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Case Report

Borderline Lepromatous Leprosy with Severe Erythema Nodosum Leprosum: A Case Report

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ABSTRACT

Background: Leprosy is a chronic granulomatous infectious disease caused by *Mycobacterium leprae* (*M. leprae*) that primarily infects Schwann cells in the peripheral nerves, leading to nerve damage and the development of disabilities. In 2018, Indonesia was the third country with the most leprosy cases in the world. Erythema nodosum leprosum (ENL), also known as type II leprosy reaction, is a severe immune-mediated complication of multibacillary leprosy. **Purpose:** To report a case of borderline lepromatous leprosy with severe ENL. **Case**: A 49-year-old Balinese man presented with multiple tender erythematous skin nodules all over his body, fever, arthralgia, bilateral cervical lymphadenopathy, and sensory loss for the past week. The acid-fast bacilli bacteriological examination showed a positive result. The patient was diagnosed with borderline lepromatous (BL) leprosy with severe ENL and was treated with multibacillary multidrug therapy (MB MDT), methylprednisolone, and other symptomatic medications. After 1 month of treatment, there was an improvement in skin lesions. The MB-MDT treatment was continued and methylprednisolone was planned to be tapered down gradually. **Discussion**: Approximately 20-50% of all leprosy patients show leprosy reactions in the course of the disease. The goals of treatment for severe ENL are to control inflammation, reduce pain, treat neuritis to prevent nerve dysfunction and contractures, and prevent recurring ENL. The prognosis of leprosy with ENL reactions depends on the severity of the occurring leprosy reaction; early diagnosis and prompt treatment; and patient compliance with treatment. **Conclusion**: Early diagnosis and treatment are essential to avoid deformities in leprosy patients.

Keywords: borderline lepromatous, leprosy, *Mycobacterium lepra*, severe ENL.

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BACKGROUND

Morbus Hansen (MH), also known as leprosy, is still a great concern in the dermatology and venereology fields. Leprosy is a chronic granulomatous infectious disease caused by infection of *Mycobacterium leprae* (*M. leprae*) that primarily affects the skin, peripheral nerves, and other tissues except for the central nervous system.[1,2] Neglected diagnosis and treatment of leprosy could cause progressive functional impairment.[3,4]

In 2018, Indonesia ranked the third-largest number of MH cases in the world after India and Brazil, with 17.017 cases, and the most cases based in the region of South East Asia, with 114.004 cases. According to the World Health Organization (WHO), the disease's prevalence reached 0,25 per 10.000 people in 2018, with 184.238 new cases.[5] In Sanglah Hospital from January 2019 to December 2020, there were 51 cases of multibacillary (MB) type and 13 cases of MB with erythema nodosum leprosum (ENL) in 2020.[6]

Riddley and Jopling classified leprosy based on clinical, histopathological, and immunological criteria into five forms of leprosy: tuberculoid polar leprosy (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL), and lepromatous polar leprosy (LL).[7,8] For therapeutic purposes, WHO

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divided patients into two groups: paucibacillary (PB) and multibacillary (MB).[7]

Leprosy reactions are acute or subacute episodes of clinical inflammation which occur during the chronic course of the disease due to the patient's sudden shift in immunological responses against the antigen of *M. leprae*.[9,10] They pose a challenging problem in morbidity due to nerve damage.[11] There are two different types of leprosy reactions, known as type 1 reversal reaction (RR) and ENL. The ENL type is related to the deposition of immune complexes (antigen-antibody reaction), which are likely present in the LL and BL leprosy types.[1,7,10,12]

Patients with severe ENL are likely to have an impaired quality of life due to the disability of neurological and muscular complications. In severe ENL, the patient might present with multiple erythema nodules, ulcers, peripheral edema, neuritis, and impaired function of other organs. Severe ENL is also often recurrent and might occur for weeks to years. Aside from complications and disability caused by this condition, managing severe ENL is still challenging. Even though steroid has been chosen as the initial treatment, the side effects of prolonged usage should be closely monitored.[13, 14] Herein, we report a

typical case of BL leprosy with severe ENL. In this report, we described and discussed the clinical picture, diagnosis, and treatment of the ENL type of leprosy reactions to improve understanding and management of this condition.

