consistent with ENL's description. The WHO has suggested a simple scheme for determining various types of HD, which is used as a treatment model.

In this model, leprosy is classified according to visible symptoms, and the absence or presence of bacilli in slit skin smears from the cooler parts of the body, including elbows, earlobes, and knees. These are the regions where bacilli proliferate. The model classifies individuals with just 1 to 5 diagnostic skin patches and no signs of bacilli in slit-skin smears as having "paucibacillary" disease [10, 12].

Those patients with less than five skin patches and bacilli visible by microscopic analysis of skin smears are classified as having "multi-bacillary" disease. The diagnosis criterion in regions without slit-skin smears is the number of physical lesions. The classification model that uses the number of identifiable lesions can lead to both over and under-diagnosis of leprosy [12].They recommended a criterion that considers the size of the lesions and accompanying nerve enlargement-the classification system of the WHO lacks treatment protocol for neuritic HD cases where skin lesions are absent.

A more improved classification system identifies an array of cell-mediated reactions to HD with five classes of the disease [13, 11]. The system groups them according to their severity or strength of immune response. They include tuberculoid (TT), borderline tuberculoid (BT), borderline borderline (BB), borderline lepromatous (BL), and lepromatous leprosy (LL) as summarised in the Table 1 below.

**Table 1: Summary of Leprosy classification**

| | |
|---|---|
| Tuberculoid (TT), | • Characterised by the presence of less than five skin lesions, which are typically hypopigmented or erythematous macules with increased erythematous borders and an atrophic centre [10].<br>• The skin lesions are hypoesthetic or anesthetic; their distribution is asymmetrical with the presence of multiple lesions [10].<br>• The skin lesions may be large and commonly occur on the face, trunk, or extrimities. However, they do not exist in the groin, axillae, or on the scalp due to the preference of *M.leprae* for lower temperatures [11]. |
| Borderline borderline (BB) | • Manifests with anesthetic discrete plaques similar to those in TT [26].<br>• Characterized by multiple lesions, usually greater than five and less than ten [26].<br>• Patients present with multiple asymmetrical annular plaques [13]. |
| Borderline lepromatous (BL) | • Characterised by numerous symmetrical small macules, papules, nodules and plaques [10].<br>• Cutaneous lesions are characteristically annular plaques with sharp interior and exterior borders [26].<br>• The number of skin lesions is moderate and they are asymmetrical and anesthetic [13]. |
| Lepromatous leprosy (LL) | • Characterised by polar and bipolar forms [11, 10].<br>• Develops from borderline or borderline-lepromatous forms by a downgrading reaction [13].<br>• Manifests with symmetrical cutaneous lesions, which includes infiltrated plaques, multiple small macules, and nodules with poorly defined borders [26].<br>• Associated with type two or ENL reaction, which occurs in 50% of patients after several months of therapy [13, 11]. |

Leprosy classification according to Ridley-Jopling is based on clinical symptoms and histologically divided into TT, BT, BB, BL, and LL [16, 17].Based on WHO, TT and BT types are included in PB leprosy, while those belonging to MB leprosy are BB, BL and LL types. In multi-bacillary leprosy, especially LL type, skin lesions tend to be multiple and symmetrical, more often found in areas of the body that have low temperatures, can be characterized by patches of hypopigmentation, erythematous, or patches of hyperpigmentation with unclear boundaries, sometimes only dry skin can be found. In advanced condition, there are infiltrating lesions that form plaques and

 

nodules; nerve damage, madarosis, and disability can be found. In the examination of skin smear in multi-bacillary leprosy, acid-fast bacilli can also be abundantly found [18].In this patient, there were more than 5 lesions on her body, in the form of erythematous nodules and patches and hyperpigmentation with indistinct borders; in the examination of skin smear from both ear lobes and lesions, many acid-fast bacilli were found, so in this case the patient was categorized as LL multi-bacillary type patient. The risk factor for the occurrence of ENL reaction is in multi-bacillary leprosy, namely BB, BL, and LL types. ENL reaction can occur in 50% of LL type multibacillary leprosy cases and 25% occur in BL type cases [19].

In this case; the patient suffers from LL type multibacillary leprosy, which carries the risk of ENL. A leprosy patient with a reaction can be diagnosed differentially with a relapse case. Relapse or recurrence in multibacillary leprosy (MB) can be defined by the discovery of a reincrease in the number of *M. Leprae* assessed by a 2-fold increase in the number of bacterial index (BI) compared to the previous value occurring after the patient has finished MDT and is accompanied by signs of clinical deterioration [5].

Recurrence can be assessed by Becx-Bleumink criteria, namely (1) an increase in *M. Leprae* bacteria (at least +2 or more than the previous value) in each visual field, (2) clinically characterized by skin lesions in the form of new nodules or new nerve damage, (3) infiltrates in pre-existing skin lesions, (4) lepromatous activity in the eyes, (5) intact germs in the histological examination of the skin or nerve biopsy [17, 10]. In this case, the relapse criteria was obtained from the AFB examination result of BI +3, whereas after the completion of the treatment the result had been BI +1, and patches and new erythematous nodules were discovered.