CASE REPORT

A 49-years-old Balinese man, from Kauh Pecatu, presented to the outpatient clinic of the Dermatology and Venereology Department of Sanglah Hospital, Denpasar, on November 25th, 2020, with chief complaints of erythematous nodules all over his body. From the anamnesis, the patient stated that the nodules appeared on both arms and trunk, neck, face, and legs in less than a week. The nodules were tender. The patient also had joint pain, especially in the elbow, which appeared at the same time as the nodules, fever, headache, and loss of appetite in the past three days.

The patient was previously diagnosed with BL leprosy in July 2020 based on several numb erythematous plaques on his body for 2 months, nerve thickening, and the finding of *M. leprae* from a skin smear test. The patient took the first regimen of multibacillary leprosy multidrug therapy (MB-MDT) in July 2020 and didn't continue the treatment until November 2020, when started the second regimen. There was no other medical history of the patient. There was no family history of similar complaints, but it was believed that one of his working colleagues had those symptoms as his, but had passed away. The patient had been working as a guide for visitors coming to villas in Pecatu for 15 years. The patient had continuous sunlight exposure for a long time.

Physical examination revealed that the patient was in good general condition, had normal vital signs (blood pressure 120/80 mmHg, heart rate 84 bpm, respiratory rate 20 bpm, and temperature 37,0ºC), and a visual analog scale (VAS) of 2/10. No signs of madarosis and lagophthalmos were found. The thorax and abdominal examinations were unremarkable. The dermatological status of this patient: in the regions of the face, anterior and posterior thoracoabdominal, upper and lower left and right extremities there were multiple erythematous nodules (>20 nodules), round-shaped with a shiny surface and defined border of 1-2,5 cm in diameter, discrete, immobile, and tender. In several regions there were multiple erythematous macules – patches, round to geographic in shape with a defined border of 0,5-2 cm in diameter and 0,5 cm x 1,5 cm – 3 cm x 5 cm in size, discrete and bilaterally distributed, with xerotic skin. In the regions of anterior and posterior thoracoabdominal there were multiple erythematous papules – plaques, round to geographic shaped with a defined border of 0,5-1,5 cm in diameter and 1 cm x 2 cm – 4 cm x 6 cm in size, discrete and bilaterally distributed, with a white squamous surface in several lesions and punched out lesions. The skin lesions are presented in Figure 1a-1i.

In the sensibility test, there was less sensation of touch, pain, and temperature stimuli marked in lesions on the face, anterior and posterior thorax, and also in the upper and lower extremities. There was also nerve thickening found in the right great auricular nerve, right ulnar nerve, as well as right and left common peroneal nerves. The monofilament Semmes-Weinstein test in the dorsal and palmar of the right and left feet showed blue. There was no muscle weakness in the voluntary muscle test (VMT). The right earlobe lesion had no acid-fast bacilli (AFB), while the sample from the left earlobe had 1-3 AFB of 10 narrow visual fields, bacteriological index (BI) +2, and the right antebrachial had 1-2 AFB of 10 narrow visual fields, BI +2 fragmented, and morphological index (MI) 0%. The patient also underwent several blood tests and showed normal results.

The patient was diagnosed with BL Leprosy with severe ENL based on clinical and slit skin smear findings. He refused hospital admission and was prescribed the second regimen of MB-MDT (consisting of 600 mg of rifampicin once a month, 100 mg of dapsone daily, and 300 mg of clofazimine once a month and 50 mg daily) until the twelfth regimen, methylprednisolone 32 mg as divided doses (16 mg

each in the morning and afternoon) and planned to be tapered down to 5-10 mg every 2 weeks if clinical improvement occurs, omeprazole 20 mg twice daily, 500 mg of mefenamic acid three times a day, vitamin B_1 B_6 B_{12} daily, and 10% topical urea cream twice daily.

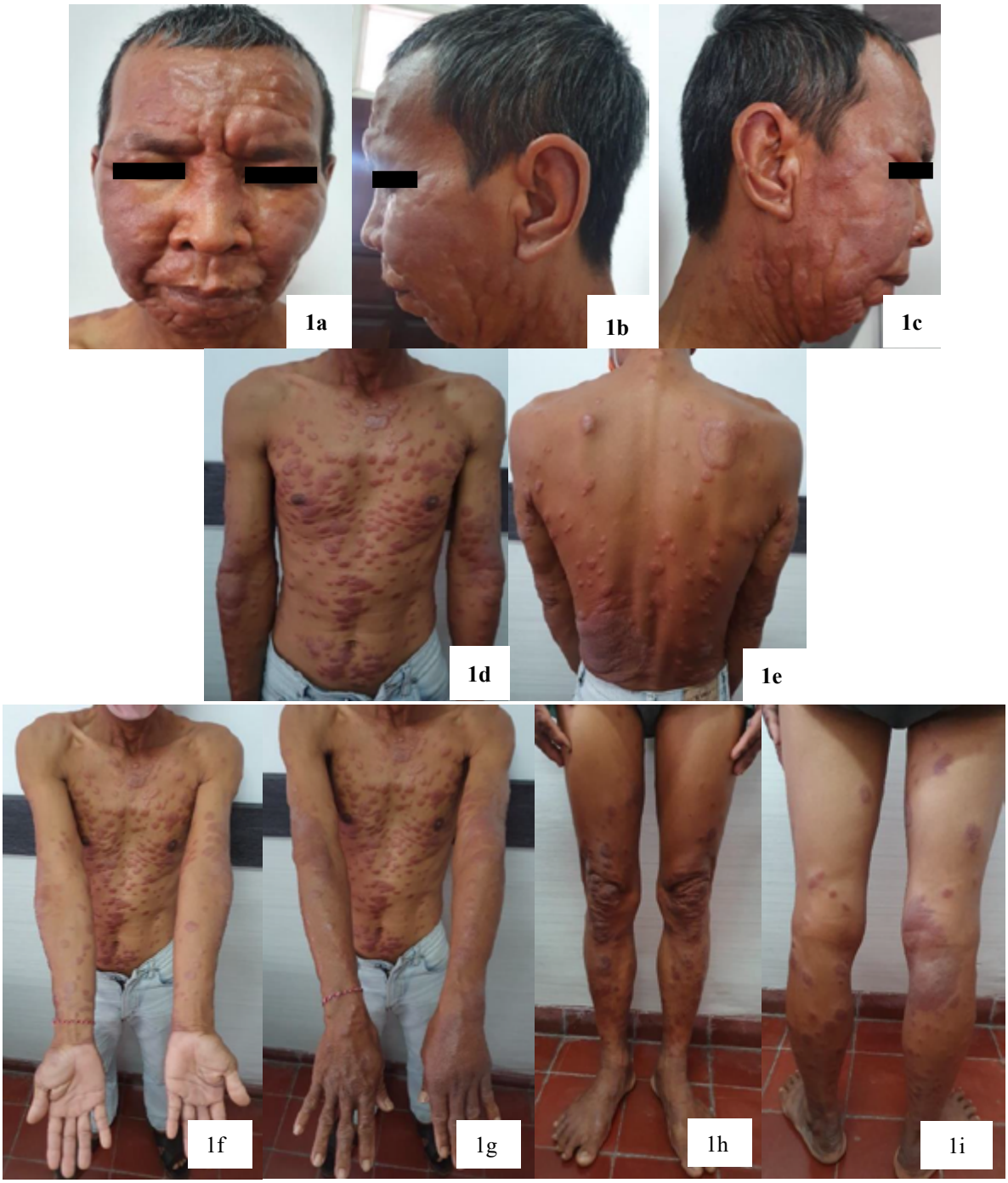

Figure 1. Before Treatment**.** Erythematous nodules and macules to patch lesions on the face region (a-c). Erythematous macules, patches, papules, plaques, and nodules lesions on the thoracoabdominal (d) with punched-out lesions (e) on the upper extremities (f-g) and lower extremities regions (h-i).