Based on the Becx-Bleumink criteria, the increased germ a criterion from AFB examination result was obtained, followed by skin lesions and new infiltrates. Histopathological examination was then performed on the patient to prove the existence of a relapse in accordance with the criteria (5).

The result of histopathological examination of LL type multi-bacillary leprosy in general is an image of flat epidermis that can be separated from the skin infiltrates by solid collagen zone, large and expanding macrophage granulomas, which consist of foamy cells with small lymphocytes. The foamy cells contain bacilli in large quantities (ranging from BI +4 to 6).

The histopathological examination of ENL reaction can find the presence of lymphocyte infiltration around the blood vessels (vasculitis) or the presence of inflammatory infiltration around the fat tissues (panniculitis). In the fite-faraco special staining, red M. Leprae bacilli can be identified, which in the ENL reaction many bacilli appear in the form of granules or fragments (bacteria) that are dead or inactive, but if there are intact rod germ forms (active bacteria), then the diagnosis of relapse can be established [20, 23].

In this patient, the histopathological examination was taken from the biopsy of the skin lesions of the patient's right arm and granulomas was found, the tubercle foci reached to the lower part of the fat with foamy macrophage cells in accordance with the description of LL type multi-bacillary leprosy and an infiltration of inflammatory cells around the lobules of the fat tissues (*lobular panniculitis*) could be seen.

The histopathological examination followed by fite-faraco (FF) staining showed that some of the *Mycobacterium Leprae* bacilli were found to be intact and the others were partially intact in several parts with the value of BI +4 (10-100 bacilli/one microscope field of view), this strengthened the relapse of the patient. The patient was diagnosed with LL type multi-bacillary relapse with ENL reaction. LL group was redefined to include the components of the sub-polar and polar of the initial description. In the US, the National Hansen's Disease Program uses the Ridley-Jopling classification system [10]. This system correlates with the immune response to *M leprae* infection.

Therefore, it can be used to determine patients who are immunologically unstable and susceptible to leprosy [10, 11]. This framework subjects patients with borderline forms of leprosy to upgrading or downgrading reactions.

 

The increased cell-mediated immune response characterizes upgrading reactions, whereas downgrading reactions occur when patients develop lesions in the lepromatous pole of the spectrum after starting with the forms of borderlines [13]. A patient who has been proven to experience a recurrence is recommended to use the MDT regimen as recommended by WHO, namely the standard MB leprosy regimen for adult patients consisting of: Rifampicin 600 mg per month, clofazimin 300 mg per month, 50 mg per day and dapsone 100 mg per day with a duration of treatment of 12 months [1].

Management of ENL should be done by giving anti-reaction drugs that can be tailored to the needs of the patient. Patient continues with MDT and can be given standard prednisolone at a dose not exceeding 1 mg/kg/day for a total duration of 12 weeks [16, 13]. In this patient, the MDT of MB leprosy is continuing and for the ENL reaction methylprednisolone has been given at a dose of 40 mg/24 hours with a decrease in dose until there is a clinical improvement in ENL and analgesics is adjusted to the condition, i.e. paracetamol at a dose of 500 mg/day.

The monitoring and evaluation of leprosy treatment are recommended to be done monthly during leprosy treatment, namely to monitor the systemic effects of MDT treatment and AFB examination once a year. The monitoring of skin lesions and bacterial counts in multi-bacillary leprosy can be used to monitor the success of therapy. Patients who have leprosy reactions can be tested weekly to monitor corticosteroid doses [17, 11].

This patient is planned to be monitored every month for the systemic effects of MDT and to have re-examination of AFB after continuing the 12-month MDT as an evaluation of multi-bacillary leprosy. It should be noted that leprosy is mild in its early stages, often presenting as a reaction and forcing patients to seek medical attention. Its symptoms do not present for many years after transmission due to the long incubation period.

Although some cases of infants and young children with leprosy have been reported, suggesting a shortened period between transmission and symptom manifestation, the WHO has stated that the incubation period for this disease is between 5-20 years [12].The absence of severity of HD when it starts presenting on the body can lead to delays in patients seeking diagnosis and delays in receiving an accurate diagnosis from physicians. HD is sometimes mistaken for other conditions that occur on the skin, such as fungal infections, allergic reactions, vitiligo, and other mycobacterial infections.

In regions where this disease is non-endemic, diagnosis can be problematic. Based on the individual's immune response, leprosy can remain a mild condition with no physical changes and spontaneous cure. To some extent, it can progress to allow the proliferation of bacilli, thus, resulting in extensive peripheral nerve damage. This damage can cause changes in physical appearance and mobility.

### Summary

A case was reported of multi-bacillary leprosy in a 43-year-old woman who had completed MDT therapy for leprosy type MB with RFT for 1.5 years. Based on the anamnesis, physical examination and AFB supporting examination as well as histopathological examination, the patient was diagnosed with LL (lepromatous leprosy) type multi-bacillary leprosy relapse with ENL with RFT for 1.5 years. In the patient's condition, a multi-bacillary leprosy relapse with an ENL reaction with RFT for 1.5 years must be differentiated from ENL reaction. Becx-Bleumink criteria can be used as a reference to establish the diagnosis of relapse. Patient should continue the treatment with the MDT regimen for MB MH recommended by WHO and be given prednisolone at appropriate dosage until there is clinical improvement in ENL.

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