After 1 month of treatment, there were no new lesions and the old lesions became hyperpigmented in several regions. The fourth regimen of MB-MDT was continued, methylprednisolone was tapered down to 24 mg/day as in divided doses, and other prescribed medicines were continued. He tolerated the whole medication well and showed improvement. No nodules were found and lesions became hyperpigmented (Figure 2a-2i). Patients were advised to consult every 2 weeks for evaluation.

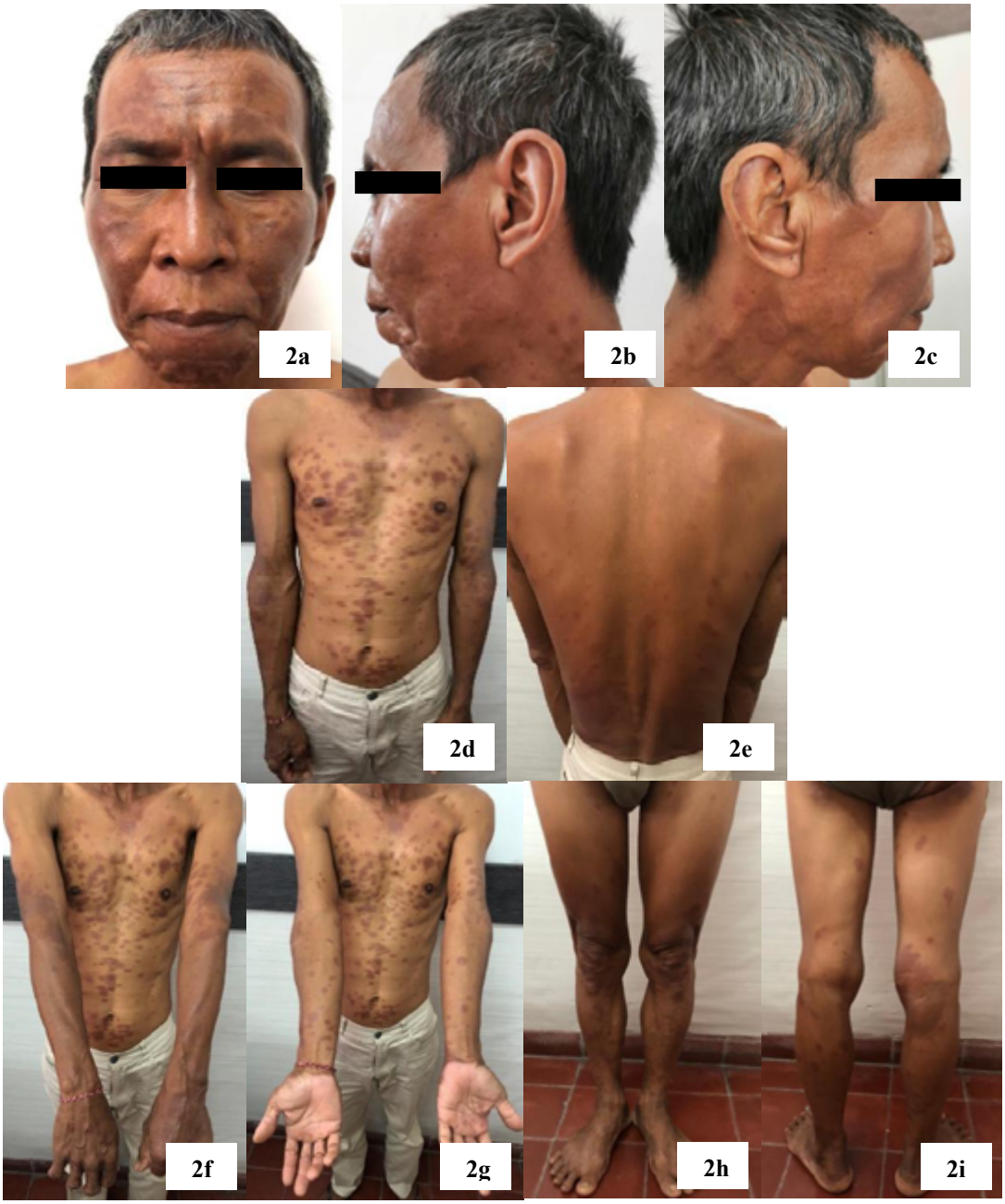

Figure 2. After 1 month of treatment. Multiple hyperpigmented macules and patches on the face (a-c), thoracoabdominal (d-e), upper extremities (f-g), and lower extremity regions (h-i).

DISCUSSION

Mycobacterium leprae is an aerobic, rod-shaped, 1.5-8 microns long and 0.2-0.5 microns in diameter, acid-resistant, intracellular obligate bacteria and cannot be cultured on artificial media. This bacterium is found in macrophage cells around the superficial blood vessels in the dermis or Schwann cells in the nerve tissues.[7,12,15] The main source of leprosy transmission is untreated patients with MB leprosy. The mode of transmission of leprosy remains uncertain, but several studies have shown that the transmission could occur through prolonged and close skin contact or inhalation of droplets. In addition, other opinions stated that *M. leprae* can be transmitted through transplacental transmission, blood transfusion, organs, and digestive tract transplantation.[7,10,12] Leprosy can affect various age groups, most commonly found in the 20-30 years old age group. The prevalence of leprosy is higher in men than women, with a ratio of 2:1.[16]

In this case, the patient was a 49-years-old male who had worked in a villa for 15 years. According to the anamnesis, he had contact with his working colleague with a similar medical history. The patient came from the village of Kauh Pecatu, Badung, where the prevalence of leprosy is high in that place.

Therefore, it could be concluded that multiple risk factors can cause leprosy infection.

Clinical diagnosis of leprosy is made by finding at least 1 out of the 3 cardinal signs, which are numb patches (macular or plaque, hypopigmented or hyperpigmented, erythematous or copper-colored skin lesions, with a rough and dry surface in some cases, or smooth and shiny surface), thickening of peripheral nerves and finding of AFB on slit skin smear.[7,12,15] The sensibility test can reveal loss of cutaneous sensations, which is often partial, before touch (anesthesia), pain (analgesia), or temperature (cold and hot) stimuli. The peripheral nerves involved in leprosy can be enlarged with or without pain and dysfunction of the affected nerve.[12]

The diagnosis of leprosy was made according to the patient's medical history, physical examinations, and slit skin smear. There were multiple types of erythematous skin lesions with defined borders and smooth shiny surfaces, decreased sensation to touch, pain, and temperature stimuli in some lesions, and thickening of the right great auricular nerve, right ulnar nerve, and right and left common peroneal nerve. Skin smear showed AFB found in the left ear lobe and right antebrachial skin lesion samples.

The skin manifestations of the patient were erythematous macules, patches, and plaques with defined borders and bilateral symmetrical distribution, as well as the presence of punched-out lesions. Nerve involvement was marked by impaired sensory function and several nerve thickenings in this patient. From the skin smear test, IB +2 fragmented AFB was obtained. Based on those findings, the differential diagnosis of BB leprosy could be ruled out and a working diagnosis of BL leprosy could be confirmed.

World Health Organization classifies leprosy into 3 groups for therapeutical purposes based on clinical criteria using the total number of skin lesions as well as the result of the skin smear test. It includes PB leprosy with a single lesion, PB leprosy (2-5 skin lesions), and MB leprosy (>5 skin lesions). In addition, patients who have positive results from skin smear tests are also classified as having MB leprosy, regardless of the clinical finding. The administration of MDT aims to prevent resistance, shorten the treatment period, and prevent disease transmission.[10] Leprosy patients who have taken MDT, both PB and MB types, according to the number of regimens, are stated as Release From Treatment (RFT) patients. After RFT, clinical and bacteriological follow-up (without treatment) is performed for 5 years. If there is no new clinical activity and the bacteriological condition remains negative, it is classified as a "Release From Control (RFC)" and patients are no longer under monitoring.[10,12,17] The MB-MDT regimen was prescribed for the patient due to having multiple lesions (> 5 lesions) and a positive result (+2) in the skin smear test. The patient started his first regimen in July 2020, dropped out for 3 months, and started again for the second regimen in November 2020.

Leprosy reactions are disruptive episodes of acute or subacute inflammation mediated by the immune system. Approximately 20-50% of all leprosy patients show leprosy reactions in the course of the disease. Leprosy reactions are divided into two types, which are type I and type II leprosy reactions.[7,9,10] Erythema nodosum leprosum (ENL), or type 2 leprosy reaction, is an immunological complication of leprosy that causes inflammation of the skin, nerves, and other organs and is a type III hypersensitivity reaction (Coomb and Gell), in the form of a humoral immune response with a reaction between the *M. leprae* antigen and antibodies (IgM, IgG) to form an antigen-antibody complex. These immune complexes generally occur in the extravascular but can be in the blood circulation so that they can deposit in various organs, especially where *M. leprae* is highly found, such as the skin, nerves, liver, and lymph.[18] Erythema nodosum leprosum was reported to occur in 50% of patients with LL leprosy and 25% of patients with BL leprosy. Factors that are thought to trigger ENL are infiltration in the skin of lepromatous patients; IB ≥+4; patient age >40 years old; primary infections caused by other bacteria, viruses, and parasites; recurrent infections; surgical procedures; physical stress; immunization; pregnancy; and post-delivery.[9]

Clinically, ENL reactions can occur in mild or severe forms, mild form with warm and tender erythematous nodules in small numbers, ulcers rarely, no constitutional symptoms, no lymphadenopathy and leg edema, no neuritis, no eye involvement, and no other organ dysfunction. Severe form with multiple erythematous nodules with fever, ulcers are common, peripheral edema is common in the legs, neuritis in single or multiple nerves, impaired organ function (iridocyclitis, epididymal-orchitis, bone or joint pain, lymphadenopathy), and recurrent episodes of ENL.[11,12,19] In addition, ENL can also be classified into 3 categories, namely acute ENL, where only 1 episode of ENL occurs in less than 24 weeks. Recurrent ENL occurs one month after ENL treatment has finished and there is a subsequent ENL episode. Chronic ENL occurs continuously for more than 24 weeks.[7,20] In this case, the patient had a complaint of painful erythematous nodules on almost all of his body. The patient also complained of joint pain, fever, and intermittent headache, as well as loss of appetite, enlarged lymph nodes, and neuritis, which was

consistent with the clinical features of severe ENL. In this case, the trigger factor was thought to be physical stress after 2 weeks of restlessness and decreased sleeping time.

The principle of leprosy reactions treatment is the provision of anti-reaction drugs, immobilization, sedative analgesics, and continuation of anti-leprosy drugs. The goals are to control inflammation, reduce pain, treat neuritis to prevent nerve dysfunction and contractures, and prevent the recurrence of ENL.[16] Mild ENL reactions can be treated with outpatient treatment and administration of analgesics or antipyretics such as aspirin, chloroquine, antimonials (stibophen), and colchicine. Meanwhile, severe ENL reactions require hospitalization, and oral corticosteroids, clofazimine, and thalidomide, either one or in combination, should be taken.[8,18,21] Oral corticosteroids are the drug of choice for ENL. The dosage range is from 0.5-1 mg/kg per day or 40-60 mg per day until there is clinical improvement. A maintenance dose of 5-10 mg per day may be needed for several weeks to prevent ENL recurrence. Second, treatment with a combination of clofazimine and corticosteroids. Initial therapy is given with a combination of prednisolone and clofazimine for 300 mg in 3 divided doses daily, then reduced to 100 mg per day and maintained for 3 to 6 months.[22] Another drug that can be used is thalidomide, which has anti-inflammatory activity and should be started with a dose of 200 mg twice a day, or 100 mg orally 4 times a day. ENL is usually under control within 72 hours. The dose can be decreased periodically, and sometimes, for some cases of chronic ENL, a maintenance dose of 50-100 mg per day is required. Unfortunately, our patient refused to be admitted and was treated as an outpatient with a second regimen of MTB MB, methylprednisolone 32 mg as divided doses and planned to be tapered down to 5-10 mg every 2 weeks if clinical improvement occurs, mefenamic acid 500 mg three times a day, Vitamin B1, B6, and B12 daily, and 10% of topical urea cream twice a day, applied on dry skin.

The most common complication of leprosy is disability due to nerve damage. The pathophysiology of disability due to leprosy can be caused by the infiltration of bacilli on the skin and nerves as well as the reaction of leprosy in the form of acute neuritis, which can cause nerve dysfunction.[23] The risk factors for disability in leprosy include the type of leprosy, disease duration, total affected trunks nervous, leprosy reaction, and neuritis.[24] Healthcare must give education regarding complications and disabilities that can occur. To assess treatment and prevention quality, the patients must be assessed for disability with WHO criteria: 0 (no anesthesia, no physical disability due to leprosy, no impaired eye and vision loss), 1 (anesthesia on the upper and lower extremities but no physical disability, low vision to 6/60 and can finger count in 6 meters), and 2 (ulcus and physical disability like foot drop, claw hand, bone resorption, and impaired eye like lagophthalmos, red eye, severe low vision below 6/60 and can't finger count in 6 meters).[21] In this case, the patient had no complications at the start of treatment and after 1 month of treatment.

Bacillus Calmette-Guerin (BCG) vaccination proves to be partially protective against leprosy, with a single dose being 50% protective and a double dose providing more protection. The WHO 2018 guidelines for prophylaxis in endemic areas include a single dose of rifampicin for children above 2 and adults.[19] History of BCG vaccination in this patient was unknown.

The prognosis of leprosy with ENL reactions depends on the severity of the occurring leprosy reaction, early diagnosis, and prompt treatment, especially when neuritis is present. Knowledge of the clinical course of ENL is important and close monitoring during follow-up is necessary to increase patient adherence to treatment.[25] Patients should also be educated about the disease and the possibility of disease transmission; the medications taken by the patient and their side effects; other possible complications of nerve damage (eyes, hands, and feet); and follow-up schedules.

One case of BL leprosy with severe ENL has been reported in a 49-years-old man. The diagnosis was made based on clinical history, physical examination, and laboratory findings. There were complaints of erythematous nodules in one week, with joint pain, fever, headache, and loss of appetite. On physical examination, there were erythematous, round-shaped, and defined borders of macules to nodules; enlarged lymph nodes; decreased sensory function in several lesions; and multiple nerve thickening in the right great auricular right ulnar nerve, and right and left common peroneal nerve. A skin smear revealed positive results of fragmented AFB with IB +2. The management was to continue administering MB-MDT, methylprednisolone, and other symptomatic medications. The prognosis was analyzed due to recurrent ENL reactions. Prompt and appropriate treatment in patients with severe ENL is necessary to improve the patient's quality of life and prevent further complications and disabilities.

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